CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

218213Orig1s001

Trade Name:	AUGTYRO
Generic or Proper Name:	Repotrectinib
Sponsor:	Bristol Myers Squibb Company
Approval Date:	June 13, 2024
Indication:	AUGTYRO (repotrectinib) capsules, for oral use, is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that: • have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, • are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

218213Orig1s001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s001

APPROVAL LETTER

NDA 218213/S-001

ACCELERATED APPROVAL

Bristol Myers Squibb Company
Attention: Lise Alessio, Pharm.D., M.S.
Associate Director, Global Regulatory Strategy & Policy
P.O. Box 5326
Princeton, NJ 08543

Dear Dr. Alessio:

Please refer to your supplemental new drug application (sNDA) received December 15, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Augtyro (repotrectinib) capsules, for oral use.

This "Prior Approval" sNDA proposes to add a new indication for Augtyro:

AUGTYRO is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510 you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement(s) specified in your submission dated June 10, 2024. These requirements are listed below.

4649-1 Conduct an analysis of patients from ongoing or planned trials intended to verify and describe the clinical benefit of repotrectinib through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and pediatric patients 12 years of age and older with solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion who have locally advanced or metastatic disease or would require surgical resection that would result

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment.

A sufficient number of patients will be evaluated to more precisely characterize response and durability of response for a spectrum of patients with different TKI-naïve and TKI-pretreated tumor types. All responding patients will be followed for at least 12 months from the onset of response or until disease progression whichever comes first.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 11/2029
Final Report Submission: 05/2030

4649-2 Complete the analysis of the 23 responding patients in the efficacy evaluable population of 40 TKI-naïve patients and the 24 responding patients in the efficacy evaluable population of 48 TKI-pretreated patients in the TRIDENT-1 trial intended to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to repotrectinib. All responding patients will be followed for at least 2 years from the onset of response or until disease progression, whichever comes first. Duration of response will be assessed by independent central review.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion: 09/2024
Final Report Submission: 03/2025

Submit clinical protocols to your IND 130465 for this product. FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this NDA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). One report will be a standalone submission and the other report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-

day report will be due 180 days after the date of approval of the original NDA (with a 60-day grace period). Submit the other 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[3] Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**NDA 218213/S-001 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval of the original NDA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of skeletal fractures or assess a signal of serious risks of long-term effects on growth, neurological outcomes, and development in pediatric patients.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risk of skeletal fractures or assess the signal of serious risks of long-term effects on growth, neurological outcomes, and development in pediatric patients.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4649-3 Conduct integrated safety analyses from an adequate number of patients enrolled in clinical trial(s) designed to characterize the known serious risk of fractures and sequelae of fractures in patients exposed to repotrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to identify mitigating measures for the risk of skeletal fractures. Include sufficient bone monitoring to achieve these objectives including but not limited to initial and serial assessment of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans, and markers of bone formation, bone resorption, and calcium metabolism.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	05/2029
Final Report Submission:	11/2029

4649-4 Conduct a clinical trial or analysis of clinical trials of repotrectinib in a sufficient number of pediatric patients 12 years of age and older with NTRK-fusion positive solid tumors to evaluate the potential serious risk of adverse long-term effects of repotrectinib on growth and development and neurological outcomes, with reasonable precision. Patients will be monitored for growth and developmental milestones using age-appropriate screening tools and undergo neurological examination at appropriate

intervals. Evaluations will include neurological exams with neurocognitive assessment, Karnofsky/Lansky score, growth as measured by height, weight, height velocity, and height standard deviation scores (SDS), age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner Stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

The timetable you submitted on June 10, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	11/2029
Final Report Submission:	05/2030

Submit clinical protocol(s) to your IND 130465 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4649-5 Complete an appropriate clinical validation study using clinical trial data to establish and support the availability of an in vitro diagnostic device that is essential to the safe and effective use of repotrectinib for patients with solid tumors that carry NTRK1/2/3 gene fusions.

The timetable you submitted on June 10, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

Submit clinical protocols to your IND 130465 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email Autumn Zack-Taylor, M.S., Senior Regulatory Health Project Manager, at Autumn.Zack-Taylor@fda.hhs.gov**.**

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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/

STEVEN J LEMERY
06/13/2024 10:49:33 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AUGTYRO safely and effectively. See full prescribing information for AUGTYRO.

AUGTYRO™ (repotrectinib) capsules, for oral use
Initial U.S. Approval: 2023

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	06/2024
Dosage and Administration (2.1)	06/2024
Warnings and Precautions (5.6)	06/2024

----------INDICATIONS AND USAGE----------

AUGTYRO is a kinase inhibitor indicated for the treatment of

- adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC). (1.1)
- adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion and
  - are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.
  - have progressed following treatment or have no satisfactory alternative therapy.

  This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Select patients for the treatment of locally advanced or metastatic NSCLC based on the presence of *ROS1* rearrangement(s) in tumor specimens. (2.1)
- Select patients for treatment of locally advanced or metastatic solid tumors based on the presence of an *NTRK* gene fusion. (2.1)
- Recommended Dosage: 160 mg orally once daily for 14 days, then increase to 160 mg twice daily, with or without food. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 40 mg, 160 mg (3)

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Central Nervous System (CNS) Effects: Can cause CNS adverse reactions including dizziness, ataxia, and cognitive impairment. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity. (5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed. (5.2)
- Hepatotoxicity: Monitor liver function tests every 2 weeks during the first month of treatment, and as clinically indicated thereafter. Based on severity, withhold and then resume at same or reduced dose, or permanently discontinue. (5.3)
- Myalgia with Creatine Phosphokinase (CPK) Elevation: Monitor serum CPK levels during treatment in patients reporting unexplained muscle pain, tenderness, or weakness. Based on severity, withhold and resume at same or reduced dose upon improvement. (5.4)
- Hyperuricemia: Monitor serum uric acid levels prior to initiating and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold and resume at same or reduced dose, or permanently discontinue based on severity. (5.5)
- Skeletal Fractures: Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. (5.6)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use an effective non-hormonal method of contraception. (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong and Moderate CYP3A Inhibitors: Avoid concomitant use. (7.1)
- P-gp inhibitors: Avoid concomitant use. (7.1)
- Strong and Moderate CYP3A Inducers: Avoid concomitant use. (7.1)
- Certain CYP3A Substrates: Avoid concomitant use with CYP3A substrates, where minimal concentration changes can cause reduced efficacy. (7.2)
- Hormonal contraceptives: Avoid concomitant use. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *ROS1*-Positive Non-Small Cell Lung Cancer

AUGTYRO is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC) *[see Dosage and Administration (2.1)]*.

1.2 *NTRK* Gene Fusion-Positive Solid Tumors

AUGTYRO is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion *[see Dosage and Administration (2.1)]*,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

This indication is approved under accelerated approval based on overall response rate and duration of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

NSCLC

Select patients for the treatment of locally advanced or metastatic NSCLC with AUGTYRO based on the presence of *ROS1* rearrangement(s) in tumor specimens *[see Clinical Studies (14.1)]*. An FDA-approved test to detect *ROS1* rearrangements for selecting patients for treatment with AUGTYRO is not currently available.

Solid Tumors

Select patients for the treatment of solid tumors with AUGTYRO based on the presence of *NTRK1/2/3* rearrangements in tumor specimens *[see Clinical Studies (14.2)]*. An FDA-approved test to detect *NTRK1/2/3* rearrangements for selecting patients for treatment with AUGTYRO is not currently available.

- In patients with secretory breast cancer or mammary analogue secretory cancer, consider treatment without confirmation of *NTRK* rearrangements in tumor specimens.

2.2 Important Information Prior to Initiating AUGTYRO

Prior to initiating AUGTYRO, discontinue strong and moderate CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

2.3 Recommended Evaluation and Testing Before Initiating AUGTYRO

Prior to initiation of AUGTYRO, evaluate:

- liver function tests including bilirubin *[see Warnings and Precautions (5.3)]*
- uric acid level *[see Warnings and Precautions (5.5)]*

2.4 Recommended Dosage

The recommended dosage of AUGTYRO for adult and pediatric patients 12 years of age and older is 160 mg taken orally once daily with or without food *[see Clinical Pharmacology (12.3)]* for 14 days, then increase to 160 mg twice daily and continue until disease progression or unacceptable toxicity.

2.5 Dosage Modifications for Adverse Reactions

The recommended dosage reductions of AUGTYRO for the management of adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for AUGTYRO Adverse Reactions

Dose	**Dose Reduction**	
	First	**Second**
160 mg Once Daily	120 mg Once Daily	80 mg Once Daily
160 mg Twice Daily	120 mg Twice Daily	80 mg Twice Daily

Recommended dosage modifications of AUGTYRO for the management of adverse reactions are provided in Table 2.

Table 2: Recommended Dosage Modifications for AUGTYRO Adverse Reactions

Adverse Reaction	**Severity***	**Dosage Modification**
Central Nervous System Effects *[see Warnings and Precautions (5.1)]*	Intolerable Grade 2	• Withhold AUGTYRO until ≤Grade 1 or baseline. • Resume at same or reduced dose, as clinically appropriate.
	Grade 3	• Withhold AUGTYRO until ≤Grade 1 or baseline. • Resume at reduced dose.
	Grade 4	• Permanently discontinue AUGTYRO.
Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*	Any Grade	• Withhold AUGTYRO if ILD/pneumonitis is suspected. • Permanently discontinue if ILD/pneumonitis is confirmed.
Hepatotoxicity *[see Warnings and Precautions (5.3)]*	Grade 3	• Withhold AUGTYRO until ≤ Grade 1 or baseline. • Resume at same dose if resolution occurs within 4 weeks.

		• Resume at a reduced dose for recurrent Grade 3 events that resolve within 4 weeks.
	Grade 4	• Withhold AUGTYRO until ≤ Grade 1 or baseline. • Resume at reduced dose. • Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.
	ALT or AST greater than 3 times ULN with concurrent total bilirubin greater than 1.5 times ULN (in the absence of cholestasis or hemolysis)	• Permanently discontinue AUGTYRO.
Creatine Phosphokinase (CPK) Elevation *[see Warnings and Precautions (5.4)]*	CPK elevation greater than 5 times ULN	• Withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at same dose.
	CPK elevation greater than 10 times ULN or second occurrence of CPK elevation of greater than 5 times ULN	• Withhold until recovery to baseline or to less than or equal to 2.5 times ULN, then resume at reduced dose.
Hyperuricemia *[see Warnings and Precautions (5.5)]*	Grade 3 or Grade 4	• Withhold AUGTYRO until improvement of signs or symptoms. • Resume AUGTYRO at same or reduced dose.
Other Clinically Relevant Adverse Reactions *[see Adverse Reactions (6.1)]*	Intolerable Grade 2 or Grade 3 or Grade 4	• Withhold AUGTYRO until ≤Grade 1 or baseline. • Resume at the same or reduced dose if resolution occurs within 4 weeks.

		• Permanently discontinue if adverse reaction does not resolve within 4 weeks. • Permanently discontinue for recurrent Grade 4 events.

*Graded per Common Terminology Criteria for Adverse Events v4.03

2.6 Administration

Take AUGTYRO at approximately the same time each day with or without food *[see Pharmacokinetics (12.3)]*.

Swallow AUGTYRO capsules whole. Do not open, chew, crush, or dissolve the capsule prior to swallowing. Do not take any AUGTYRO capsules that are broken, cracked, or damaged.

If a dose of AUGTYRO is missed or if vomiting occurs at any time after taking a dose, skip the dose and resume AUGTYRO at its regularly scheduled time.

3 DOSAGE FORMS AND STRENGTHS

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

Capsules: 160 mg, blue, opaque, immediate release, Size 0, hard shell capsule, filled with white to off-white powder which may appear as a plug, imprinted with “REP 160” in white text on the cap.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Adverse Reactions

AUGTYRO can cause central nervous system adverse reactions.

Among the 426 patients who received AUGTYRO in Study TRIDENT-1, a broad spectrum of central nervous system (CNS) adverse reactions including dizziness, ataxia, and cognitive disorders occurred in 77% of patients, with Grade 3 or 4 events occurring in 4.5% of patients.

Dizziness, including vertigo, occurred in 65% of patients; Grade 3 dizziness occurred in 2.8% of patients. The median time to onset was 7 days (1 day to 1.4 years). Dose interruption was required in 9% of patients, and 11% required dose reduction of AUGTYRO due to dizziness.

Ataxia, including gait disturbance and balance disorder, occurred in 28% of patients; Grade 3 ataxia occurred in 0.5% of patients. The median time to onset was 15 days (1 day to 1.4 years). Dose interruption was required in 5% of patients, 8% required dose reduction, and one patient (0.2%) permanently discontinued AUGTYRO due to ataxia.

Cognitive impairment, including memory impairment and disturbance in attention, occurred in 25% of patients. Cognitive impairment included memory impairment (15%), disturbance in attention (12%), and confusional state (2%); Grade 3 cognitive impairment occurred in 0.9% of patients. The median time to onset of cognitive disorders was 37 days (1 day to 1.4 years). Dose

interruption was required in 2% of patients, 2.1% required dose reduction, and 0.5% patients permanently discontinued AUGTYRO due to cognitive adverse reactions.

Mood disorders occurred in 6% of patients. Mood disorders occurring in > 1% of patients included anxiety (2.6%); Grade 4 mood disorders (mania) occurred in 0.2% of patients. Dose interruption was required in 0.2% of patients and 0.2% of patients required a dose reduction due to mood disorders.

Sleep disorders including insomnia and hypersomnia occurred in 18% of patients. Sleep disorders observed in > 1% of patients were somnolence (9%), insomnia (6%) and hypersomnia (1.6%). Dose interruption was required in 0.7% of patients, and 0.2% of patients required a dose reduction due to sleep disorders.

The incidences of CNS adverse reactions observed were similar in patients with and without CNS metastases.

Advise patients and caregivers of the risk of CNS adverse reactions with AUGTYRO. Advise patients not to drive or use machines if they are experiencing CNS adverse reactions. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity *[see Dosage and Administration (2.5)]*.

5.2 Interstitial Lung Disease/Pneumonitis

AUGTYRO can cause interstitial lung disease (ILD)/pneumonitis.

Among the 426 patients treated with AUGTYRO, ILD/pneumonitis (pneumonitis [2.8%] and ILD [0.2%]) occurred in 3.1% of patients; Grade 3 ILD/pneumonitis occurred in 1.2% of patients. The median time to onset was 45 days (19 days to 0.9 years). Dose interruption was required in 1.4% of patients, 0.5% of patients required dose reduction, and 1.1% of patients permanently discontinued AUGTYRO due to ILD/pneumonitis.

Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold AUGTYRO in patients with suspected ILD/pneumonitis and permanently discontinue AUGTYRO if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.5)]*.

5.3 Hepatotoxicity

AUGTYRO can cause hepatotoxicity.

Among the 426 patients treated with AUGTYRO, increased alanine transaminase (ALT) occurred in 38%, increased aspartate aminotransferase (AST) occurred in 41%, including Grade 3 or 4 increased ALT in 3.3% and increased AST in 2.9%. The median time to onset of increased ALT or AST was 15 days (range: 1 day to 1.9 years). Increased ALT or AST leading to dose interruptions or reductions occurred in 2.8% and 1.2% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.5%.

Monitor liver function tests, including ALT, AST and bilirubin, every 2 weeks during the first month of treatment, then monthly thereafter and as clinically indicated. Withhold and then resume at the same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on the severity *[see Dosage and Administration (2.5)]*.

5.4 Myalgia with Creatine Phosphokinase Elevation

AUGTYRO can cause myalgia with or without creatine phosphokinase (CPK) elevation.

Among the 426 patients treated with AUGTYRO, myalgia occurred in 13% of patients, with Grade 3 in 0.7%. Median time to onset of myalgia was 19 days (range: 1 day to 2 years). Concurrent increased CPK within a 7-day window was observed in 3.7% of patients. AUGTYRO was interrupted in one patient with myalgia and concurrent CPK elevation.

Advise patients to report any unexplained muscle pain, tenderness, or weakness.

Monitor serum CPK levels during AUGTYRO treatment and monitor CPK levels every 2 weeks during the first month of treatment and as needed in patients reporting unexplained muscle pain, tenderness, or weakness. Initiate supportive care as clinically indicated. Based on severity, withhold and then resume AUGTYRO at the same or reduced dose upon improvement *[see Dosage and Administration (2.5)]*.

5.5 Hyperuricemia

AUGTYRO can cause hyperuricemia.

Among the 426 patients treated with AUGTYRO, 21 patients (5%) experienced hyperuricemia reported as an adverse reaction and 0.7% of patients experienced Grade 3 or 4 hyperuricemia. One patient without pre-existing gout required urate-lowering medication.

Monitor serum uric acid levels prior to initiating AUGTYRO and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold and then resume at the same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity *[see Dosage and Administration (2.5)]*.

5.6 Skeletal Fractures

AUGTYRO can cause skeletal fractures.

Among 426 adult patients who received AUGTYRO, fractures occurred in 2.3%. Fractures involved the ribs (0.5%), feet (0.5%), spine (0.2%), acetabulum (0.2%), sternum (0.2%), and ankles (0.2%). Some fractures occurred at sites of disease and prior radiation therapy. The median time to fracture was 71 days (range: 31 days to 1.4 years). AUGTYRO was interrupted in 0.3% of patients.

Of 26 evaluable patients in an ongoing open-label study in pediatric patients, fractures occurred in one 12-year-old patient (ankle/foot) and one 10-year-old patient (stress fracture). AUGTYRO was interrupted in both patients. AUGTYRO is not approved for use in pediatric patients less than 12 years of age *[see Pediatric Use (8.4)]*.

Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. There are no data on the effects of AUGTYRO on healing of known fractures and risk of future fractures.

5.7 Embryo-Fetal Toxicity

Based on literature reports in humans with congenital mutations leading to changes in tropomyosin receptor tyrosine kinase (TRK) signaling, findings from animal studies, and its mechanism of action, AUGTYRO can cause fetal harm when administered to a pregnant woman.

Oral administration of repotrectinib to pregnant rats during the period of organogenesis resulted in fetal malformations at doses approximately 0.3 times the recommended 160 mg twice daily dose based on body surface area (BSA).

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months following the last dose, since AUGTYRO can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AUGTYRO and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Central Nervous System Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Myalgia with Creatine Phosphokinase Elevation *[see Warnings and Precautions (5.4)]*
- Hyperuricemia *[see Warnings and Precautions (5.5)]*
- Skeletal Fractures *[see Warnings and Precautions (5.6)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates reported in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in WARNINGS AND PRECAUTIONS and below reflects exposure to AUGTYRO in 426 patients with *ROS1*-positive NSCLC (n=320), *NTRK1/2/3*-positive solid tumors (n=104), or other solid tumors (n=2) in TRIDENT-1. Patients received AUGTYRO at a dose of 160 mg orally once daily for the first 14 days, then increased to 160 mg orally twice daily until disease progression or unacceptable toxicity *[see Clinical Studies (14.1, (14.2)]*. Eligible patients had an ECOG status of ≤1. Patients with a history of ILD, drug-related pneumonitis, significant, uncontrolled, active cardiovascular disease, or prolonged QTc interval were excluded from enrollment in this trial. Forty-eight percent of patients were exposed to AUGTYRO for at least 6 months, and 28% were exposed for greater than 1 year.

The median age of patients who received AUGTYRO was 57 years (range: 18 to 93); 59% female; 43% White, 47% Asian, 2.8% Black, 0.5% Native Hawaiian or Other Pacific Islander, 0.5% American Indian or Alaska Native, 6.1% race not reported or other, and 0.7% unknown.

Serious adverse reactions occurred in 35% of patients who received AUGTYRO. Serious adverse reactions in ≥2% of patients included pneumonia (6.3%), dyspnea (3.1%), pleural effusion (2.8%), and hypoxia (2.6%). Fatal adverse reactions occurred in 3.5% of patients who received AUGTYRO, including pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.

Permanent discontinuation of AUGTYRO due to an adverse reaction occurred in 7% of patients. There were no specific adverse reactions that accounted for ≥1% of permanent discontinuations.

Dosage interruptions of AUGTYRO due to an adverse reaction occurred in 50% of patients. Adverse reactions that required dosage interruption in ≥2% of patients were dizziness, dyspnea, muscular weakness, ataxia, pneumonia, peripheral neuropathy, anemia, and vomiting.

Dose reductions of AUGTYRO due to an adverse reaction occurred in 38% of patients. Adverse reactions that required dosage reductions in ≥2% of patients included dizziness, ataxia, muscular weakness, peripheral neuropathy, and cognitive impairment.

The most common (≥20%) adverse reactions that occurred in patients receiving AUGTYRO were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness and nausea.

Table 3 summarizes the adverse reactions that occurred in TRIDENT-1.

Table 3: Adverse Reactions (≥10%) in Patients with *ROS1*-Positive NSCLC or *NTRK*-Positive Solid Tumors Who Received AUGTYRO in TRIDENT-1

Adverse Reaction[1]	AUGTYRO N=426	
	All Grades (%)	Grade 3 or 4 (%)
Nervous System Disorders		
Dizziness[a]	65	2.8
Dysgeusia[b]	54	0
Peripheral neuropathy[c]	49	1.4
Ataxia[d]	28	0.5
Cognitive impairment[e]	25	0.9
Headache[f]	19	0
Gastrointestinal Disorders		
Constipation	38	0.2
Nausea	20	0.7
Diarrhea	14	0.7
Vomiting	12	1.2
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[g]	30	6
Cough[h]	18	0.2
Pneumonia[i]	11	6
General Disorders		
Fatigue[j]	30	1.2
Edema[k]	15	0.5
Decreased appetite	11	0.2
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness	20	2
Myalgia[l]	13	0.7
Metabolism and Nutritional		
Increased weight	16	3
Eye Disorders		
Vision disorders[m]	12	0.5

[1] Based on NCI CTCAE v4.03

[a] Includes terms dizziness, vertigo, dizziness postural, dizziness exertional, vertigo positional

[b] Includes terms dysgeusia, ageusia, anosmia, hypogeusia

[c] Includes terms neuralgia, neuropathy peripheral, peripheral sensory neuropathy, dysesthesia, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, hyperesthesia

[d] Includes terms ataxia, gait disturbance, balance disorder, cerebellar ataxia and coordination abnormal

[e] Includes terms memory impairment, disturbance in attention, cognitive disorder, confusional state, amnesia, attention deficit hyperactivity disorder, delirium, altered state of consciousness, aphasia, delusion, depressed level of consciousness, hallucination, mental status changes, neurological decompensation

[f] Includes terms headache, migraine, tension headache

[g] Includes terms dyspnea and dyspnea exertional

[h] Includes terms productive cough, cough, and upper-airway cough syndrome

[i] Includes terms pneumonia, pneumonia aspiration, lower respiratory tract infection, pneumonia viral, pneumonia bacterial, lower respiratory tract infection bacterial, pneumonia klebsiella
[j] Includes terms fatigue and asthenia
[k] Includes terms generalized edema, periorbital edema, localized edema, face edema, edema peripheral, edema, eye edema, scrotal edema
[l] Includes terms myalgia, myositis, musculoskeletal discomfort, musculoskeletal pain
[m] Includes terms vision blurred, dry eye, visual impairment, visual field defect, cataract, conjunctivitis, eye pain, photophobia, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, color blindness, diplopia, eye hematoma, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, night blindness, ophthalmic herpes zoster

Clinically relevant adverse reactions occurring in <10% of patients receiving AUGTYRO were pyrexia (9.2%) and fall (3.8%).

Table 4 summarizes the laboratory abnormalities in TRIDENT-1.

Table 4: Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with *ROS1*-Positive NSCLC or *NTRK*-Positive Solid Tumors Who Received AUGTYRO in TRIDENT-1

Laboratory Abnormality[1]	**AUGTYRO[2] N=426**	
	All Grades (%)	**Grade 3 or 4 (%)**
Hematology		
Decreased hemoglobin	79	8.4
Decreased lymphocytes	43	10
Decreased neutrophils	34	9
Increased activated partial thromboplastin time	26	0.3
Increased INR	24	0
Chemistry		
Increased creatine phosphokinase	61	7
Increased gamma glutamyl transferase	50	13
Increased aspartate aminotransferase	41	2.9
Increased alanine aminotransferase	38	3.3
Increased sodium	33	0.2
Increased alkaline phosphatase	29	2.1
Increased glucose	26	2.4
Increased urate	23	12
Decreased phosphate	22	6
Increased potassium	22	0.7
Decreased glucose	20	0.2

[1] Based on NCI CTCAE v4.03
[2] The denominator used to calculate the rate varied from 233 to 423 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on AUGTYRO

Strong and Moderate CYP3A Inhibitors

Avoid concomitant use with strong or moderate CYP3A inhibitors. Concomitant use of AUGTYRO with a strong or a moderate CYP3A inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO. Discontinue CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor prior to initiating AUGTYRO *[see Clinical Pharmacology (12.3)]*.

P-gp Inhibitors

Avoid concomitant use with P-gp inhibitors. Concomitant use of AUGTYRO with a P-gp inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO *[see Clinical Pharmacology (12.3)]*.

Strong and Moderate CYP3A Inducers

Avoid concomitant use with strong or moderate CYP3A inducers. Concomitant use of AUGTYRO with a strong or moderate CYP3A inducer may decrease repotrectinib plasma concentrations, which may decrease efficacy of AUGTYRO *[see Clinical Pharmacology (12.3)]*.

7.2 Effects of AUGTYRO on Other Drugs

Certain CYP3A4 Substrates

Avoid concomitant use unless otherwise recommended in the Prescribing Information for CYP3A substrates, where minimal concentration changes can cause reduced efficacy. If concomitant use is unavoidable, increase the CYP3A4 substrate dosage in accordance with approved product labeling.

Repotrectinib is a CYP3A4 inducer. Concomitant use of repotrectinib decreases the concentration of CYP3A4 substrates *[see Clinical Pharmacology (12.3)]*, which can reduce the efficacy of these substrates.

Contraceptives

Repotrectinib is a CYP3A4 inducer, which can decrease progestin or estrogen exposure to an extent that could reduce the effectiveness of hormonal contraceptives.

Avoid concomitant use of AUGTYRO with hormonal contraceptives *[see Use in Specific Populations (8.1, 8.3)]*. Advise females of reproductive potential to use an effective nonhormonal contraceptive *[see Use in Specific Populations (8.1, 8.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on literature reports in humans with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action *[see Clinical Pharmacology*

(12.1)], AUGTYRO can cause fetal harm when administered to a pregnant woman. There are no available data on AUGTYRO use in pregnant women. Oral administration of repotrectinib to pregnant rats during the period of organogenesis resulted in fetal malformations at doses approximately 0.3 times the recommended dose of 160 mg twice daily based on BSA *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Published reports of individuals with congenital mutations in TRK pathway proteins suggest that decreases in TRK-mediated signaling are correlated with obesity, developmental delays, cognitive impairment, insensitivity to pain, and anhidrosis.

Animal Data

In an embryo-fetal development study, once daily oral administration of repotrectinib to pregnant rats during the period of organogenesis from gestation day 6 to 17 resulted in maternal effects of increased body weight and skin abrasions/ulcerations at doses ≥6 mg/kg, fetal malformations of malrotated hindlimbs and lower fetal body weights at doses ≥12 mg/kg [approximately 0.3 times the recommended dose of 160 mg twice daily based on BSA]. No embryolethality was observed.

8.2 Lactation

Risk Summary

There are no data on the presence of AUGTYRO in human milk or its effects on either the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed children from AUGTYRO, advise a lactating woman to discontinue breastfeeding during treatment with AUGTYRO and for 10 days after the last dose.

8.3 Females and Males of Reproductive Potential

AUGTYRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of childbearing potential prior to initiating AUGTYRO *[see Use in Specific Populations (8.1)]*.

Contraception

AUGTYRO can cause embryo-fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of childbearing potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months following the last dose. AUGTYRO can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Males

Based on genotoxicity findings, advise male patients with female partners of childbearing potential to use effective contraception during treatment with AUGTYRO and for 4 months following the last dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of AUGTYRO in pediatric patients with *ROS1*-positive NSCLC have not been established.

The safety and effectiveness of AUGTYRO have not been established in pediatric patients younger than 12 years of age with solid tumors who have an *NTRK* gene fusion.

The safety and effectiveness of AUGTYRO for the treatment of locally advanced or metastatic *NTRK*-positive solid tumors have been established in pediatric patients 12 years of age or older. Use of AUGTYRO in this age group is supported by evidence from an adequate and well-controlled study in adult patients with additional pharmacokinetic and safety data in pediatric patients aged 12 years and older. This includes data demonstrating that the exposure of repotrectinib in pediatric patients 12 years of age and older is expected to result in similar safety and efficacy to that of adults, and that the course of locally advanced or metastatic *NTRK*-positive solid tumors is sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data in adult to pediatric patients 12 years of age or older *[see Dosage and Administration (2.4), Warnings and Precautions (5.7), Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

Juvenile Animal Data

Daily oral administration of repotrectinib to juvenile rats for 8 weeks starting on postnatal day 12 (approximately equal to a human pediatric age of a newborn) resulted in toxicities similar to those observed in adult rats, though juvenile animals showed decreased body weight gain at doses ≥1 mg/kg (approximately ≥0.04 times the human exposure based on AUC at the recommended clinical dose of 160 mg BID) and decreased femur lengths at 3 mg/kg (approximately 0.1 times the human exposure based on AUC at the recommended clinical dose of 160 mg BID). Decreased body weight gain and decreased femur lengths persisted following 4 weeks of recovery.

8.5 Geriatric Use

Of the 426 patients who received AUGTYRO, in the TRIDENT-1 study for *ROS1*-positive non-small cell lung cancer or *NTRK* gene fusion-positive solid tumors, 19% were 65 to 75 years old, and 6% were 75 years of age or older. There were no clinically meaningful differences in safety and efficacy between patients younger than 65 years of age and patients 65 years of age or older.

8.6 Renal Impairment

The recommended dosage of AUGTYRO has not been established in patients with severe renal impairment or kidney failure (eGFR <30 mL/min) and patients on dialysis *[see Clinical Pharmacology (12.3)]*.

No dosage modification is recommended for patients with mild or moderate renal impairment (eGFR 30 to 90 mL/min).

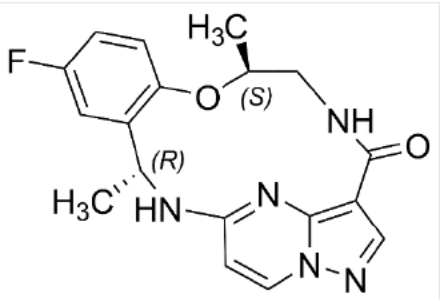
8.7 Hepatic Impairment

The recommended dosage of AUGTYRO has not been established in patients with moderate (total bilirubin >1.5 to 3 times upper limit of normal [ULN] with any AST) or severe (total bilirubin >3 times ULN with any AST) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

No dosage modification is recommended for patients with mild (total bilirubin >1 to 1.5 times ULN or AST > ULN) hepatic impairment.

11 DESCRIPTION

Repotrectinib is a kinase inhibitor. The molecular formula for repotrectinib is $C_{18}H_{18}FN_5O_2$ and the molecular weight is 355.37 Daltons. The chemical name is (3R,11S)-6-Fluoro-3,11-dimethyl-10-oxa-2,13,17,18,21-pentaazatetracyclo[13.5.2.$0^{4,9}$.$0^{18,22}$]docosa-1(21),4,6,8,15(22),16,19-heptaen-14-one. The chemical structure of repotrectinib is as follows:



Repotrectinib is a white to off-white powder.

AUGTYRO (repotrectinib) capsules for oral use are supplied as printed hard shell capsules containing 40 mg of repotrectinib. Inactive ingredients are microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, and colloidal silicon dioxide.

The white opaque capsule shell contains gelatin and titanium dioxide. The printing ink contains shellac and FD & C blue #2 aluminum lake.

AUGTYRO (repotrectinib) capsules for oral use are supplied as printed hard shell capsules containing 160 mg of repotrectinib. Inactive ingredients are microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide.

The blue opaque capsule shell contains gelatin, titanium dioxide and FD & C blue #1. The printing ink contains shellac and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC.

Fusion proteins that include ROS1 or TRK domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Repotrectinib exhibited anti-tumor activity in cultured cells expressing *ROS1* fusions and mutations including SDC4-ROS1, SDC4-ROS1^{G2032R}, CD74-ROS1, CD74-ROS1^{G2032R}, CD74-ROS1^{D2033N}, and CD74-ROS1^{L2026M}. Repotrectinib also inhibited cell proliferation in cultured cells expressing *NTRK* fusions and mutations including LMNA-TRKA, LMNA-TRKA^{G595R}, EVT6-TRKB^{G639R}, and ETV6-TRKC^{G623R}.

12.2 Pharmacodynamics

Repotrectinib exposure-response relationships and the time course of pharmacodynamic responses are not fully characterized.

Cardiac Electrophysiology

AUGTYRO 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 dosage.

12.3 Pharmacokinetics

The geometric mean (CV%) of repotrectinib steady state peak concentration ($C_{max,ss}$) is 713 (32.5%) ng/mL and the area under the time concentration curve ($AUC_{0-24h,ss}$) is 7210 (40.1%) ng•h/mL following the approved recommended twice daily dosage in patients with cancer. Repotrectinib C_{max} and AUC_{0-inf} increases approximately dose proportional (but less than linear with estimated slopes of 0.78 and 0.70, respectively) over the single dose range of 40 mg to 240 mg (0.25 to 1.5 times the approved recommended dosage). Steady state PK was time-dependent with an autoinduction of CYP3A4. Steady state is achieved within 14 days of daily administration of 160 mg.

Absorption

The geometric mean (CV%) absolute bioavailability of repotrectinib is 45.7% (19.6%). Peak repotrectinib concentration occurred at approximately 2 to 3 hours post a single oral dose of 40 mg to 240 mg (0.25 to 1.5 times the approved recommended dosage) under fasted conditions.

Effect of Food

No clinically significant differences in repotrectinib pharmacokinetics were observed in patients with cancer following administration of a high-fat meal (approximately 800-1000 calories, 50% fat).

Distribution

The geometric mean (CV%) apparent volume of distribution (Vz/F) was 432 L (55.9 %) in patients with cancer following a single 160 mg oral dose of AUGTYRO.

AUGTYRO binding to plasma protein was 95.4% *in vitro*. The blood-to-plasma ratio was 0.56 *in vitro*.

Elimination

Repotrectinib elimination is time-dependent due to autoinduction of CYP3A4.

The repotrectinib mean terminal half-life is approximately 60.7 h for patients with cancer following a single dose. The steady state repotrectinib terminal half-life is approximately 40.3 h for patients with cancer.

The geometric mean (CV%) apparent oral clearance (CL/F) was 15.9 L/h (45.5%) in patients with cancer following a single 160 mg oral dose of AUGTYRO.

Metabolism

Repotrectinib is primarily metabolized by CYP3A4 followed by secondary glucuronidation.

Excretion

Following a single oral 160 mg dose of radiolabeled repotrectinib, 4.84% (0.56% as unchanged) was recovered in urine and 88.8% (50.6% unchanged) in feces.

Specific Populations

No clinically significant differences in the pharmacokinetics of repotrectinib were observed based on age (12 to 93 years), sex, race (White 50%, Asian 38%, Black 7%), mild to moderate renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin >1 to 1.5 times ULN or AST > ULN). The effect of moderate (total bilirubin >1.5 to 3 times ULN with any AST) or severe (total bilirubin >3 x ULN with any AST) hepatic impairment, severe renal impairment, kidney failure (eGFR < 30 mL/min), or dialysis on repotrectinib pharmacokinetics is unknown or not fully characterized.

Drug Interaction Studies

Clinical Studies

Strong CYP3A and P-gp inhibitors: Repotrectinib $AUC_{0\text{-}inf}$ increased by 5.9-fold and C_{max} by 1.7-fold following concomitant use with itraconazole (strong CYP3A and P-gp inhibitor).

Strong CYP3A and P-gp inducers: Repotrectinib $AUC_{0\text{-}inf}$ decreased by 92% and C_{max} by 79% following concomitant use with rifampin (strong CYP3A and P-gp inducer).

CYP3A substrates: Midazolam (CYP3A substrate $AUC_{0\text{-}inf}$ decreased by 69% and C_{max} by 48% following concomitant use in subjects who were previously administered 160 mg repotrectinib once daily for 14 days followed by 160 mg twice daily for 7 days.

In vitro Studies

CYP Enzymes: Repotrectinib induces CYP3A4, CYP2B6, CYP2C8, CYP2C19, CYP2C9 and inhibits CYP3A4/5 (GI tract). Repotrectinib does not induce CYP1A2.

Other Metabolic Pathways: Repotrectinib inhibits UGT1A1.

Transporter Systems: Repotrectinib inhibits P-gp, BCRP, OATP1B1, and MATE2-K. Repotrectinib is a substrate for P-gp.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with repotrectinib were not conducted.

Repotrectinib was genotoxic in an in vitro assay in human lymphoblastoid TK6 cells and in an in vivo rat bone marrow micronucleus assay via an aneugenic mechanism of action. Repotrectinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay.

Dedicated fertility studies were not conducted with repotrectinib. There were no effects on male and female reproductive organs observed in general repeat-dose toxicology studies of up to 3 months in duration in rats and monkeys at any dose level tested, which equated to exposures of up to approximately 3 times the human exposure at the 160 mg twice daily dose based on AUC.

14 CLINICAL STUDIES

14.1 Locally Advanced or Metastatic *ROS1*-Positive NSCLC

The efficacy of AUGTYRO was evaluated in TRIDENT-1, a multicenter, single-arm, open-label, multi-cohort clinical trial (NCT03093116). Patients were required to have *ROS1*-positive locally advanced or metastatic NSCLC, ECOG performance status ≤1, measurable disease per RECIST v 1.1, and ≥8 months from first dose. All patients were assessed for CNS lesions at baseline, and patients with symptomatic brain metastases were excluded from the trial. Patients received AUGTYRO 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity. Tumor assessments were performed at least every 8 weeks. Identification of *ROS1* gene fusions in tumor specimens was prospectively determined in local laboratories using next-generation sequencing (NGS), polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) tests. All *ROS1*-positive patients by local FISH testing required central laboratory confirmation of *ROS1* fusion using an analytically validated NGS test. *ROS1* fusions were identified by NGS in 51%, FISH in 26%, and PCR in 23%. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) according to RECIST v1.1 as assessed by blinded independent central review (BICR). Intracranial response according to modified RECIST v1.1 was assessed by BICR. Tumor assessments with imaging were performed every 8 weeks. The efficacy populations included 71 ROS1 TKI-naïve patients who received up to 1 prior line of platinum-based chemotherapy and/or immunotherapy and 56 patients who received 1 prior ROS1 TKI with no prior platinum-based chemotherapy or immunotherapy.

Among the 71 ROS1 TKI-naïve patients, the median age was 57 years (range: 28 to 80); female (60.6%); Asian (67.6%), White (25.4%), Hispanic or Latino (4.2%), Black or African American (1.4%); never smoked (63.4%); and ECOG performance status of 1 at baseline (66.2%). At baseline, 94.4% of patients had metastatic disease, 25.4% of patients had CNS metastases by BICR; 97.2% had adenocarcinoma; and 28.2% patients had prior chemotherapy consisting of platinum-based chemotherapy and/or immunotherapy for locally advanced or metastatic disease.

Among the 56 patients who had received 1 prior ROS1 TKI (including crizotinib [82%] and entrectinib [16%]) with no prior platinum-based chemotherapy or immunotherapy, the median age was 57 years (range: 33 – 78); female (67.9%); Asian (48.2%), White (44.6%), Black or African American and Hispanic or Latino (1.8% each); never smoked (64.3%); and ECOG performance status of 1 at baseline (67.9%). At baseline, 98.2% patients had metastatic disease, 42.9% with CNS metastases by BICR, and 94.6% had adenocarcinoma.

Efficacy results are summarized in Table 5.

Table 5: Efficacy Results for Patients with *ROS1*-Positive NSCLC in TRIDENT-1

Efficacy Parameters	**ROS1 Inhibitor Naïve Patients (N=71)**	**ROS1 Inhibitor Pretreated Patients (N=56)**
Confirmed Overall Response Rate, % (95% CI)	79% (68, 88)	38% (25, 52)
Complete Response	6%	5%
Partial Response	73%	32%
Duration of Response (DOR)[a]		
Median in Months (95% CI)[b]	34.1 (25.6, NE)	14.8 (7.6, NE)
Range (months)	1.4+, 42.4+	3.6, 22.9+
% DOR ≥12 months[c]	70	48

Abbreviations: CI = confidence interval; NE = not evaluable; "+" indicates ongoing response

[a] DOR results are based on the updated data as of 19 December 2022.

[b] Median DOR (95% CI) are based on Kaplan-Meier estimates.

[c] DOR landmark analysis is based on the observed DOR.

Among TKI-naïve patients, 8 had measurable CNS metastases at baseline as assessed by BICR; responses in intracranial lesions were observed in 7 of these 8 patients. Among the TKI pretreated patients with no prior platinum-based chemotherapy, 12 had measurable CNS metastases at baseline as assessed by BICR; responses in intracranial lesions were observed in 5 of these 12 patients.

Among the 56 ROS1 inhibitor-pretreated patients, 8 had resistance mutations following TKI therapy. Responses were observed in 6 of these 8 patients; responders included patients with solvent front (*ROS1*^{G2032R}), gatekeeper (*ROS1*^{L2026M}), and other mutations (*ROS1*$^{S1986F/Y}$).

14.2 Locally Advanced or Metastatic *NTRK* Gene Fusion-Positive Solid Tumors

The efficacy of AUGTYRO was evaluated in TRIDENT-1 (NCT03093116), a multi-center, single-arm, open-label, multi-cohort clinical trial in 88 adult patients with locally advanced or metastatic *NTRK* gene fusion-positive (*NTRK1/2/3*) solid tumors who had either received a prior TKI treatment or were TKI-naïve. All patients were assessed for CNS lesions at baseline, and patients with symptomatic brain metastases were excluded from the trial. Patients received AUGTYRO 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity. Tumor assessments were performed every 8 weeks. *NTRK* gene fusions were identified prospectively using NGS in 94%, FISH in 5%, and PCR in 1%. *NTRK* gene fusion-positive tumors identified by local FISH testing required central laboratory confirmation using an analytically validated NGS test. The major efficacy outcome measures were ORR and DOR according to RECIST v1.1 as assessed by BICR. Intracranial response according to modified RECIST v1.1 was assessed by BICR.

Among the 40 TRK TKI-naïve patients, the median age was 61 years (range: 25 to 84); 60% were female patients; race was Asian 53%, White 25%, Black or African American 5%, and other or not reported 18%; ethnicity was Hispanic or Latino 5%, not Hispanic or Latino 87%, and not reported 8%; and ECOG performance status of 1 at baseline was 55%. At baseline, 98% of patients had metastatic disease and 23% of patients had CNS metastases by BICR. Seventy percent (n=28) of patients received prior systemic therapy with a median of one prior systemic regimen, and 7.5% (n=3) received three or more prior systemic regimens.

Among the 48 TRK TKI-pretreated patients, the median age was 58 years (range: 20 to 81); 48% were female patients; race was White 65%, Asian 25%, Black or African American 2%, and not reported 8%; ethnicity was not Hispanic or Latino 92%, and missing 8%; and ECOG performance status of 1 at baseline was 60%. At baseline, 96% of patients had metastatic disease and 25% of patients had CNS metastases by BICR. Seventy-seven percent (n=37) of patients received 2 or more prior systemic regimens, and 46% (n=22) received three or more prior systemic regimens, and 7 patients (15%) received 2 prior TKI therapies.

Efficacy results are summarized in Table 6.

Table 6: Efficacy Results for Patients with *NTRK* Gene Fusion-Positive Tumors in TRIDENT-1

Efficacy Parameters	**TKI-Naïve Patients (n=40)**	**TKI-Pretreated Patients (n=48)**
Confirmed Overall Response Rate, % (95% CI)	58 (41, 73)	50 (35, 65)
Complete Response, %	15	0
Partial Response, %	43	50
Median Duration of Response (mDOR)[a], in Months (95% CI)	NE (NE, NE)	9.9 (7.4, 13.0)
Range (months)	3.7+, 43.9+	1.8, 26.5+
% with DOR $\geq$ 6 months[b]	87	71
% with DOR $\geq$ 9 months[b]	83	63

% with DOR ≥ 12 months[b]	83	42

NE = not evaluable; "+" indicates ongoing response

[a] Median DOR (95% CI) are based on Kaplan-Meier estimates.

[b] DOR landmark analysis is based on the observed DOR.

Among the 88 patients, 5 had measurable CNS metastases at baseline as assessed by BICR. Responses were seen in 2 (100%) TKI-naïve patients and 3 (100%) TKI-pretreated patients. One out of 2 TKI-naïve and 2 out of 3 TKI-pretreated patients received prior radiotherapy to the brain, all more than 2 months prior to study entry.

Twenty-six of the TRK TKI-pretreated patients had a resistance mutation at baseline, including 24 with solvent front mutations (*NTRK1*^{G595R} and *NTRK3*$^{G623L/R/E/V}$ mutations), one with both a solvent front mutation and a gatekeeper mutation (*NTRK1*^{F589L}), and one with another mutation (*NTRK1*^{G667C}). In the 25 TKI-pretreated patients with solvent front mutations at baseline, ORR was 60% (95% CI: 39, 79).

ORR and DOR by tumor type in adult patients with *NTRK* gene fusion-positive solid tumors are presented in Tables 7 and 8 below.

Table 7: Efficacy Results by Tumor Type in TKI-naïve *NTRK* Gene Fusion Patients

Tumor type	**Patients (n=40)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (months)**
NSCLC	21	13 (62)	38, 82	3.7+, 31.3+
Thyroid Cancer	5	5 (100)	48, 100	4.7, 43.9+
Salivary Gland Cancer	3	3 (100.0)	29, 100	17.7+, 31.4+
Secretory carcinoma	1	PR	NA	23.0+
Sarcoma, Soft tissue	3	1 (33)	0.8, 91	14.7+
Breast Cancer (adenocarcinoma)	2	PD, PD	NA	NA
Other*	2	SD, SD	NA	NA
Glioblastoma	1	SD	NA	NA
Cholangiocarcinoma	1	PD	NA	NA
Colorectal cancer	1	SD	NA	NA
Peripheral Nerve Sheath Tumor	1	PR	NA	23.0+

* Includes esophageal cancer and head and neck cancer

PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable

"+" indicates ongoing response

Table 8: Efficacy Results by Tumor Type in TKI-pretreated *NTRK* Gene Fusion-Positive Patients

Tumor type	**Patients (n=48)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (months)**
NSCLC	14	6 (43)	18, 71	1.9, 23.0+
Salivary Gland Cancer	8	7 (88)	47, 100	3.7, 26.5+
Secretory carcinoma	3	3 (100)	29, 100	7.9, 26.5+
Sarcoma, Soft tissue	6	1 (17)	0.4, 64	5.6
Thyroid Cancer	4	2 (50)	7, 93	2.0, 9.6
Glioblastoma	3	1 (33.3)	0.8, 91	23.5
Cholangiocarcinoma	2	PR, PD	NA	1.8

Tumor type	Patients (n=48)	ORR		DOR
		n (%)	95% CI	Range (months)
Colorectal cancer	2	PR, SD	NA	17.5
Peripheral Nerve Sheath Tumor	2	PR, PR	NA	5.5, 11.1
Neuroendocrine Tumor	2	PR, PR	NA	5.5, 9.1
Pancreatic Cancer	2	PD, PD	NA	NA
Other*	2	SD, PD	NA	NA
Breast Cancer (adenocarcinoma)	1	PR	NA	15.6+

* Includes gallbladder cancer and unknown primary cancer
PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable
"+" indicates ongoing response

ORR and DOR in adult patients are presented by *NTRK* gene fusion partner Tables 9 and 10 below.

Table 9: Efficacy Results by *NTRK* Gene Fusion Partner in TRK TKI-Naïve Patients

***NTRK* Partner**	**Subjects (n=40)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (Months)**
ETV6-NTRK3	12	9 (75)	(43, 95)	4.7, 31.4+
TPM3-NTRK1	7	5 (71)	(29, 96)	3.8, 23.1+
EML4-NTRK3	2	Missing, PR	NA	14.8+
IRF2BP2-NTRK1	2	PR, PR	NA	3.7+, 20.3+
PEAR1-NTRK1	2	Missing, PD	NA	NA
Unknown	2	PD, SD	NA	NA
ATP2B2-IT2-NTRK1	1	SD	NA	NA
GOLGB1-NTRK1	1	SD	NA	NA
IL1RL2-NTRK2	1	SD	NA	NA
LRPPRC-NTRK3	1	SD	NA	NA
LRRC71-NTRK1	1	Missing	NA	NA
Multiple	1	PR	NA	28.6+
RBPMS-NTRK3	1	PR	NA	34.3+
SLC28A3-NTRK2	1	PD	NA	NA
SQSTM1-NTRK1	1	PR	NA	15.7+
STRN3-NTRK1	1	PR	NA	23.9+
TMED3-NTRK3	1	PD	NA	NA
TPR-NTRK1	1	PR	NA	43.9+
TRIM33-NTRK1	1	CR	NA	17.8+

PD: progressive disease; PR: partial response; SD: stable disease; NA: not applicable
"+" indicates ongoing response

Table 10: Efficacy Results by *NTRK* Gene Fusion Partner in TRK TKI-Pretreated Subjects

***NTRK* Partner**	**Subjects (n=48)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (Months)**
ETV6-NTRK3	24	16 (67)	(45, 84)	1.8, 26.5+
EML4-NTRK3	5	4 (80)	(28, 99)	1.9, 12.9
LMNA-NTRK1	4	1 (25)	(0.6, 81)	5.6
TPM3-NTRK1	3	0 (0)	(0, 71)	NA

ATP1B1-NTRK1	1	PD	NA	NA
BCR-NTRK2	1	SD	NA	NA
ETV6-NTRK2	1	NE	NA	NA
GP2-NTRK1	1	PD	NA	NA
IRF2BP2-NTRK1	1	Missing	NA	NA
KANK2-NTRK2	1	PR	NA	23.5
Multiple	1	PD	NA	NA
PRDX1-NTRK1	1	Missing	NA	NA
RBPMS-NTRK3	1	PD	NA	NA
SEL1L-NTRK1	1	PD	NA	NA
SQSTM1-NTRK3	1	PR	NA	5.5
STRN3-NTRK3	1	PR	NA	11.1

PR = partial response; PD = progressive disease; SD = stable disease; NA = not applicable; NE = not evaluable
"+" indicates ongoing response

16 HOW SUPPLIED/STORAGE AND HANDLING

AUGTYRO (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)

AUGTYRO (repotrectinib) 160 mg, Size 0, blue opaque cap, blue opaque body, hard shell capsules, filled with a white to off-white powder which may appear as a plug, imprinted with "REP 160" in white text on the cap are supplied as follows:

- Bottles of 14 capsules (NDC 0003-4160-14)
- Bottles of 60 capsules (NDC 0003-4160-60)

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]*.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Central Nervous System (CNS) Effects

- Advise patients to inform their healthcare provider if they experience new or worsening CNS symptoms. Instruct patients not to drive or operate hazardous machinery if they are experiencing CNS adverse reactions *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

- Advise patients to inform their healthcare provider if they experience new or worsening pulmonary symptoms indicative of ILD/pneumonitis *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

- Advise patients of the need for laboratory tests to monitor liver function and to immediately report symptoms of hepatotoxicity *[see Warnings and Precautions (5.3)]*.

Myalgia with Creatine Phosphokinase Elevation

- Advise patients to inform their healthcare provider if they experience muscle pain *[see Warnings and Precautions (5.4)]*.

Hyperuricemia

- Advise patients to inform their healthcare provider if they experience signs or symptoms associated with hyperuricemia *[see Warnings and Precautions (5.5)]*.

Skeletal Fractures

- Inform patients that bone fractures have occurred in patients taking AUGTYRO and advise patients to report symptoms to their healthcare provider *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7), Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months after the last dose, since AUGTYRO can render some hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AUGTYRO and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise females not to breastfeed during treatment with AUGTYRO and for 10 days after the last dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

- Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7)]*.
- Advise patients to avoid grapefruit or grapefruit juice while taking AUGTYRO *[see Drug Interactions (7)]*.
- Advise patients that hormonal contraceptives can be ineffective while taking AUGTYRO *[see Drug Interactions (7)]*.

Administration

- Advise patients to swallow AUGTYRO capsules whole with or without food *[see Dosage and Administration (2.6), Pharmacokinetics (12.3)]*.
- Instruct patients if they miss a dose, or vomit at any time after taking a dose of AUGTYRO, not to "make it up," but take the next dose of AUGTYRO at the next scheduled time *[see Dosage and Administration (2.6)]*.

For more information, go to www.AUGTYRO.com or call 1-877-284-8976.

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Princeton, NJ 08543 USA
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PATIENT INFORMATION
AUGTYRO™ [Aug-TYE-ro]
(repotrectinib)
capsules

What is the most important information I should know about AUGTYRO?

AUGTYRO may cause serious side effects, including:

- **Central nervous system (CNS) effects.** Tell your healthcare provider right away if you experience any new or worsening symptoms of CNS effects during treatment with AUGTYRO, including:
  - dizziness
  - vertigo
  - changes in mood, such as anxiety, irritability, and depression
  - balance or coordination problems
  - problems with thinking, such as forgetfulness or confusion
  - seeing or hearing things that are not real (hallucinations)
  - problems with concentration, attention, memory, and sleep
- **Lung problems (pneumonitis).** Tell your healthcare provider if you have any new or worsening symptoms of lung problems, including a dry cough (without mucus), productive cough (with mucus), wheezing, or trouble breathing.
- **Liver problems.** Your healthcare provider will do blood tests to check your liver function before starting treatment with AUGTYRO, every 2 weeks for the first month and as needed during treatment. Tell your healthcare provider right away if you develop symptoms of liver problems including:
  - your skin or the white part of your eyes turns yellow
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - loss of appetite
  - nausea or vomiting
  - pain on the upper right side of your stomach area
- **Muscle problems.** Your healthcare provider will do blood tests before starting treatment with AUGTYRO, every 2 weeks for the first month and as needed during treatment. Tell your healthcare provider right away if you get new or worsening signs and symptoms of muscle problems, including unexplained muscle pain or muscle pain that does not go away, tenderness, or weakness.
- **Increased uric acid level in your blood (hyperuricemia).** AUGTYRO may cause an excess of uric acid in your blood. Your healthcare provider will do tests before and during your treatment with AUGTYRO to check the uric acid level in your blood. Your healthcare provider may prescribe medicines if you have high blood uric acid levels. Tell your healthcare provider if you experience symptoms of increased uric acid including:
  - red, hot, tender, or swollen joints, especially in your big toe
  - pain in your stomach-area or sides
  - decrease in your amount of urine or no urine at all
  - nausea or vomiting
  - pink or brown urine or blood in your urine
- **Bone fractures.** AUGTYRO may increase your risk for bone fractures. Bone fractures may happen with or without a fall or other injury. Tell your healthcare provider right way if you have pain, changes in movement, or bone abnormalities.

See **"What are the possible side effects of AUGTYRO?" for more information about side effects.**

What is AUGTYRO?

AUGTYRO is a prescription medicine used to treat:

- adults with non-small cell lung cancer (NSCLC) that has spread within your chest or to other parts of the body and is caused by an abnormal *ROS1* gene.
- adults and children 12 years of age and older with solid tumors (cancer) that:
  - are caused by certain abnormal *NTRK* genes, **and**
  - have spread to other parts of the body, or if surgery to remove your cancer is likely to cause severe complications, **and**
  - have grown or spread after other treatment or there is no satisfactory alternative treatment option.

It is not known if AUGTYRO is safe and effective in children with *ROS1*-positive NSCLC or in children younger than 12 years of age with *NTRK*-positive solid tumors.

Before taking AUGTYRO, tell your healthcare provider about all your medical conditions, including if you:

- have nervous system (neurological) problems.
- have lung or breathing problems other than lung cancer.
- have liver or kidney problems.
- are pregnant or plan to become pregnant. AUGTYRO can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with AUGTYRO.

  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with AUGTYRO.
  - You should use effective non-hormonal birth control (contraception) during treatment and for 2 months after the last dose of AUGTYRO.
  - Birth control methods that contain hormones (such as birth control pills, injections, or transdermal system patches) may not work as well during treatment with AUGTYRO.
  - Talk to your healthcare provider about birth control methods that may be right for you.

  Males with female partners who are able to become pregnant:
  - You should use effective birth control during treatment with AUGTYRO and for 4 months after the last dose.
- are breastfeeding or plan to breastfeed. It is not known if AUGTYRO passes into your breast milk. Do not breastfeed during treatment and for 10 days after the last dose of AUGTYRO. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

Taking AUGTYRO with certain other medicines may affect the amount of AUGTYRO or other medicines in your blood and may cause side effects or affect the way that AUGTYRO or other medicines work. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take AUGTYRO?

- Take AUGTYRO exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking AUGTYRO unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with AUGTYRO if you develop side effects.
- Take AUGTYRO at about the same time each day with or without food.
- Swallow AUGTYRO capsules whole with water. Do not open, crush, chew or dissolve the capsule. Do not take a capsule if it is broken, cracked, or damaged.
- If you miss a dose, or vomit at any time after taking a dose of AUGTYRO, do not take an extra dose. Just skip the dose and take your next dose at the regularly scheduled time. Do not take 2 doses at the same time to make up a missed or vomited dose.

What should I avoid while taking AUGTYRO?

- You should not drink grapefruit juice or eat grapefruit during your treatment with AUGTYRO. It may increase the amount of AUGTYRO in your blood to a harmful level.
- Do not drive or operate machinery until you know how AUGTYRO affects you. If you experience dizziness, blurred vision, memory loss, changes in mental status, confusion, hallucinations or have trouble with balance or coordination or problems with concentration and attention, do not drive or operate machinery until your symptoms have resolved.

What are the possible side effects of AUGTYRO?

AUGTYRO may cause serious side effects, including:

- See **"What is the most important information I should know about AUGTYRO?"**

The most common side effects of AUGTYRO include:

- dizziness
- change in sense of taste
- feeling of numbness or tingling in your arms or legs
- constipation
- tiredness
- trouble with balance, coordination, and walking
- problems with thinking, such as forgetfulness or confusion, memory problems and hallucinations

- shortness of breath
- muscle weakness
- nausea

These are not all of the possible side effects of AUGTYRO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AUGTYRO?

- Store AUGTYRO at room temperature between 68°F to 77°F (20°C to 25°C).

Keep AUGTYRO and all medicines out of the reach of children.

General information about the safe and effective use of AUGTYRO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AUGTYRO for a condition for which it was not prescribed. Do not give AUGTYRO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about AUGTYRO that is written for health professionals.

What are the ingredients of AUGTYRO?

Active ingredient: repotrectinib

Inactive ingredients: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium, and colloidal silicon dioxide. Capsule shell contains gelatin and titanium dioxide. Printing ink contains shellac.

- White opaque capsules, printing ink contains in addition FD & C blue #2 aluminum lake.
- Blue opaque capsules contain in addition magnesium stearate and FD & C blue #1. Printing ink contains in addition titanium dioxide.

Distributed by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA; U.S. License No. 1713

For more information, go to www.AUGTYRO.com or call 1-877-284-8976.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 06/2024

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/

STEVEN J LEMERY
06/13/2024 10:49:33 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s001

OFFICER/EMPLOYEE LIST

Officer/Employee List
NDA 218213 S-001

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s001

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	505(b)(1)/SE1
Application Number(s)	NDA 218213 S-001
Priority or Standard	Priority
Submit Date(s)	December 15, 2023
Received Date(s)	December 15, 2023
PDUFA Goal Date	June 15, 2024
Division/Office	DO3/OOD
Review Completion Date	Refer to electronic stamp date
Established Name	Repotrectinib
(Proposed) Trade Name	Augtyro
Pharmacologic Class	Kinase Inhibitor
Code name	BMS-986472, TPX-0005
Applicant	Bristol Myers Squibb Company
Formulation(s)	40 mg capsules
Dosing Regimen	160 mg orally once daily for 14 days, then increase to 160 mg twice daily, with or without food
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult and pediatric patients 12 years of age and older with solid tumors that: • have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, • are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and • have progressed following treatment or have no satisfactory alternative therapy.

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OPQ=Office of Pharmaceutical Quality
RBPM=Regulatory Business Project Manager
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDRH= Center for Devices and Radiological Health
AD=Associate Director
SRPM=Safety Regulatory Project Manager

Glossary

ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AJCC	American Joint Committee on Cancer
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve over the last 24-h dosing interval
AUC_{inf}	area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of last measurable concentration
Ba/F3	pro-B murine cell line dependent on interleukin-3 for growth
BID	twice daily
BICR	blinded independent central review
BLA	biologics license application
BLQ	below limit of quantification
BMI	body mass index
BOR	best overall response
BRA	benefit-risk assessment
BRAF	a human gene encoding protein kinase b-raf
CBR	clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
ClinRO	Clinician reported outcome
C_{max}	maximum serum concentration
C_{maxss}	maximum serum concentration at steady state
CL_{max}	maximum clearance rate
CMC	chemistry, manufacturing, and controls
C_{avg}	average plasma concentration
C_{avgss}	average plasma concentration at steady state
CNS	central nervous system
COA	clinical outcome assessment
cORR	confirmed objective response rate
CPK	creatine phosphokinase

CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DEPI	Division of Epidemiology
DLT	dose-limiting toxicity
DMEPA	Division of Medication Error Prevention and Analysis
DO2	Division of Oncology 2
DOR	duration of response
DRISK	Division of Risk Management
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
eGFR	estimated glomerular filtration rate
E_{max}	maximal effect at high drug concentrations when all the receptors are occupied by the drug
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-LC-13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EOT	end of treatment
E-R	exposure-response
EXP	expansion cohort
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	good clinical practice
GHS	global health status
GI	gastrointestinal
GIST	gastrointestinal stromal tumors
GLP	good laboratory practice
Gr	grade
HCP	healthcare provider
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use

IO	immune-oncology
IC-ORR	intracranial objective response rate
IC-PFS	intracranial progression-free survival
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KRAS	Kirsten rat sarcoma virus
2L	second line *(setting)*
MDR	multidisciplinary review
MedDRA	Medical Dictionary for Regulatory Activities
MET	MET proto-oncogene, receptor tyrosine kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NA	not applicable
NCI	National Cancer Institute
NDA	New Drug Application
NE	not estimable
NEAE	neurological adverse event
NGS	next-generation sequencing
NCCN	National Comprehensive Cancer Network
NDA	new drug application
NME	new molecular entity
NR	not reported
NSCLC	non-small cell lung cancer
NTRK	neurotrophin receptor kinase
ObsRO	observer reported outcome
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PerfO	performance outcome

PFS	progression-free survival
PK	pharmacokinetic
PMA	premarket approval
PMC	postmarketing commitment
PMR	postmarketing requirement
PopPK	population PK
PPK	population pharmacokinetics
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
Q	quadrant
QD	once daily
QOL	quality of life
qPCR	quantitative polymerase chain reaction
QTcF	QT interval corrected for heart rate using Fridericia formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
ROS1	receptor tyrosine kinase encoded by the ROS1 gene
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SFM	solvent front mutations
sNDA	Supplemental New Drug Application
SOC	system organ class
$t_{1/2}$	elimination half-life
TDD	time to definitive deterioration
TEAE	treatment emergent adverse event
TFI	time to first improvement
TKI	tyrosine kinase inhibitor
Tlag	lag time (time delay between drug administration and first observed concentration)
T_{max}	time to reach maximum (peak) plasma drug concentration
TRK	tropomyosin receptor kinase
TRKA	tropomyosin receptor kinase A
TRKB	tropomyosin receptor kinase B
TRKC	tropomyosin receptor kinase C
TTR	time to response
Vd_{ss}	volume of distribution

UK	United Kingdom
ULN	upper limit normal
US	United States
USPI	United States Prescribing Information
V2	central volume of distribution
V3	peripheral volume of distribution
Vd_{ss}	steady-state volume of distribution
VPC	visual predictive check
WOCBP	women of childbearing potential
WT	wild type

1. Executive Summary

1.1. Product Introduction

Repotrectinib (AUGTYRO®) is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1); tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC; and anaplastic lymphoma kinase (ALK). It is FDA-approved for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC).

The Applicant's proposed indication is for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted by the Applicant has provided substantial evidence for the effectiveness of repotrectinib 160 mg orally once daily (QD) for 14 days, then increased to 160 mg twice daily, with or without food, for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

This conclusion is based on the results of one clinical trial, TPX-005-01 (TRIDENT-1) in adult and pediatric patients that demonstrated a clinically meaningful overall response rate (ORR) and durability of response. Substantial evidence of effectiveness was established with one adequate investigation (i.e., Study TRIDENT-1), with highly persuasive results, that is considered to be the scientific equivalent of two clinical investigations. Although the sponsor conducted one trial, clinically meaningful response rates were observed in two independent cohorts of patients.

FDA amended the Applicant's proposed indication to include patients who have progressed following treatment or have no satisfactory alternative therapy. Although 12 patients did not receive prior therapy, this criterion in the indication states that patients have either progressed following treatment or have no satisfactory alternative therapy; therefore, FDA retained this criterion to best characterize the patient population enrolled on the TRIDENT-1 study. Additionally, for an accelerated approval, a drug should provide a meaningful advantage over

available therapies which was not addressed across the tissue agnostic indication (note that flexibility remains for prescribers in disease settings without satisfactory alternative therapies). The revised indication is consistent with the other approvals for NTRK rearrangement (NTRK+) solid tumors.

Although adolescent patients ages 12-17 were eligible for the Phase 2 portion of TRIDENT-1, none were enrolled. However, an ongoing pediatric study in patients with NTRK+ solid tumors, CARE, is underway. Data from this study concludes that the observed repotrectinib exposures in adolescent patients 12 years and older were within range of values observed in adults following administration of 160 mg QD for 15 days. (Refer to FDA assessment in Sections 6.2 and 10 for details).

TRIDENT-1 is a first-in-human, dose escalation and expansion, multicenter, open-label, single-arm, multi-cohort trial in patients ≥12 years of age (Phase 2 only) with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements. The focus of this indication comes from the results of Cohorts EXP-5 (TRK TKI-naïve NTRK+ solid tumors [up to n=110]) and EXP-6 (TRK TKI-pretreated NTRK+ solid tumors [up to n=80]). A total of 88 patients were enrolled; 40 in the EXP-5 Cohort and 48 in the EXP-6 Cohort. The primary efficacy endpoint ORR by blinded independent review committee (BICR) per RECIST v1.1. ORR was 58% (95% confidence interval [CI]: 41, 73) with 15% having a complete response for EXP-5 and 50% (95% CI: 35, 65) with all patients experiencing a partial response in EXP-6. The duration of response (DOR) was at least ≥6 months for 87% of patients and ≥12 months for 83% of patients, and 71% and 42% for patients in Cohorts EXP-5 and EXP-6, respectively. (Refer to Section 8.1.2.8 for further details).

The safety of adult patients who received repotrectinib has been previously characterized during the review of the ROS+ NSCLC indication and is consistent with other NTRK inhibitors. Preliminary safety data in adolescent patients 12-17 years of age with NTRK+ solid tumors comes from a small number of patients enrolled on the ongoing CARE study, a single-arm, multicenter, multicohort study to evaluate the safety in pediatric and young adult patients with advanced or metastatic solid tumors with ALK, ROS1, or NTRK alterations. There were 10 patients ages 13-15 years with 7 having an NTRK alteration. Based on this limited information, there does not appear to be any new safety signals identified in the adolescent patients 13-15 with NTRK+ solid tumors. (Refer to Sections 8.1.3 and 10 for additional information regarding the CARE study). In addition, the safety and effectiveness of repotrectinib for the treatment of locally advanced or metastatic NTRK+ solid tumors have been established in adolescent patients 12 to 17 years of age. Use of repotrectinib in this age group is supported by evidence from an adequate and well-controlled study in adult patients with additional pharmacokinetic (PK) and safety data in adolescent patients 12 years of age and older that demonstrate the exposure of repotrectinib in this age group is expected to result in similar safety and efficacy to that of adults.

The review team believes that the response rate and durability of response provides a benefit that outweighs the risks associated with systemic treatment of repotrectinib for this patient population. Given the observed response rates (including about 10% of patients with complete radiographic responses), it is unlikely that there would be equipoise to conduct randomized controlled trials in NTRK+ solid tumors. Furthermore, the rarity of specific NTRK+ solid tumors would further complicate the ability to conduct a randomized controlled trial.

Therefore, the review team recommends granting Accelerated Approval to repotrectinib for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

NTRK+ solid tumors are a group of heterogenous tumors with an overall incidence of 0.3 to 0.70%. The annual incidence of NTRK fusion-driven tumors is estimated to be 1500-5000 cases in the United States (U.S.) (Kheder 2018). High NTRK fusion prevalence rates were confirmed in previously identified rare cancers of infantile fibrosarcoma, secretory carcinoma of the breast, and secretory carcinoma of the salivary gland (>90%). Additional cancer types with an incidence of >10% NTRK fusion are largely pediatric cancers; (congenital mesoblastic nephroma [19–23%], differentiated or papillary thyroid cancer [12–26%], infantile high-grade glioma [28%], and rare skin neoplasms such as spitzoid tumors [14–16%] and spindle cell nevus of reed [57%]). The prevalence of NTRK fusions in common cancer types is low, with many around 0.2% incidence. The most common partners are NTRK1 and NTRK3 and the most frequent fusion is ETV6-NTRK3 (O'Haire 2023). There are two drugs, larotrectinib and entrectinib (USPIs for entrectinib and larotrectinib), with Accelerated Approved specifically for the treatment of patients with metastatic or unresectable solid tumors harboring an NTRK fusion. When metastatic or unresectable, these tumors are rarely curable and generally convey a poor prognosis. Although there are approved treatments for many common adult cancers that rarely have an NTRK fusion, such as lung, prostate, and colon cancer, this indication is limited to such patients who have progressed on approved treatments for adult solid tumors. There are few reports in the literature regarding the racial and ethnic backgrounds of patients with NTRK+ solid tumors. In one report, there was a higher NTRK prevalence in patients with primarily East Asian ancestry (0.46%, p=0.015) compared to South Asian (0.37%), American (0.34%), European (0.29%) or African (0.32%) (Wilson 2019).

A favorable benefit-risk assessment has been established, based on the results of one clinical trial, TRIDENT-1, for repotrectinib for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

Accelerated Approval of repotrectinib is recommended based on a demonstrated effect on overall response rate ORR. The clinical benefit across a broader spectrum and number of tumor types will be verified and described via a postmarketing requirement (PMR). The additional data will provide increased precision of treatment effect on the intermediate endpoint (and more data in different tumor types) as well as information on the durability of the treatment effect.

The efficacy of repotrectinib in patients 12 years of age and older was established based on the results of TRIDENT-1, a multi-center, open-label, multiple cohort study in 88 (40 TKI-naïve NTRK+ solid tumors [EXP-5] and 48 TKI-pretreated NTRK+ solid tumors [EXP-6]) patients with NTRK+ solid tumors. The ORR was 58% (95% confidence interval [CI]: 41, 73) with 15% having a complete response for EXP-5 and 50% (95% CI: 35, 65) with all patients experiencing a partial response in EXP-6. The duration of response (DOR) was at least ≥6 months for 87% of patients and ≥12 months for 83% of patients, and 71% and 42% for patients in EXP-5 and EXP-6, respectively. Although the ORR for repotrectinib is high among certain NTRK+ tumor types (i.e., NSCLC, thyroid cancer, salivary gland cancer), the treatment effects of repotrectinib in some of the less well represented tumor types for which NTRK fusions are rare are less well characterized due to small numbers of patients. However, in the context of the acceptable safety profile observed in 426 patients, this degree of uncertainty is acceptable in patients with NTRK+ solid tumors that are metastatic or who would otherwise undergo a morbid or life-threatening surgical procedure or who have no remaining satisfactory treatment options.

Safety data supporting the proposed indication reflected exposure to repotrectinib in 88 adult patients enrolled on TRIDENT-1. The safety of repotrectinib in adults has been well-characterized in the treatment of patients with locally advanced or metastatic *ROS1*-positive NSCLC and is generally consistent with the known safety profile of other NTRK inhibitors larotrectinib and entrectinib. The across drug class of adverse drug events include central nervous system effects, hepatotoxicity, hyperuricemia, and skeletal fractures. Two Warnings and Precautions (W&P) not included in the larotrectinib or entrectinib United States Prescribing Information (USPIs) were myalgia with creatine phosphokinase elevation and interstitial lung disease (ILD). These two W&P were included in the ROS+ NSCLC indication and were similar in incidence with the new indication for NTRK+ solid tumors. No new safety signals were identified in the TRIDENT-1 study. The safety and effectiveness of repotrectinib in adolescent patients 12 to 17 years of age is supported by evidence from an adequate and well-controlled study in adult patients (TRIDENT-1), with supportive data from the CARE study, with additional pharmacokinetic and safety data in adolescent patients 12 years of age and older. Although assessment of a causal relationship between repotrectinib and adverse events (AEs) was somewhat limited in the context of the single-arm design of trials providing safety data, AEs observed in patients treated with repotrectinib were consistent with the mechanism of action (multiple kinase inhibition) and toxicities observed in clinical and preclinical studies with ROS+ NSCLC, and for the entrectinib and larotrectinib approvals. Although repotrectinib poses a risk of toxicity, these risks are considered acceptable in the context of the observed clinical efficacy. Risk minimization via the product label includes the current management guidelines for AEs and a Medication Guide.

The review team recommends granting accelerated approval to repotrectinib for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy.

Because of the limited number of patients, subgroup analysis results are uninterpretable. Although preclinical and clinical data support efficacy in a wide range of NTRK+ solid tumor types, granting Accelerated Approval allows for a broader and larger number of tumor types to be assessed. In addition, approval based on a smaller number of tumor types is warranted as these patients currently have no curative therapy available. Therefore, as part of the conditional of Accelerated Approval, a PMR will be issued to strengthen the confidence in the efficacy of repotrectinib across multiple tumor types.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Solid tumors with NTRK mutations are a group of heterogenous tumors with an annual incidence of approximately 1500-5000 patients. • The incidence of NTRK+ solid tumors vary depending on the specific tumor type and are most commonly found in infantile fibrosarcoma, secretory carcinoma of the breast, and secretory carcinoma of the salivary gland. • When metastatic or unresectable, solid tumors are rarely curable.	NTRK+ solid tumors that have progressed following treatment or have no satisfactory alternative treatment options are life-threatening. Patients have a poor outcome.
Current Treatment Options	• Patients with NTRK+ solid tumors are treated with standard of care therapy for their specific tumor type. • There are two FDA-approved treatments (Accelerated Approval) for rare cancers that commonly harbor NTRK fusions, larotrectinib and entrectinib.	Although standard treatment regimens exist for most patients with locally advanced or metastatic solid tumors, such treatment generally is not curative and additional treatment options are needed. Given the poor prognosis there remains a need for treatment options for this patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Efficacy analyses from TRIDENT-1 demonstrated a clinically meaningful ORR with durability of response. • ORR was 58% (95% confidence interval [CI]: 41, 73) with 15% having a complete response in EXP-5 and 50% (95% CI: 35, 65) with all patients experiencing a partial response in EXP-6. The duration of response (DOR) was at least ≥6 months for 87% of patients and ≥12 months for 83% of patients, and 71% and 42% for patients in EXP-5 and EXP-6, respectively. Refer to Section 8.1.2.8 for further details.	The magnitude and DOR observed in patients with NTRK+ solid tumors who have progressed following prior treatment or who had no available treatment options was clinically meaningful. For unresectable or metastatic solid tumors that are refractory to available therapy or for which there is no satisfactory therapy, ORR may be considered an intermediate endpoint reasonably likely to predict clinical benefit when the treatment effect is large and the responses are durable. The submitted evidence meets the statutory evidentiary standard for Accelerated Approval. As a condition of approval, the Applicant is required to submit additional evidence to verify and confirm the clinical benefit of repotrectinib in patients with NTRK+ solid tumors (PMR).
Risk and Risk Management	• The safety profile of repotrectinib appears acceptable for a therapy used to treat a serious and life-threatening condition. • Repotrectinib in adult patients has a well-characterized safety profile based on the approval in ROS+ NSCLC patients and is similar to that of other NRTK inhibitors. • Use of repotrectinib in adolescent patients 12-17 years of age is supported from an adequate and well-controlled study in adult	The safety data submitted was sufficient to characterize the toxicity profile of repotrectinib for both adults and adolescent patients and the risks are considered acceptable in the context of the clinical efficacy in the advanced or metastatic disease setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients (TRIDENT-1) with additional pharmacokinetic and safety data in adolescent patients 12 years of age and older. • Premature data from the CARE study in pediatric patients along with data from the TRIDENT support, support the safety in adolescent patients 12-17 years of age.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1.2.14
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	X	Other: (Please specify): See below			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

A secondary objective in TRIDENT-1 was to assess treatment-related symptoms and general health status, using EORTC-QLQ-C30 and LC-13 when applicable, in patients treated with repotrectinib. There was no formal analysis testing for patients with NTRK+ solid tumors.

X _____

Leslie Doros
Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:
TRKA, TRKB, and TRKC, encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively, are high-affinity receptors for neurotrophins. Oncogenic aberrations of *NTRK1-3* (hereafter referred to as *NTRK*) have been identified across multiple adult and pediatric tumor histologies, with *NTRK* gene fusions being the most common mechanisms of oncogenic TRK activation (Albert 2018; Cocco 2018). Commonly used methods for *NTRK* fusion detection include IHC, FISH, NGS, and PCR assays (NCCN NSCLC 2023; Hechtman 2022).

The annual incidence of *NTRK* gene fusion-driven tumors in the United States is estimated to be approximately 1,500 – 5,000 cases (Kheder 2018). In solid tumors, oncogenic rearrangement of *NTRK* leading to TRK fusions are rare but have been identified in many common cancer types including lung or pancreatic adenocarcinomas, head and neck squamous cell, bile duct, breast, colorectal and renal cell carcinomas, melanomas, primary adult brain tumors (e.g., astrocytomas or glioblastomas), and non-GIST soft tissue sarcomas (Vaishnavi 2015; Cocco 2018). In addition, many rare cancer types are highly enriched for *NTRK* gene fusions, some with prevalence > 90% (Cocco 2018) and are even considered a defining genetic feature in tumors such as secretory breast carcinoma, mammary analogue secretory carcinoma, congenital mesoblastic nephroma, and infantile fibrosarcoma (Albert 2018; Vaishnavi 2015; Cocco 2018). Other tumors found to harbor *NTRK* gene fusions in frequencies of up to 25% include papillary thyroid cancers, Spitzoid neoplasms, GIST, and some pediatric gliomas (Vaishnavi 2015; Cocco 2018).

Overall, *NTRK*-positive advanced malignancies such as the ones described above are life-threatening with poor prognoses and represent an area of high unmet medical need in adult and pediatric patients.

The FDA's Assessment:
FDA generally agrees with the Applicant's analysis of NTRK+ solid tumors. NTRK fusions are rare in most tumors except certain rare tumors such as mammary analogue secretory cancer, secretory breast cancer, infantile fibrosarcoma, and congenital mesoblastic nephroma. Although the expectation is that metastatic or unresectable NTRK+ solid tumors are fatal diseases, the natural history of the different tumors may vary by specific diagnoses. In addition, NTRK1 and NTRK3 fusions are more common than NTRK2 fusions with ETV6/NTRK3 and TPM3/NTRK1 being the most common fusions detected (Marchetti 2022).

2.2. Analysis of Current Treatment Options

Data:

TKI-naïve NTRK-Positive Solid Tumors:

Non-targeted therapies are frequently used as front-line treatment in patients with *NTRK*-positive solid tumors due to unknown mutational status at the time of systemic treatment initiation. Systemic therapy regimens commonly used for select solid tumors are presented in Table 1.

Table 1: Applicant Summary of Current non-TRK TKI Systemic Treatment Options Commonly Used for Advanced/Metastatic Disease in Selected Tumor Types Without Known Oncogenic Driver

Tumor Type	First-line	Second-line
NSCLC	Platinum doublet + Pembrolizumab/Atezolizumab/Cemiplimab, Nivolumab + Ipilimumab ± Chemo, Durvalumab + Tremelimumab ± Chemo; Pembrolizumab/ Atezolizumab/Cemiplimab (PD-L1≥50%)	Docetaxel± Ramucirumab, Pembrolizumab/ Nivolumab/Atezolizumab; Pemetrexed/Gemcitabine/Albumin-bound paclitaxel; Platinum doublet (after anti-PD-L1 progression)
Colorectal cancer (pMMR/MSS)	FOLFOX/FOLFIRI/CAPEOX/FOLFIRINOX-based regimens (if intensive therapies recommended)	Oxaliplatin- and/or Irinotecan-based regimens depending on prior treatment, Cetuximab, Panitumumab, Trifluridine + Tipiracil ± Bevacizumab
Melanoma	Nivolumab ± Ipilimumab, Nivolumab ± Relatlimab, Pembrolizumab ± Ipilimumab	Nivolumab ± Ipilimumab, Nivolumab ± Relatlimab, Pembrolizumab ± Ipilimumab, Ipilimumab, High-dose IL-2, cytotoxic agents (e.g., Dacarbazine)
Thyroid cancer (papillary, follicular)	Lenvatinib, Sorafenib	Cabozantinib
Salivary gland carcinoma	Cisplatin + Vinorelbine, Cisplatin + Doxorubicin + Cyclophosphamide, Paclitaxel, Carboplatin + Paclitaxel/Gemcitabine	•
Soft tissue sarcoma	Anthracycline- or Gemcitabine-based regimens	Trabectedin, Pazopanib, Eribulin, Dacarbacine, Regorafenib, Ifosfamide, Temozolomide, Vinorelbine, Gemcitabine-based regimens
Gastrointestinal stromal tumor	Imatinib	Sunitinib

Should *NTRK* fusions be detected at the time of initial diagnosis, the use of front-line TRK TKIs is recommended as an option in the NCCN guidelines. Currently, larotrectinib (Vitrakvi® USPI 2023) and entrectinib (Rozlytrek® USPI 2023) are the only approved targeted therapies under Subpart H accelerated approval (21 CFR 314.510) for the treatment of solid tumors that have an *NTRK* gene fusion, without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.

Larotrectinib was originally approved by accelerated approval pathway in November 2018 for use in adult and pediatric patients (Vitrakvi® USPI 2018). The accelerated approval was based on efficacy data assessed in 55 patients (age range 4 months to 76 years) with solid tumors harboring *NTRK* gene fusions pooled across 3 studies (LOXO-*TRK*-14001, SCOUT, and NAVIGATE). The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). The confirmed ORR by BICR was 75% (N = 55; 95% CI: 61 – 85) **Error! Reference source not found.**. Recently, updated efficacy results from solid tumors (including CNS primary tumors) showed an ORR of 61% (N=313, 95% CI: 55, 66). In the adult sub-population (n=178), the ORR was 58%. In the pediatric sub-population (n=94), the ORR was 84%.

Entrectinib was originally approved by accelerated approval pathway for use in adult and pediatric patients (≥ 12 years of age) in August 2019. The accelerated approval was based on efficacy data assessed in 54 adult patients with solid tumors harboring *NTRK* gene fusions pooled across 3 studies including patients dosed at different doses and schedules (ALKA, STARTRK-1, and STARTRK-2). The most common cancers were sarcoma (24%), lung cancer (19%), salivary gland tumors (13%), breast cancer (11%), thyroid cancer (9%), and colorectal cancer (7%). A confirmed ORR of 57% by BICR (95% CI: 43 – 71) was achieved (Rozlytrek™ USPI 2019). Updated data on the same set of patients report confirmed ORR of 59% by BICR (95% CI: 45 – 72) (Rozlytrek® USPI 2023) (Table 2). The efficacy of entrectinib in pediatric patients ≥ 12 years was based on extrapolation of data from three open label, single-arm clinical trials in adult patients with solid tumors harboring a *NTRK* gene fusion (ALKA, STARTRK-1 and STARTRK-2), and efficacy and PK data in 30 pediatric patients enrolled in STARTRK-NG (Rozlytrek MDR 2019). Of these 30 patients, 2 (7%) were < 2 years, 23 (77%) were 2 to < 12 years, and 5 (17%) were 12 to < 18 years; the most common cancers were neuroblastoma (47%), primary CNS tumors (30%), and sarcoma (10%).

Table 2: Applicant Efficacy and Safety of TRK TKI Historical Benchmarks in TKI-Naïve NTRK-Positive Solid Tumors

NTRK+ Solid Tumors, TKI-Naïve	Larotrectinib[a] (Vitrakvi USPI) (Includes Primary CNS, Adults and Pediatrics)	Larotrectinib[b] (Vitrakvi SmPC) (Includes Primary CNS, Adults, and Pediatrics)	Larotrectinib[b] (Vitrakvi SmPC) (Adult Only Subpopulation ; Not Including Primary CNS)	Entrectinib[c] (Rozlytrek USPI) (Includes Primary CNS and Adults Only)	Entrectinib[d] (Rozlytrek SmPC) (Includes Primary CNS and Adults Only)
Key Efficacy Data	**N=55**	**N=313**	**N=178**	**N=54**	**N=150**
ORR, % (95% CI)	75 (61, 85)	61 (55, 66)	58 (-)	59 (45, 72)	61 (53, 69)
DOR					
Median DOR, months (95% CI)	32.9 (14.8, NE)	41.5 (-)	-	-	20 (13.2, 31.1)
DOR Range	1.6+, 50.6+	0.0+, 65.4+	-	2.8, 47.8+	-
DOR Landmark Analyses (Kaplan Meier), % (95% CI)					
DOR ≥ 6 months	-	-	-	-	83 (75, 91)
DOR ≥ 12 months	-	79 (-)	-	-	66 (56, 76)
IC-ORR, % (n/N)	-	22 (9/41)	-	75 (3/4)	69 (9/13)
Safety Data	**N=279**	**N=335**	**N=335**	**N=355**	**N=504**
Key Warnings and Precautions	CNS effects Skeletal fractures Hepatoxicity	Neurological reactions Hepatotoxicity	Neurological reactions Hepatotoxicity	Congestive heart failure CNS effects Skeletal fractures Hepatoxicity Hyperuricemia QT interval prolongation Vision disorders	Cognitive disorders Fractures Hyperuricemia Congestive heart failure QTc interval prolongation

Abbreviations: BICR = Blinded Independent Central Review; CI = confidence interval; CNS = central nervous system; DOR = duration of response; IC-ORR = intracranial objective response rate; n/N = number of patients (numerator/denominator); NE = not evaluable; NTRK = neurotrophin receptor kinase ; ORR = objective response rate; RECIST = Response

Evaluation Criteria in Solid Tumors; SmPC = Summary of Product Characteristics; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase; USPI = United States Package Insert.
Notes: A "-" is included if information was not available/not reported.
[a] *Vitrakvi® USPI 2023; best overall response was determined by BICR using RECIST v1.1.*
[b] *Vitrakvi SmPC 2023; best overall response was determined by BICR using RECIST v1.1.*
[c] *Rozlytrek® USPI 2023; best overall response was determined by BICR using RECIST v1.1.*
[d] *Rozlytrek SmPC 2023; best overall response was determined by BICR using RECIST v1.1.*

TKI-pretreated NTRK-Positive Solid Tumors:

There are no approved TRK targeted therapies providing meaningful efficacy for *NTRK*-positive patients who have progressed after prior TRK TKIs with or without prior chemotherapy.

Palliative therapy or clinical trials for investigational TRK TKIs are usually offered to patients progressing on first-line TRK TKIs (Xu 2022). Regarding investigational candidates, among patients who had progressed or were intolerant to at least 1 prior TRK inhibitor, selitrectinib, an investigational TRK TKI treatment, resulted in a 34% ORR by Investigator assessment in a small set of patients (n=29) (Hyman 2019). However, this compound is not known to have any ongoing clinical development and the unmet need remains high for this population.

TRK TKI Resistance Mechanisms

Similar to treatment with other targeted drugs, patients eventually develop resistance to TRK inhibitors during the course of treatment. Known variants that cause resistance to first-generation TRK inhibitors include: (1) SFMs, such as *NTRK1* G595R and *NTRK3* G623R; (2) gatekeeper mutations, such as *NTRK1* F589L; (3) xDFG motif mutations, such as *NTRK1* G667C and *NTRK3* G696A; (4) bypass pathway mutations, such as *BRAF* mutations, IGF1R activation, *KRAS* mutations, and MET amplifications; and (5) other or unknown mutations, such as *NTRK1* A608D (Xu 2022). Among variants, solvent-front mutations are the most frequently observed resistance mechanism, comprising approximately 45% of patients with progression following treatment with TRK inhibitors or patients that are TRK inhibitor intolerant (Xu 2022). In a study of patients with *NTRK* fusions progressing on treatment with larotrectinib or entrectinib, the most common resistance mutations identified were solvent-front mutations (n = 13/18), followed by gatekeeper mutations (n = 2/18) (Harada 2022).

<u>The Applicant's Position:</u>

For patients with *NTRK*-positive solid tumors, disease specific standard of care has limited efficacy. Existing targeted therapies (i.e., larotrectinib and entrectinib) have demonstrated clinical benefit but have limitations related to efficacy with the development of resistance mutations (Harada 2021). In addition, confirmation of their clinical benefits leading to full regulatory approval is pending. (b) (4)

In the TKI-pretreated setting, there is a high unmet medical need as there are currently no approved targeted therapies in this setting, and many patients progress following treatment with existing targeted therapies, often due to acquired resistant mutations (e.g., SFMs). In addition to the development of acquired resistance, other subpopulations of patients with *NTRK*-driven tumors such as those with intracranial disease continue to represent a high unmet medical need.

Repotrectinib is an oral ATP-competitive small molecule inhibitor of ROS1, TRK, and ALK. To gain high binding affinity, most kinase inhibitors, including entrectinib and larotrectinib, are larger and have additional interactions with the kinase domain outside the ATP-binding pocket, making these inhibitors vulnerable to acquired resistance mutations such as SFMs that can sterically block drug binding (Awad 2013; Drilon 2016). Repotrectinib was rationally designed as a differentiated compact macrocycle to allow for tight binding in the ATP-binding site while minimizing steric interference that results in resistance seen with bulkier kinase inhibitors, especially the solvent-front and gatekeeper mutations of ROS1, TRK and ALK kinases. In nonclinical studies, repotrectinib exhibited potent activity against WT and mutated ROS1, TRK, and ALK, including a variety of clinically reported resistance mutations, especially SFMs. Repotrectinib also inhibited cell proliferation in cultured cells expressing *NTRK* fusions and mutations including LMNA-TRKA, LMNA-TRKA^{G595R,} EVT6-TRKB^{G639R}, and ETV6-TRKC^{G623R}. In addition, repotrectinib induced profound anti-tumor activity in the CNS with efficient blood–brain barrier penetrating properties in brain-metastasis mouse models (Yun 2020).

The available clinical data presented here demonstrate that repotrectinib has a favorable benefit-risk profile in the context of historical benchmarks of currently available therapies in the TKI-naïve setting and in the TKI-pretreated settings where there are currently no approved targeted therapies.

The FDA's Assessment:

Initial treatment of patients with most solid tumors is based on tumor-specific regimens that are described in treatment guidelines or FDA approved labeling. Although the Applicant's Table 1 describes frequently used regimens for certain tumor types, there may be exceptions based on individual patient's circumstances or tumor biology. Larotrectinib and entrectinib are approved for patients with NTRK+ solid tumors without satisfactory available therapy. FDA agrees there are no anti-NTRK therapies approved in patients who received a prior NTRK inhibitor. The Applicant's Table 2 also shows additional efficacy and safety data for approvals outside the US for entrectinib and larotrectinib; however, FDA has not reviewed these data and would not consider these results as part of the overall risk: benefit for the proposed indication.

Although the Applicant stated that the (b) (4)

(b) (4)

Finally, although repotrectinib may have demonstrated anti-tumor effects in non-clinical models, FDA would not agree with characterizations such as "profound anti-tumor activity" as such characterizations are not specific and may not be helpful in characterizing drug effects in human patients.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
AUGTYRO™ (repotrectinib) was approved in the United States on 15 Nov 2023 for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC. AUGTYRO has not been approved or marketed in any other region.

The repotrectinib clinical development program is being conducted under the Division of Oncology 2 with IND 130,465 (TRIDENT-1 protocol) and IND 169,833 (Pediatric CARE protocol). A pre-IND (PIND 157,539) was requested to specifically discuss activities for the *NTRK*-positive solid tumors development program with the Division of Oncology 3.

The FDA's Assessment:
FDA agrees with the Applicant's position. Repotrectinib received traditional approval for the treatment of adult patients with locally advanced or metastatic ROS1+ NSCLC.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicants Position:
Key Agency interactions for the repotrectinib development program are summarized in Table 3.

Table 3: Applicant Overview of Key US Regulatory Interactions and Timelines for NTRK-positive Solid Tumor indication

Date	IND/NDA	Content
30 Sep 2016	IND 130,465	**Submission of initial IND (130,465) 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*
24 Aug 2020	IND 130,465	**Granted: Fast Track Designation** (advanced solid tumors that have an NTRK gene fusion who have progressed following treatment with at least one prior line of chemotherapy and one or 2 prior TRK TKIs and have no satisfactory alternative treatments)
28 Sep 2021	pre-IND 157,539	**Granted: Breakthrough Therapy Designation (NTRK advanced solid tumor TKI pre-treated, EXP-6)**
15 Dec 2021	pre-IND 157,539	Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting (NTRK-positive advanced solid tumor)

Date	IND/NDA	Content
		Outcome: Feedback on the nonclinical package, proposed efficacy and safety population for NTRK indication, TRIDENT-1 statistical analysis plan, clinical pharmacology plan and companion diagnostic.
15 Dec 2021	IND 130,465	**Agreement reached with FDA on initial Pediatric Study Plan (iPSP)** Proposed General Plan: Proposed pediatric population and indication is for the (b) (4) . Phase 1/2, Open-label, Safety, Tolerability, PK, and Anti-tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring ALK, ROS1, or NTRK1-3 Alterations (Study TPX-0005-07 [CARE]) is ongoing.
12 Oct 2023	pre-IND 157,539	**Type B pre-sNDA Meeting (Clinical)** Outcome: Discussion and agreements regarding the clinical efficacy, safety and pharmacology plans for a supplemental NDA submission for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a NTRK gene fusion.
06 Nov 2023	IND 169,833	**Initial IND (169,833) submission for repotrectinib pediatric program, including the CARE protocol and a request to waive the 30-day safety review** "A Phase1/2, Open-label, Safety, Tolerability, Pharmacokinetics, and Anti-tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring ALK, ROS1, or NTRK1-3 Alterations (CARE)"
15 Nov 2023	NDA 218,213	**NDA Approval** AUGTYRO™ (repotrectinib) was approved for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC

Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion cohort; IND = Investigational New Drug; iPSP = initial Pediatric Study Plan; NDA = New Drug Application; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ORR = objective response rate; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; sNDA = supplemental NDA; TKI = tyrosine kinase inhibitor.

The FDA's Assessment:

FDA agrees with the Applicant's timeline of events. The current NDA was submitted on December 15, 2023. Because the NRTK+ solid tumor indication was granted orphan drug designation, the drug product for this indication is exempt from the requirements under the Pediatric Research Equity Act (PREA). The approval letter for the ROS1+ NSCLC indication (dated November 15, 2023) has a postmarketing requirement (PMR) 4547-1 to submit the final study report for the CARE study. A deferral was requested for results of the CARE study, an ongoing, single arm study in pediatric and young adult patients with solid tumors harboring ALK, ROS1 and NTRK alterations treated with repotrectinib. The study is expected to be completed in September 2026 with final report submission in March 2027.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

FDA elected not to perform inspections as investigator and site inspections were recently performed for the ROS1+ NSCLC indication with a final OSI report on September 6, 2023. 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, TRIDENT-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, BMS appear acceptable in support of the proposed indication.

4.2. Product Quality

There are no new product quality issues that impact safety or efficacy and would preclude approval.

4.3. Clinical Microbiology

There are no new clinical microbiology issues that impact safety or efficacy and would preclude approval.

4.4. Devices and Companion Diagnostic Issues

In TRIDENT-1, assessment of NTRK fusion status was determined by tissue-based local test for enrollment and central confirmation was required. NTRK fusion status was assessed locally by fluorescence in situ hybridization (FISH), next generation sequencing (NGS) or qualitative polymerase chain reaction (qPCR). Those tested by FISH were retested retrospectively by central laboratory. Only patients with central diagnostic laboratory test confirmation were included in the integrated efficacy analysis.

The development of a companion diagnostic (CDx) for the detection of NTRK fusion-positive solid tumors (b) (4). A postmarketing commitment (PMC) for the development of an in vitro diagnostic device will be included in the PMR/PMC language for this NDA submission. Refer to Section 13.

5. Nonclinical Pharmacology/Toxicology

No new information is provided in the current submission.

6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:
The Applicant seeks Accelerated Approval of repotrectinib for the treatment of adult and pediatric patients 12 years of age and older that have locally advanced or metastatic solid tumors with an NTRK gene fusion. The proposed recommended dosage is 160 mg orally QD for 14 days, then increased to 160 BID (160 QD/BID), with or without food, which is the same dosage as the first approved indication of repotrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.

Clinical pharmacology reviewed the adequacy of the proposed recommended dosage for the proposed population. The proposed recommended dosage appears acceptable based on the clinical data, population pharmacokinetic (PK) analysis, and exposure-response relationships for efficacy and safety. Repotrectinib at the recommended dosage in adult patients with solid tumors with an NTRK gene fusion demonstrated ORRs of 58% and 50% in TKI-naïve and TKI-pretreated patients, respectively. The safety profile in the NTRK+ solid tumor population was consistent with what is known for repotrectinib in the approved ROS+ NSCLC population.

Exposure-response analyses for efficacy showed a positive relationship between repotrectinib exposure and progression-free survival (PFS) and exposure response analyses for safety showed a positive relationship with the incidence of Grade ≥2 AEs, including dizziness and nervous system events, that determined whether patients were eligible to receive the full 160 mg BID dosage after 14 days. Repotrectinib exposures in adolescent patients 12 years of age and older was comparable to that of adults, and responses were observed in an ongoing study using the proposed recommended dosage. It should be noted that the exposure-response analyses were limited to the proposed dosing regimen.

Recommendation:
The proposed recommended dosage of 160 mg orally QD for 14 days, then increased to 160 BID with or without food is acceptable and the NDA supplement is approvable from FDA's clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Repotrectinib inhibits TRKA/B/C with biochemical IC_{50} values of 0.83, 0.05, and 0.10 nM, respectively. Repotrectinib inhibits cell proliferation of Ba/F3 cells engineered to express WT fusion proteins LMNA–TRKA, TEL–TRKB, TEL–TRKC or corresponding solvent-front substitutions ($TRKA^{G595R}$, $TRKB^{G639R}$, $TRKC^{G623R}$, $TRKC^{G623E}$) with IC_{50} values ranging from < 0.2 to 8.4 nM. Repotrectinib PK in adult patients was described in the Summary of Clinical Pharmacology (SCP) from the initial ROS1 NDA. Repotrectinib PK was similar across different genetic mutation (e.g., *NTRK* versus *ROS1*) based on the population PK (PopPK) analysis.

Repotrectinib PK in pediatric (<12 years) and adolescent (≥ 12 to <18 years) patients was evaluated in the CARE study (all patients enrolled were <18 years). Similar to adult PK, repotrectinib was absorbed with a median Tmax of 2 to 4 hours after oral administration of suspension or capsules in pediatric and adolescent patients with advanced solid tumors. The oral suspension formulation was developed primarily for the pediatric patients in the CARE study who cannot swallow capsules and is not in the scope of proposed adolescent indication.

Repotrectinib exposures decreased from Cycle 1 Day 1 to Cycle 1 Day 15 following once daily dosing, consistent with adult PK with demonstrated autoinduction. Repotrectinib exposures in pediatric and adolescent patients at 160 mg AED (adult equivalent dose) QD were comparable to those in adult patients with solid tumors at 160 mg QD.

The FDA's Assessment:
FDA agrees with the Applicant's conclusion that following administration of 160 mg QD for 15 days, observed repotrectinib exposures in adolescent patients 12 to 17 years of age enrolled in the CARE study were within range of values observed in the TRIDENT-1 study which only enrolled patients 18 years of age or older.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:
The repotrectinib approved dose for adult patients with *ROS1*-positive NSCLC is 160 mg orally QD for 14 days, with the option to titrate to 160 mg BID on Day 15 if tolerated, with or without food. The same dose regimen is recommended for adult and adolescent patients with *NTRK*-positive solid tumors and is supported by the clinical data, PK data, and exposure-response analysis.

Adult Dose Selection for the TRIDENT-1 study:
The safety and tolerability of repotrectinib were initially evaluated in TRIDENT-1 Phase 1 for QD doses ranging from 40 mg – 240 mg QD and BID doses ranging from 160 mg – 200 mg. The

160 mg QD for 7 days followed by 160 mg BID titration regimen was evaluated in TRIDENT-1 Phase 1c and provided adequate efficacy with an acceptable safety profile. The RP2D was selected as 160 mg QD for 14 days with the potential to titrate up to 160 mg BID on Day 15, if tolerated, since the majority of the CNS-related AEs were reported within the first 14 days. PK of repotrectinib is time-dependent with steady-state exposure on Day 15 reduced as compared to the single dose exposure, thus titrating up to BID regimen can help compensate for the exposure lost due to time-dependent auto-induction seen in QD regimen.

Confirmation of Adult Dose regimen

The clinical results of TRIDENT-1 Phase 2 study as well as the population PK (PopPK) and exposure-response (E-R) analysis confirm the 160 mg QD/BID dosing regimen as the optimized dose for patients with *NTRK*-positive solid tumors.

- TRIDENT-1 clinical data: Repotrectinib at the recommended dose demonstrated clinically meaningful efficacy for the treatment of *NTRK*-positive solid tumors (TKI-naïve ORR 63% [22/35] and TKI-pretreated ORR 52% [23/44]) and a tolerable and manageable safety profile in the Phase 2 portion of the TRIDENT-1 study (N = 426).
- PopPK: Simulation showed that repotrectinib C_{avg} following 160 mg QD was reduced at steady state compared to the first dose due to autoinduction of CYP3A4. Increasing 160 mg QD dosing to BID dosing after 14 days would compensate for the PK exposure loss due to autoinduction and maintain effective repotrectinib exposure throughout the treatment duration.
- E-R analyses: E-R efficacy analysis showed the median probability of PFS increased with dose and the 160 mg QD/BID dosing regimen showed higher median probability of PFS than 160 mg QD across *NTRK1-2* and 3. There was no meaningful increase in efficacy at a dose higher than 160 mg QD/BID (i.e., 200 mg QD/BID). The dose-efficacy relationship for *NTRK*-positive solid tumors was similar to *ROS1*-positive NSCLC, and the same dose of 160 mg QD/BID is recommended for *NTRK*-positive solid tumors. The E-R efficacy also supports the proposed dose reductions of 120 mg QD/BID and 80 mg QD/BID to manage safety events with a predicted efficacy benefit. The predicted median probabilities of Gr2+ dizziness, Gr2+ NEAEs, and DRDI were higher at higher dose level, but 160 mg QD and 160 mg QD/BID had comparable probabilities with overlapping 90% prediction intervals and the absolute rates of these events were manageable (e.g., 1-year Gr2+ dizziness at 160 mg QD and 160 mg QD/BID doses was 13% and 15%, respectively).

Adolescent Dose Selection for pediatric CARE study

The RP2D selected for the CARE study (refer to Section 8.1.3) in pediatric patients was 160 mg adult equivalent dose (AED) QD for the first 14 days and could increase to 160 mg AED BID if tolerated. The AED doses for adolescents (≥ 12 to ≤ 18 years) in the CARE Study were body weight-tiered (i.e., body weight >50 kg, 160 mg; body weight ≥ 40 kg and <50 kg, 140 mg; body weight ≥30 kg and <40 kg: 120 mg). The AED evaluated in the pediatric CARE study were originally determined based on preliminary PopPK projections for pediatrics ≥4 years old and

PBPK-based projections for pediatrics <4 years old. Most adolescent patients (7 out of 8) in the CARE study received the adult dose of 160 mg.

The selection of the pediatric RP2D was based on review of the totality of available data from the Phase 1 portion of the CARE study, including the observed safety, tolerability, PK, and preliminary clinical activity of repotrectinib.

Confirmation of Adolescent Dose regimen for proposed NTRK indication
The same adult recommended dose is confirmed for adolescents based on the totality of comparable PK and the expected similarity in efficacy/safety response to TKI treatment between adolescent and adult patients.

- CARE clinical data: Despite the small number of pediatric (<12 years) and adolescent patients (≥ 12 to <18 years) treated for *NTRK*-positive solid tumors, there is an initial encouraging clinical benefit across pediatric and adolescent patients similar to that seen in adults. Repotrectinib at RP2D demonstrated a manageable and tolerable safety profile in pediatric and adolescent patients, and the safety profile was generally similar with the safety profile reported in adult patients in the TRIDENT-1 study.
- Exposure-match: The same adult dose regimen is recommended for adolescents based on a PopPK assessment of observed PK data from adults (502 adult patients, 118 adult healthy subjects) and pediatrics (24 pediatric patients 0.8 to 16 years old). The PopPK model was used to conduct simulations to demonstrate that adult and adolescent exposures (C_{max}, C_{min}, C_{avg} after first dose and steady state) were similar with the same flat dosing regimens (i.e., 160, 120 and 80 mg QD/BID).

- Other Approved TRK inhibitors: The extrapolation of efficacy and safety to adolescents is further supported by the extensive clinical pediatric data from other approved TRK inhibitors (i.e., entrectinib and larotrectinib). These literature analyses confirm that the efficacy of TRK inhibitors is age- and histology-agnostic with comparable efficacy reported across pediatric and adult patients. Overall, similar exposure-response between pediatric and adult patients for TRK inhibitors is expected.

The FDA's Assessment:
FDA agrees that the proposed recommended dosage of 160 mg QD/BID, with or without food, which is consistent with the current approved labeling, has an acceptable benefit-risk profile in adult and pediatric patients 12 years of age and older with NTRK+ solid tumors. In the CARE study, adolescent patients 12 to 17 years of age who received the 160 mg QD had maximum concentrations and AUC_{0-24} on Cycle 1 Day 15 within 11% and <1% of adults. The majority of patients younger than 12 years of age enrolled in the CARE study received the repotrectinib suspension formulation at doses less than 120 mg either once or twice daily. See Section 17.4.2

for further details and FDA review of the updated population PK analysis.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

In the approved repotrectinib USPI for *ROS1*-positive NSCLC, no dose adjustment is required based on age (≥ 18 years), body weight, race, or sex, in patients with mild and moderate renal impairment or those with mild hepatic impairment. In this sNDA submission, the updated population PK analysis confirmed the prior results and showed the adolescents had similar exposure as adults at the same flat dose regimens (i.e., 160 mg QD/BID, 120 mg QD/BID, and 80 mg QD/BID). Therefore, no dose adjustment is required for age (≥ 12 years). Recommendations made in the proposed labelling on the drug interactions for *NTRK*-positive solid tumors are the same as the approved USPI for *ROS1*-positive NSCLC. No new data are presented.

The FDA's Assessment:
FDA agrees that there were no clinically meaningful effects of age (12 to 93 years old), sex, race (Asian, Black, White), mild-to-moderate renal impairment, and mild hepatic impairment on repotrectinib PK; the findings from the updated PPK analyses were similar to that of PPK submitted with the original NDA.

The Applicant provided a comparison of simulated repotrectinib exposure metrics following a single 160 mg dose in adolescent patients 12 to 17 years of age with body weights ranging from 30 kg to 110 kg in 10 kg increment groups and found that, except for C_{max} and C_{min} in pediatric patients <40 kg and >110 kg, exposures were within the expected adult range of median values and all exposure metrics were within the predicted 5th and 95th percentile of adult values. FDA conducted similar analyses using the 160 mg QD/BID dosage and found that the steady-state C_{avg}, C_{max}, and C_{min} was comparable to adults across the 30 kg to 110 kg body weight range. Both the FDA's and the Applicant's analysis results were consistent with the PK parameters observed in adolescent patients 12 to 17 years of age. See Section 17.4.2 for further details and FDA review of the updated population PK analysis.

FDA agrees that the risk mitigation strategies, which address CYP3A and P-gp active substances and hormonal contraceptives, listed in the approved labeling for drug-drug interactions (DDIs) are applicable to adult and pediatric patients 12 years of age and older with solid tumors with an NTRK gene fusion. The Applicant did not address the PMRs or PMCs for (b) (4) .

6.2.2.3. Outstanding Issues

The Applicant's Position:
None.

The FDA's Assessment:
None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

No new information is provided in the current submission. General Pharmacology and Pharmacokinetic Characteristics were previously described in the Summary of Clinical Pharmacology and Summary of Biopharmaceutic Studies from the initial ROS1 NDA.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:
Adult: Evidence of effectiveness was obtained from pivotal trial TRIDENT-1 in patients with *NTRK*-positive solid tumors (Section 8.1.2.8).

To support the clinical efficacy observed with repotrectinib, exposure-response analysis was performed based on data from pooled EXP-5 (TRK TKI-naïve) and EXP-6 (TRK TKI-pretreated) population in the TRIDENT-1 study.

For *NTRK*-positive solid tumors, the exposure-OR relationship was shallow, but the effect of exposure on OR was trending to be positive (Figure 12). E-R model predicted ORR (TKI-naïve 62.4%; TKI-pretreated 52.6%) at the recommended dose of 160 mg QD/BID was similar to the observed pooled ORR [TKI-naïve 57.5% (23/40); TKI-pretreated 50.0% (24/48)] and the observed ORR at RP2D [TKI-naïve 63% (22/35); TKI-pretreated 52% (23/44)].

There was a trend of longer PFS with increased exposure (Figure 13). The median probability of PFS increased with dose and the 160 mg QD/BID dosing regimen showed higher median probability of PFS than 160 mg QD (Figure 14).

The predicted OR and PFS at 120 mg QD/BID and 80 mg QD/BID support the recommended dose reductions to 120 mg or 80 mg for management of adverse events.

Adolescent:
Efficacy from CARE Study: Activity was observed in pediatric patients with *NTRK* alterations, as demonstrated in the CARE interim results. 6 of 16 *NTRK*-positive patients were efficacy evaluable with centrally confirmed measurable disease with at least 6 months of follow-up from their first post baseline scan. Of these 6 patients, 2 patients achieved confirmed responses. Based on a modified *NTRK* efficacy evaluable dataset, which included patients with measurable disease and < 6 months follow-up from the first post-baseline scan, additional responses (1 confirmed PR; 3 unconfirmed ongoing PR) were observed (Section 8.1.3.2).

Similarity in response to repotrectinib treatment: The repotrectinib exposures in pediatric (< 12 years) and adolescent (≥ 12 to < 18 years) patients from CARE study were comparable to those in adult patients from TRIDENT-1 Study (Section 6.2.1). The similar exposure between pediatric/adolescents and adult patients was associated with a consistent clinical profile of repotrectinib (i.e., efficacy and safety) across pediatric and adult patients with *NTRK*-positive solid tumors. Despite the small number of pediatric and adolescent patients treated for *NTRK*-positive solid tumors, there is an initial encouraging clinical benefit across pediatric and adolescent patients similar to that seen in adults. The comparable efficacy response between adolescent and adult patients are expected given the totality of nonclinical and clinical evidence indicating that *NTRK* is the primary oncogenic driver across tissue histologies harboring *NTRK* fusions. The clinical benefit observed in the pediatric and adolescent patients from CARE study in combination with the consistent efficacy between young and older adults (i.e., age did not have significant effect on efficacy in the exposure-response efficacy analysis) with diverse tumor histologies from TRIDENT-1 study suggest repotrectinib is likely an age-agnostic treatment for *NTRK*-positive solid tumors.

Based on PK exposure-match (PopPK-based simulations, Section 17.4) and expected similarity of response to treatment, the same adult dose for adolescents is expected to provide similar efficacy as adult patients.

The Applicant's Position:
In summary, the E-R efficacy analysis established the relationship between repotrectinib exposure and efficacy (i.e., OR and PFS), and predicted the similar ORR as the observed ORR from TRIDENT-1 at the recommended dose. The same adult dose for adolescents is expected to provide similar efficacy as adult patients based on the totality of exposure-match and similarity of response to treatment. Therefore, the clinical pharmacology program, including E-R analyses for efficacy and PopPK-based simulations, provides the supportive evidence of a clinically meaningful benefit of repotrectinib in adult and adolescent patients with *NTRK*-positive solid tumors.

The FDA's Assessment:

The Applicant's exposure-response model predicted slightly higher ORRs than what was observed in TRIDENT-1 but was reasonably comparable (i.e., 2-5% higher). There was a positive relationship between exposure and efficacy; however, the relationship was not statistically significant and should be interpreted with caution. Subgroup analyses comparing patients who were escalated to 160 mg BID versus those who remained at 160 mg QD due to toxicity suggested that efficacy is maintained at the lower exposures associated with the 160 mg QD dosage. The ORRs were not significantly different (62% [95% CI: 38, 82] for 160 mg BID versus 64% [95% CI: 35, 87]) for 160 mg QD; however, the 160 mg BID group had more complete responses (4 versus 1) and fewer Grade ≥3 and serious adverse events. This may support the Applicant's prediction of continued efficacy at lower dosages (e.g., following dosage reductions).

The Applicant's use of population PK simulations to match pediatric and adult exposures supported the choice to use and propose same dosage in adult and pediatric patients 12 years of age and older. Preliminary efficacy and safety data from CARE suggest this approach is reasonable as 2 out of 6 pediatric patients had responses at the time of submission and the safety profile was consistent with adult population. FDA therefore agrees that the clinical observation, exposure-response analyses, and population PK simulations provide adequate supportive evidence of a clinically meaningful benefit of repotrectinib in the adult and pediatric patients 12 years and older. See Section 17.4.1 for further details and FDA review of the Applicant's exposure-response and population PK analyses.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

The proposed dosing regimen of 160 mg QD/BID for both adult and adolescent is supported by clinical efficacy and safety data as well as the population PK and E-R analyses (refer to above Section 0 for details of dose justification).

The FDA's Assessment:

The majority (90%) of patients in the Applicant's exposure-response analyses received the 160 mg QD/BID dosage; thus, the exposure-response analyses may be limited in terms of identifying an optimized dosage. However, there were trends suggesting that higher exposures resulted in a higher incidence of AEs including dizziness and neurological AEs, both of which are criteria used to determine patients' eligibility to receive the full 160 mg BID dosage after 2 weeks of treatment at 160 mg QD. Overall, FDA agrees that the proposed dosing regimen demonstrates a favorable risk-benefit profile in adolescent and adult patients aged 12 and older.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g., race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:
The initial PopPK model for initial ROS1 NDA for repotrectinib was updated by adding additional data from Phase 1/2 study TRIDENT-1 (TPX-0005-01, data cutoff 19-Dec-2022) and adding pediatric study CARE [TPX-0005-07] to the dataset. The updated PopPK analysis confirmed the prior results on the intrinsic factors including age (≥ 18 years), body weight, sex, race/ethnicity, renal impairment (mild and moderate), hepatic impairment (mild), and genetic mutation. No dose adjustment is required for these intrinsic factors. In the update PopPK analysis, pediatric patients (range 0.8 to 16 years) had more autoinduction in CL as indicated by the significant age effect on the CLMAX (i.e., increased CLMAX with increased age < 18 years). However, the age effect was not considered to be clinically relevant in adolescents as shown by a maximum of 13% increase in CLMAX in a typical 12-year-old adolescent compared to adults. The PopPK model was used to conduct simulations to demonstrate that adult and adolescent exposures (Cmax, Cmin, Cavg after first dose and steady state) were similar at the same flat dosing regimens (i.e., 160, 120 and 80 mg QD/BID). Therefore, no dose adjustment is required for adolescent patients (i.e., age ≥ 12 years).

The Applicant's Position:

Based on the population PK analysis, no dose adjustment is required for intrinsic factors including age ≥ 12 years (i.e., the same dose for adolescents and all ages of adults), body weight, sex, race/ethnicity, renal impairment (mild and moderate), hepatic impairment (mild), and genetic mutation.

The FDA's Assessment:

FDA generally agrees with the Applicant. See Section 6.2.2 and Section 17.4.1 for more details.

NTRK Fusion Partner
Patients in TRIDENT-1 had NTRK status prospectively assessed using central next-generation sequencing (NGS) or local NGS testing, polymerase chain reaction (PCR), or fluorescence in situ hybridization (FISH). A total of 16 NTRK1 fusion partners, 5 NTRK2 fusion partners, and 9 NTRK3 fusion partners were identified across the TKI-Naïve (Pooled EXP 5, N = 40) and TKI-Pretreated (Pooled EXP 6, N = 48) cohorts. In the TKI-Naïve cohort, 1 patient reported by the Applicant as having multiple fusion partners had a SPECC1L/SPECC1L-ADORA2A-NTRK3 fusion, 1 patient had a PEAR1-NTRK1 fusion only detected by local FISH, and 2 patients did not have fusion partner determined by either local or central testing (not tested by local/QC failure by central and not detected by local/not tested by central). In the TKI-Pretreated cohort, 1 patient reported by the Applicant as having multiple fusion partners had a TRIM24-NTRK3 fusion based on local testing

and a SLC34A2-ROS1 based on central testing. Responses were observed across most NTRK fusion partner subgroups containing more than a single patient, supporting the proposed indication (Section 8.1.2.15, **Error! Reference source not found.** and **Error! Reference source not found.**).

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Baseline Resistance Mutations in TKI-Pretreated Patients

Resistance mutations at baseline were assessed in 47/48 TKI-pretreated patients (pooled EXP-6 cohort) based on local and/or central testing. Resistance mutations were identified in 26 (55%) TKI-pretreated patients assessed and consisted of 17 patients with 1 solvent front mutation (SFM; 4 NTRK1^{G595R}, 9 NTRK3^{G623R}, 3 NTRK3^{G623E}, 1 NTRK3^{G623L}), 7 patients with 2 SFMs (5 NTRK3$^{G623E/G623R}$, 1 NTRK3$^{G623L/G623R}$, 1 NTRK3$^{G623V/G623R}$), 1 patient with and SFM and gatekeeper mutation (1 NTRK1$^{G595R/F589L}$), and 1 patient with a mutation (NTRK1^{G667C}) that has been reported to impact the catalytic region of the kinase domain by occurring in the amino acid preceding the activation loop DFG motif (xDFG mutation) (Somwar 2020). Responses (PR) were observed in patients with NTRK3 SFMs (14 or 20, 70%) but not in patients with NTRK1 resistance mutations (0 of 6, 0%) (**Error! Reference source not found.**). Additional data on response in patients with NTRK1 and NTRK2 resistance mutations (b) (4)

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Table 4: FDA Best Overall Response by NTRK Gene and Resistance Mutation in TKI-Pretreated Patients Positive for NTRK Resistance Mutations (N=426), TRIDENT-1

NTRK Gene	Resistance Mutation	N	Best Response (N)		
			PR	SD	PD
NTRK1	G595R	4	0	2	2
	G667C	1	0	0	1
	G595R, F589L	1	0	1	0
NTRK3	G623E	3	1	0	1
	G623E, G623R	5	3	1	0
	G623L	1	0	1	0
	G623L, G623R	1	1	0	0
	G623R	9	9	0	0
	G623V, G623R	1	0	1	0

Source: Reviewer analysis using TRIDENT-1 MI.xpt, ADSL.xpt, and ADEFF.xpt.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data*:*

Food-Drug Interactions

Updated PopPK and E-R analysis for *NTRK*-positive solid tumors confirmed that the food effect is not clinically relevant (same as *ROS1*-positive NSCLC).

PopPK-based simulations showed the food effect was attenuated on Day 14 or at steady state following 160 mg BID compared with 160 mg single dose. The ratio of geometric means of fed/fasted were 1-2 (1.79, 1.05, 1.46 for C_{max}, C_{min}, and C_{avg}, respectively) at steady state versus 2-3 (2.81, 3.24, 2.03 for C_{max}, C_{min}, and C_{avg}, respectively) after single dose. The patients with unknown food status showed comparable single dose or steady-state exposures to the patients with fed status.

The impact of food effect on efficacy and safety was further evaluated with E-R analysis in patients with *NTRK*-positive solid tumors. The model-predicted probabilities of all evaluated efficacy endpoints and AEs are overlapping among the different food conditions with relatively small numeric differences and supports repotrectinib dosing without regard to food.

In summary, based on the totality of the clinical benefit/risk assessment of the pivotal TRIDENT-1 study where efficacy and safety data of repotrectinib at recommended dose were evaluated without regard to food and PopPK and E-R evaluations suggesting no clinically meaningful impact of food on efficacy and safety, repotrectinib can be administered without regard to food.

Drug-Drug Interactions

Refer to approved USPI for the drug interactions. No new data are presented in this sNDA submission.

The Applicant's Position:

Updated PopPK and E-R analysis for *NTRK*-positive solid tumors confirmed that the food effect is not clinically relevant (same as *ROS1*-positive NSCLC). Repotrectinib can be taken with or without food.

Refer to approved USPI for the drug interactions.

The FDA's Assessment:

FDA agrees that food does not have a clinically meaningful effect on repotrectinib PK and that this submission did not include new drug-drug interaction data.

X

Clinical Pharmacology Reviewer
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7. Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 5: Applicant Table of Clinical Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
Primary Study to Support Efficacy and Safety								
TPX-0005-01 (TRIDENT-1)	NCT03093116	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						
	Phase 1	Phase 1a dose escalation (fasted conditions); Phase 1b food-effect substudy; Phase 1c dose escalation (fed conditions); Midazolam DDI substudy	All phases - oral administration; 28-day cycles Phase 1a: 40 mg QD – 200 mg BID Administered under modified fasted conditions Phase 1b: Food effect: single dose administered with either high-fat meal or under modified fasted conditions. After food effect: 40 mg - 160 mg QD under modified fasted conditions. Phase 1c:	Primary: DLT MTD RP2D Secondary Safety and tolerability PK Preliminary efficacy	Until disease progression, intolerable toxicity, death, or withdrawal from treatment.	Phase 1a,b,c: 93 Midazolam DDI Substudy: 10	Patients with confirmed locally advanced or metastatic solid tumor that harbors an *ALK, ROS1, NTRK1, NTRK2,* or *NTRK3* gene rearrangement	8 centers 3 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
			120 mg QD – 160 mg QD/BID[a] Administered with food Midazolam DDI Substudy: 160 mg QD/BID[a] repotrectinib, 5 mg midazolam, Day -2 and Day 22					
	Phase 2	Open-label, multi-center, efficacy, and safety. Expansion phase in patients with *ROS1*+ and *NTRK*+ solid tumors	oral administration; 28-day cycles 160 mg QD/BID[b]	Primary[c]: ORR (BICR) Secondary: DOR, CBR, TTR PFS, OS Safety and Tolerability IC-ORR IC-PFS PK PROs	Until disease progression, intolerable toxicity, death, or withdrawal from treatment	Total: 417 (416 dosed) *ROS1+* NSCLC (EXP-1 to EXP-4): 294 (293 dosed) *NTRK+* Solid Tumors (EXP-5, EXP-6): 104 Ongoing[d]	*ROS1+* NSCLC: EXP-1: TKI-naïve EXP-2: 1 prior ROS1 TKI + 1 Pt-based chemo EXP 3: 2 prior ROS1 TKI/No chemo or IO EXP 4: 1 prior ROS1 TKI/No chemo *NTRK+* solid tumors: EXP-5:	152 centers 19 countries

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers/ Countries
							TRK TKI-naïve EXP-6: TRK TKI-pretreated	
		Studies to Support Safety						
TPX-0005-07 (CARE)	NCT04094610	Phase 1/2, open-label, single-arm, multicenter, multicohort	Phase 1: DL1: 160mg QD DL2: 160mg QD for 14 days then, if tolerated 160 mg BID for 28 days If DLT ≥ 2: 120 mg QD Phase 2: 12 to ≤ 25 y and > 50Kg: repotrectinib adult RP2D Route: Oral	Phase 1: Safety, tolerability, pediatric RP2D, PK Phase 2: Anti-tumor activity	Until disease progression, intolerable toxicity, death, or withdrawal from treatment	Total: 26 Phase 1: 10 Completed Phase 2: 16 Ongoing[d]	Pediatric and young adult patients with advanced or metastatic solid tumors, primary central nervous system (CNS) tumors, or ALCL with *ALK*, *ROS1*, or *NTRK* alterations	28 centers 6 countries

Abbreviations: ALCL = anaplastic large cell lymphoma; BA = bioavailability; BCR = clinical benefit rate; BE = bioequivalence; BICR = Blinded Independent Central Review; BID = twice daily; DDI = drug-drug interaction; DLT = dose-limiting toxicities; DOR = duration of response; EXP = expansion cohort; IC-ORR = intracranial overall response rate; IC-PFS = intracranial progression-free survival; IO = immunotherapy; MTD = maximum tolerated dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; Pt = platinum; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = Recommended Phase 2 Dose; sNDA = supplemental New Drug Application; TKI = tyrosine kinase inhibitor; TTR= time to response.

[a] 160 QD for the first 7 days; if well tolerated and no DLTs were observed, an increase to 160 mg BID is permitted.

[b] 160 QD for the first 14 days; an increase to 160 mg BID is permitted based on patient safety and tolerability and assuming specific criteria are met while on 160 mg QD (no evidence of grade ≥ 3 TRAE, unmanageable grade ≥ 2 dizziness, ataxia, or paresthesia; or grade ≥ 3 clinically meaningful lab abnormalities).
[c] By RECIST 1.1. d Status ongoing as of the 19-Dec-2022 data cutoff date.

The Applicant's Position:

The analyses described in the Integrated SAP of the pivotal, ongoing TRIDENT-1 study (TPX-0005-001), a Phase 1/2, first-in-human, open-label, multi-center study evaluating the safety, PK, and anti-tumor activity of repotrectinib in patients with advanced solid tumors harboring *ROS1*, *ALK*, or *NTRK* rearrangements, serve as the primary source of evidence of efficacy and safety for this application to support approval for the treatment of adult patients with advanced or metastatic malignancies whose tumors are *NTRK*-positive. For the integrated analysis plan, patient data were pooled from Phase 1 and Phase 2 of the TRIDENT-1 study. All *NTRK*-positive patients who initiated treatment on and before 19-April-2022 were included for the primary efficacy analysis to allow ≥ 6 months of follow-up after the first post-baseline scan and at least 8 months of follow up from the time of enrollment across all cohorts with all responding patients having completed at least 6 months of follow up.

The integrated efficacy analysis focuses on the *NTRK*-positive solid tumor patients, including the following EXP cohorts for the primary efficacy analysis:

- Pooled EXP-5 (TKI-naïve *NTRK*-positive solid tumors): 40 patients (5 from Phase 1 and 35 from Phase 2)
- Pooled EXP-6 (TKI-pretreated: *NTRK*-positive solid tumors with 1 prior TKI and no prior platinum-based chemotherapy): 48 patients (4 from Phase 1 and 44 from Phase 2)

Preliminary efficacy data from the CARE study (TPX-0005-07; n = 13) for the *NTRK*-positive solid tumor pediatric patient population are presented as supportive for the proposed indication, as these cohorts have yet to meet the protocol-defined total patient population.

The primary safety dataset supporting the assessment of safety of repotrectinib comprises pooled results of 519 patients from Phase 1 and Phase 2 of TRIDENT-1, including all patients who received at least 1 dose of repotrectinib.

Preliminary safety data from the pediatric study CARE (TPX-0005-07, n = 26) provide supportive evidence for the assessment of the repotrectinib safety profile in adolescent patients.

Given the seriousness of the disease in this rare patient population as well as the high unmet medical need in the TRK TKI-naïve and TKI-pretreated settings, the clinical development program is considered adequate to evaluate the benefit/risk of repotrectinib for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic *NTRK*-positive solid tumors.

The FDA's Assessment:

FDA agrees with the Applicant's description of the population in the integrated efficacy dataset from the TRIDENT-1 study. FDA clarifies that as per the integrated statistical analysis plan (SAP), patients had a minimum of 6 months of follow-up after the first post-baseline scan, rather than first confirmed response. However, all responding patients except for one (5.2 months) had 6

months of follow-up from the time of initial response.

FDA clarifies that supportive efficacy data from the CARE study included 16 patients with NTRK+ solid tumors of which 13 received the RP2D. Only 6 (n=2 <12 years old and TKI-naïve; n=4 <12 years old and TKI-pretreated) of these 13 patients were evaluable for efficacy with centrally confirmed measurable disease with at least 6 months of follow-up from their first post-baseline scan. Of the 13 patients treated at the RP2D, 7 patients were 12-17 years of age.

FDA clarifies that the overall safety population (n=519) includes all patients treated with at least one dose of repotrectinib at any dose. The primary safety analysis population for inclusion in the USPI for repotrectinib included 426 patients treated with at least one dose of repotrectinib at the RP2D. The three subgroups included in the safety population were 104 patients with NTRK+ solid tumors, 320 patients with ROS1+ NSCLC and 2 patients with other solid tumors (1 centrally discordant ROS1+ NSCLC and 1 ROS1+ pancreatic cancer). Refer to Section 8.2 regarding FDA's approach to the safety analysis.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. TPX-0005-01 (TRIDENT-1)

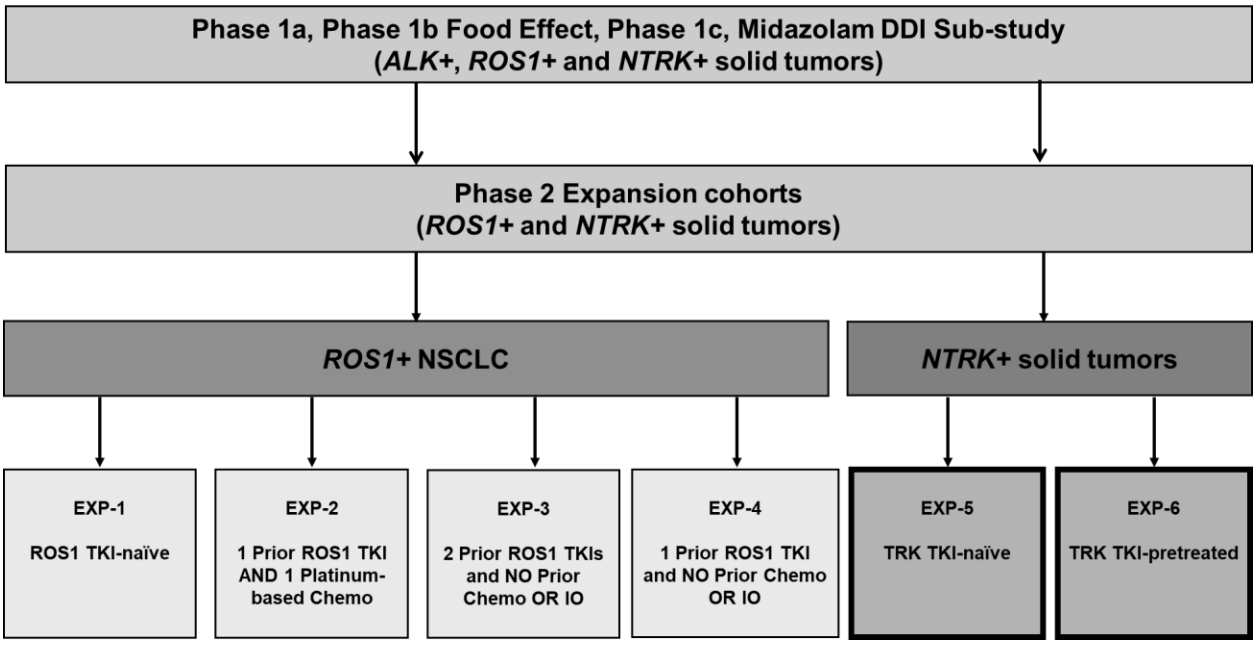
8.1.1.1. Trial Design

The Applicant's Description:

Basic Study Design

TRIDENT-1 is a Phase 1/2, open-label, multicenter, safety, PK, pharmacodynamic, and anticancer efficacy exploration study of repotrectinib as a single agent in patients with *ALK*-positive, *ROS1*-positive, *NTRK1*-positive, *NTRK2*-positive, or *NTRK3*-positive advanced solid malignancies. The study consists of 2 parts, Phase 1 and Phase 2.

Figure 1: Applicant Schema of Phase 1/2 Study TRIDENT-1



Abbreviations: ALK = anaplastic lymphoma kinase; chemo = chemotherapy; DDI = drug-drug interaction; EXP = expansion cohort; IO = immunotherapy; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.

Trial location

This study is being conducted at 152 sites globally, including the US, UK, Canada, the European Union, Asia, and Australia.

The FDA's Assessment:
TRIDENT-1 is an ongoing study which includes patients with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic NTRK+ solid tumors. NTRK fusion was detected in a Clinical Laboratory Improvement Amendments (CLIA) lab or equivalent.

From the Phase 1 and 2 portions of TRIDENT-1, 40 patients with NTRK+ solid tumors who were TKI-naive were enrolled into pooled Cohort EXP-5 (5 from Phase 1 and 35 from Phase 2). An additional 48 patients with NTRK+ solid tumors who were TKI-pretreated were enrolled into pooled Cohort EXP-6 (4 from Phase 1 and 44 from Phase 2). All patients included in the primary efficacy analysis were treated at the RP2D. This study allowed for an assessment of tumor shrinkage (as tumors generally do not shrink in the absence of therapy); however, the single-arm study did not allow for assessments of PFS or OS due to lack of a control arm.

Eligibility Criteria

The Applicant's Description:
In Phase 1, eligible patients were adults aged 18 years or older (or ≥ 20 years of age as required by local regulation) with a histologically or cytologically confirmed diagnosis of locally advanced or metastatic solid tumor (including primary CNS tumors; Stage IV, AJCC v.7) that harbors an *ALK*, *ROS1*, *NTRK1*, *NTRK2*, or *NTRK3* gene rearrangement. At the time of enrollment, all patients must have had archival tissue sample or de novo tissue sample available for central laboratory confirmation of *ALK*, *ROS1*, or *NTRK* rearrangement status, an ECOG performance status of 0 or 1, and at least one measurable lesion according to RECIST v1.1. Participants with treated brain metastases must have had a 14-day washout period from whole-brain radiation therapy to be included in the study.

In Phase 2, eligible patients were aged 12 years or older (or ≥ 20 years of age as required by local regulation) with a histologically or cytologically confirmed diagnosis of locally advanced, or metastatic solid tumor (including primary CNS tumors) that harbors a *ROS1* or *NTRK1*-3 gene fusion. At the time of enrollment, all patients must have had archival tissue sample (or have de novo tissue sample available at the time of screening) for central laboratory confirmation of *ROS1* or *NTRK* rearrangement status, an ECOG performance status of 0 or 1, and at least 1 measurable lesion according to RECIST v1.1 prospectively confirmed by BICR prior to enrollment.

Key exclusion criterion included symptomatic brain metastases or leptomeningeal involvement; peripheral neuropathy, paresthesia, dizziness, dysgeusia, muscle weakness, ataxia grade ≥ 2; history of extensive, disseminated, bilateral, or presence of CTCAE grade 3 or 4 interstitial fibrosis or ILD; current use or anticipated need for drugs that are known to be strong CYP3A inhibitors or inducers.

The FDA's Assessment:
FDA generally agrees with the Applicant's description of the eligibility criteria with the following clarifications. Patients eligible for Phase 2 must have NTRK gene fusion determined by NGS or qPCR. Tumor tissue tested by FISH required confirmatory testing by central laboratory. Although patients 12-17 were eligible to enroll in the Phase 2 portion, none were enrolled.

Patients in pooled EXP-5 were allowed to have received any number of prior lines of chemotherapy or immunotherapy but must not have received prior TKI therapy. Patients in pooled EXP-6 must have progressed on or were intolerant to 1 or 2 prior TKI therapies limited to entrectinib, larotrectinib, selitrectinib (LOXO-195) and cabozantinib, though other prior TKI therapies may have been allowed after discussion with Sponsor Medical Monitor. Patients were allowed to receive any number of prior lines of chemotherapy or immunotherapy.

In general, the trial allowed for the enrollment of patients with good performance status, so the results of this study should not necessarily be extrapolated to patients with poor performance status. Additionally, the study excluded patients with clinically significant cardiovascular disease and known active infections requiring treatment (including for example, HIV).

8.1.1.2. Study Endpoints

The Applicant's Description:
A brief summary and description of key efficacy endpoints are provided in Table 6. Detailed methodology for summary and statistical analyses are provided in the TPX-0005-01 Integrated SAP, including full definitions and censoring rules.

Table 6: Applicant Definitions of Key Efficacy Endpoints in TRIDENT-1

Endpoint	Definition
ORR	The proportion of patients with BICR-confirmed CR or PR; a confirmed response is a response that persists on repeat-imaging ≥ 4 weeks (28 days) after initial documentation of response.
DOR	The first date of objective response (either CR or PR) to first documentation of radiologic disease progression (PD), or death, as assessed by RECIST v1.1.
TTR	The time from the first dose of repotrectinib to the first documentation of objective response (either CR or PR), as assessed by RECIST v1.1.
PFS	The time from the first dose of repotrectinib to first documentation of radiologic disease progression or death.
IC-ORR	The proportion of patients with a ≥ 30% reduction from baseline (PR/CR) in intracranial target lesions, as assessed by modified RECIST v1.1, in the subset of patients with baseline measurable CNS metastases by BICR.

Endpoint	Definition
CBR	The proportion of patients with CR, PR, or Stable Disease, as assessed by RECIST v1.1.
OS	The time from the first dose of repotrectinib to the date of death (on study or in long-term follow-up).

Abbreviations: BICR = Blinded Independent Central Review; CBR = clinical benefit rate; CNS = central nervous system; CR = complete response; DOR = duration of response; IC-ORR = intracranial objective response rate; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1= Response Evaluation Criteria in Solid Tumors, Version 1.1; TTR = time to response.

The primary endpoints for Phase 1 were first cycle DLTs to determine the MTD and the RP2D. Secondary efficacy endpoints included ORR, as assessed by BICR using RECIST v1.1, and CBR in patients with advanced solid tumors that harbor a *ROS1*, *NTRK1-3*, or *ALK* gene rearrangement. Other key efficacy variables assessed included DOR, TTR, PFS, OS, and IC-ORR.

The primary endpoint for Phase 2 is ORR, as assessed by BICR using RECIST v1.1, in each patient population expansion cohort of advanced solid tumors that harbor a *ROS1* or *NTRK1-3* gene rearrangement. The secondary endpoints include DOR, TTR, CBR, IC-ORR, IC-PFS, PFS, OS, and PROs (EORTC-QLQ-C30 and QLQ-LC-13).

Safety and tolerability are assessed based on extent of exposure, treatment compliance, AEs, clinical laboratory data, physical examinations, vital signs, ECG parameters, ECHO/MUGA scan, pregnancy, concomitant medications and procedures, survival follow-up, and death report.

Assessment of AEs includes type, incidence, severity (graded by the CTCAE, v4.03), timing, seriousness, and relatedness. Adverse events were assessed at every clinic visit.

Complete physical examination, neurological examination, ECOG performance scale assessment, extensive clinical laboratory assessments (hematology, chemistry, coagulation, urinalysis, serum pregnancy tests [for WOCBP] and hypogonadism blood samples [male patients only]) and vital signs (body temperature, blood pressure, heart rate, respiratory rate, pain level [0 to 10], body weight, and height) provided a complete assessment of safety and tolerability in the study.

The FDA's Assessment:

FDA agrees with the Applicant's description of study endpoints. ORR was the primary efficacy endpoint used for regulatory purposes. ORR can be assessed in single-arm studies because tumors generally do not shrink in the absence of therapy. Although ORR in single-arm trials has some limitations (e.g., with respect to assessing risk/benefit in a single-arm trial), ORR has been used, depending on the context, for both accelerated approvals and regular approvals. Considerations for use of ORR include very high magnitude of effect (which may include complete responses), unmet need, relative favorability of adverse event profile, and rarity of the population, such that there may not be equipoise to conduct a randomized trial.

FDA notes that time-to-event endpoints such as PFS and OS are difficult to interpret in a non-randomized setting, and therefore results are considered descriptive only and not to be considered for labeling purposes. Per the TRIDENT-1 protocol, patient's imaging studies were reviewed by a BICR.

Although PROs (EORTC-QLQ-C30 and QLQ-LC-13) were a secondary endpoint, no formal testing was conducted.

8.1.1.3. Statistical Analysis Plan and Amendments

The Applicant's Description:
The primary evidence of the efficacy and safety of repotrectinib is based on the pre-specified analysis of pooled efficacy and safety data from the Phase 1 and Phase 2 portions of the ongoing TRIDENT-1 study (TPX-0005-01), detailed in the Integrated NTRK SAP (v1.0, dated 24 February 2023) and agreed with the Agency at the pre-sNDA meeting held on 12 October 2023 (Ref ID 5261887).

To support this sNDA, two expansion cohorts were used to assess the primary evidence for efficacy, i.e., Pooled EXP-5 (TRK TKI-naïve) and Pooled EXP-6 (TRK TKI-pretreated). A summary of the primary efficacy analysis sets for the pooled efficacy populations (Pooled EXP-5 and Pooled EXP-6), along with the pooling criteria, is provided in Table 7.

Table 7: Applicant Integrated Efficacy Analysis Sets and Pooled Expansion Cohorts for Phase 1 and Phase 2 of the TRIDENT-1 Study

Expansion Cohort (Pooled Phase 1 and Phase 2)	Pooling Criteria for the Phase 1 and Phase 2 Integrated Efficacy Analysis Set	Number of Patients in the Efficacy Analysis Set
NTRK-positive TKI-naïve solid tumor cohort (Pooled EXP-5)	Cohort included all *NTRK*-positive metastatic or locally advanced solid tumor patients in the Phase 1 and Phase 2 portions of the TRIDENT-1 study who met the following criteria: 1) Confirmation by central laboratory (Almac) test for *NTRK* rearrangement per the requirement in each phase of TRIDENT-1 study protocol. a) In Phase 1, central confirmation of gene fusion status was not required for enrollment. However, patients with *NTRK*-positive based on local FISH test will be retested retrospectively by central laboratory. Only patients with confirmed *NTRK* positivity by central laboratory will be included in the integrated efficacy analysis, in addition to those *NTRK*-positive patients tested locally by NGS or qPCR.	40 patients (5 from Phase 1 and 35 from Phase 2)

Expansion Cohort (Pooled Phase 1 and Phase 2)	Pooling Criteria for the Phase 1 and Phase 2 Integrated Efficacy Analysis Set	Number of Patients in the Efficacy Analysis Set
	b) In Phase 2, patients entering with local results by FISH must have gene fusion status confirmed prospectively prior to enrollment. 2) No prior exposure to a *NTRK* TKI. 3) Started treatment at least 8 months prior to the data cutoff date (19-Apr-2022); 6 months of follow-up for tumor assessment after first post-baseline scan.	
NTRK-positive TKI-pretreated solid tumor cohort (Pooled EXP-6)	Cohort included all *NTRK*-positive metastatic or locally advanced solid tumor patients in the Phase 1 and Phase 2 portions of the TRIDENT-1 study who met the following criteria: 1) Confirmation by the central laboratory test for *NTRK* rearrangement per the requirement in each phase of TRIDENT-1. a) In Phase 1, central confirmation of gene fusion status was not required for enrollment. However, patients with *NTRK*-positive based on local FISH test will be retested retrospectively by central laboratory. Only patients with confirmed *NTRK* positivity by central laboratory will be included in the integrated efficacy analysis, in addition to those *NTRK*-positive patients tested locally by NGS or qPCR. b) In Phase 2, patients entering with local results by FISH must have gene fusion status confirmed prospectively prior to enrollment. 2) Disease progression or intolerant to at least 1 prior line of a *NTRK* TKI treatment, including: entrectinib, larotrectinib, selitrectinib (LOXO-195), and cabozantinib. Other prior TRK TKIs that are not listed may be allowed after discussion with the Sponsor Medical Monitor. 3) Started treatment at least 8 months prior to the data cutoff date (19-Apr-2022); 6 months of follow-up for tumor assessment after first post-baseline scan.	48 patients (4 from Phase 1 and 44 from Phase 2)

Primary Efficacy Analysis:
The TRIDENT-1 study was designed to evaluate clinical benefit of repotrectinib in *NTRK*-positive solid tumors which are very rare populations with significant unmet need. For this single arm study, targets for each cohort were determined mainly by sample size determination using approximations from point estimates of the most commonly used standard of care treatments within each setting in order to infer clinical benefit, as predefined in the SAP:

- **EXP-5 (TRK TKI-naïve, *NTRK*-positive solid tumors):** 55 TRK TKI-naïve *NTRK*-positive eligible solid tumor patients will be enrolled into the cohort. If the ORR is 35% or less, then it is not considered as effective. If 27 patients out of 55 patients have a confirmed

objective response (ORR = 49.1%; 95% CI: 35.4 – 62.9) where the lower limit of the 95% CI is > 35%, repotrectinib is considered to be efficacious in this expansion cohort.

- **EXP-6 (TRK TKI-pretreated, *NTRK*-positive solid tumors):** 40 TRK TKI-pretreated *NTRK*-positive eligible solid tumor patients will be enrolled into the cohort with 1 or 2 prior TRK TKI treatments. For this cohort, if the ORR is 10% or less, then it is assumed that repotrectinib is not effective. If 9 out of 40 patients have a confirmed objective response (ORR = 22.5%; 95% CI: 10.8 – 38.5) where the lower limit of 95% CI >10%, repotrectinib will be considered efficacious in this cohort.

Safety Analysis:

- The Safety Analysis Set includes all patients who are enrolled and have received any dose of repotrectinib in either the Phase 1 or Phase 2 portion of TRIDENT-1.
    1. In addition, safety data are presented for the following patient subpopulations:
        - Patients who were dosed with at least 1 dose of repotrectinib with *ROS1*-positive NSCLC (N = 352) or *NTRK*-positive solid tumors (N = 113), or other treated patients (N = 54).
        - Patients receiving at least 1 dose of repotrectinib at the RP2D,
        - *ROS1*-positive solid tumor patients receiving at least 1 dose of repotrectinib at the RP2D, and
        - *NTRK*-positive solid tumor patients receiving at least 1 dose of repotrectinib at the RP2D.

The FDA's Assessment:

FDA generally agrees with the Applicant's description for the integrated SAP; however, FDA clarifies that the formal hypothesis test to compare ORR with the threshold at 35% for EXP-5 and 10% for EXP-6 was not considered in FDA's evaluation. FDA does not consider inferential procedures to evaluate treatment effects observed in a single-arm study. FDA adds that 95% CI of ORR was estimated by the Clopper-Pearson method. Median DOR and 95% CI of the median were estimated by Kaplan-Meier methodology based on a linear transformed CI for the survival function. In addition, DOR was censored at the date of last tumor assessment if there was no documented progression prior to start of new anticancer therapy or tumor-related surgery, or if death or radiologic progression happens after two or more consecutive missing visits for tumor assessment.

FDA clarifies that the primary efficacy analysis population for inclusion in the USPI for repotrectinib consisted of 88 patients with NTRK+ solid tumors treated with at least one dose of repotrectinib at the RP2D. The primary safety analysis population for inclusion in the USPI for repotrectinib consisted of 426 patients treated with at least one dose of repotrectinib at the RP2D in TRIDENT-1. This group consisted of 320 patients with ROS1+ NSCLC, 104 patients with NTRK+ solid tumors, and 2 patients with other solid tumors (centrally discordant ROS1+ NSCLC

and ROS1+ pancreatic cancer).

8.1.1.4. Protocol Amendments

The Applicant's Description:
The original global protocol for the TRIDENT-1 study (dated 29 September 2016) was amended 12 times as of the data cutoff date of 19-Dec-2022 for this sNDA. Since the initial repotrectinib NDA (Jun 2022 DCO), the TRIDENT-1 protocol has been amended one time (version 13.0, dated 15-Nov-2022). A summary of key changes is briefly described in Table 8. The Applicant does not believe that any of the amendments impacted the integrity of the trial or the interpretation of the primary efficacy endpoint or safety results.

Table 8: Applicant TRIDENT-1 Protocol Amendments – Key Changes

Protocol Version Date	Description
Version 13.0 15 November 2022	• Clarified the eligibility criteria allowing different country-specific requirements for age and legal consent. • Contraception guidelines were aligned between Phase 1 and Phase 2.

The FDA's Assessment:
FDA agrees with the Applicant's description of protocol amendments that have occurred since the DCO of the initial approval. FDA reviewed the previous 12 amendments for the TRIDENT-1 study and concluded that none of the changes significantly impacted the NTRK+ patient cohort that supports this application.

8.1.2. Study Results (TRIDENT-1)

8.1.2.1. Compliance with Good Clinical Practices

Data:
The TRIDENT-1 study was conducted in accordance with the US FDA regulations, the ICH E6 GCP Guideline), and applicable local, state, and federal laws, as well as other applicable country laws, and the principles of the Declaration of Helsinki.

The Applicant's Position:
The TRIDENT-1 study was GCP compliant.

The FDA's Assessment:
FDA agrees with the Applicant's position that the study appeared to be conducted using good

clinical practice guidelines which is located in the CSR addendum Section 5.

8.1.2.2. Financial Disclosure

Data:
TRIDENT-1 study financial interests/arrangements with clinical investigators were tracked and disclosed. Details of financial disclosure are presented in Section 17.2.

The Applicant's Position:
The integrity of the TRIDENT-1 study data was not affected by the financial interest of the Investigators.

The FDA's Assessment:
FDA agrees that financial disclosures are included without notable conflicts. A financial disclosure certification document was included in the NDA submission and is provided in more detail in Section 17.2

8.1.2.3. Patient Disposition

Data:

Table 9: Applicant Disposition in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors (Efficacy Analysis Set)

	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	**TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)**
Patients Dosed, n (%)	40 (100.0)	48 (100.0)
Patients Ongoing Study Treatment, n (%)	21 (52.5)	12 (25.0)
Patients Who Discontinued Study Treatment, n (%)	19 (47.5)	36 (75.0)
Radiographic Disease Progression[a]	8 (20.0)	20 (41.7)
Physician Decision	5 (12.5)	7 (14.6)
Adverse Event	4 (10.0)	5 (10.4)
Withdrawal of Consent	1 (2.5)	3 (6.3)
Death	1 (2.5)	1 (2.1)
Patients Ongoing Long-Term Follow Up, n (%)	6 (15.0)	6 (12.5)

	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)
Patients Who Discontinued the Study, n (%)	13 (32.5)	30 (62.5)
Death	12 (30.0)	23 (47.9)
Withdrawal of Consent	1 (2.5)	6 (12.5)
Lost to Follow-up	0	1 (2.1)
Overall Duration of Follow-up, months[b]		
Median	17.82	20.07
Min, Max	8.7, 64.6	8.7, 69.4

Abbreviations: BICR = Blinded Independent Central Review; EXP = expansion cohort; max = maximum; min = minimum; NTRK = neurotrophin receptor kinase; PI = Principal Investigator; TKI = tyrosine kinase inhibitor.
Notes: Data cutoff date of 19-Dec-2022.
[a] Radiographic progression includes patients confirmed by BICR and/or PI assessment.
[b] Overall duration of follow-up is calculated as time from first dose of study drug to data cutoff date for all patients (TKI-naïve, N = 40; TKI-pretreated, N = 48), regardless of disposition
Source: ISE Table 14.1.1.2.n.

The Applicant's Position:

Pooled EXP-5

In Pooled EXP-5 (N = 40), as of the data cutoff date of 19-Dec-2022 majority of patients (52.5%) continued on treatment. The median follow-up time was 17.82 months (range: 8.7, 64.6). The most frequently reported reasons for treatment discontinuation were disease progression (20.0%) followed by physician decision (12.5%) and adverse event (10.0%). 13 (32.5%) patients discontinued the study, primarily due to death (12 [30.0%]).

Pooled EXP-6

In Pooled EXP-6 (N = 48) 12 (25.0%) patients continued on treatment as of the data cutoff date of 19-Dec-2022. The median follow-up time was 20.07 months (range: 8.7, 69.4). Similar to the TKI-naïve population, the most frequently reported reasons for treatment discontinuation were disease progression (41.7%) followed by physician decision (14.6%) and adverse event (10.4%). 30 (62.5%) patients discontinued the study; primarily due to death (47.9%) followed by withdrawal of consent (12.5%).

Overall, the disposition of the patients in the primary efficacy population, with progressive disease as the most common reason for treatment discontinuation and death as one of the most common reasons for study discontinuation, is as expected for a population of patients with advanced or metastatic *NTRK*-positive solid tumors.

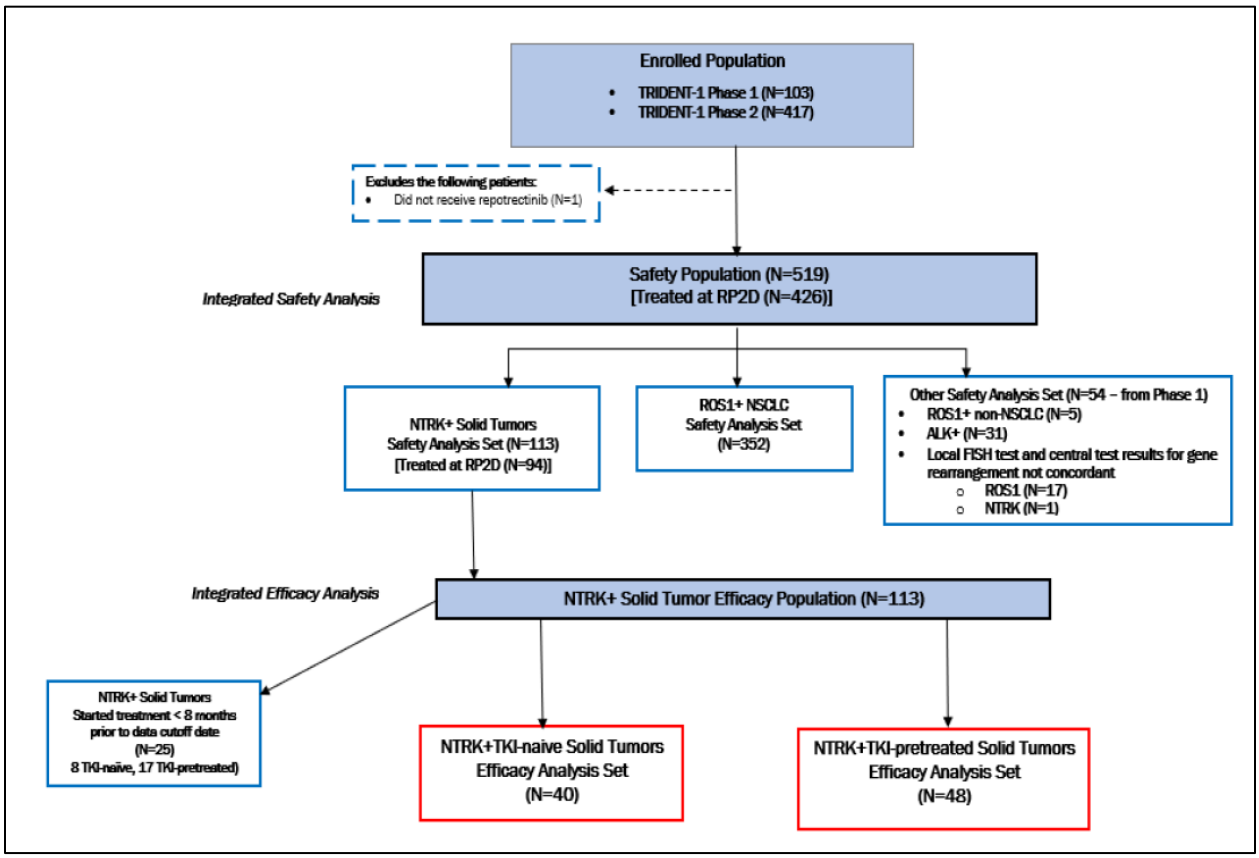
The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition for the EXP-5 and EXP-6 pooled cohorts. More patients in the TKI-pretreated cohort (75%) discontinued treatment than

in the TKI-naïve cohort (48%). Pretreated patients, likely to have more refractory disease, had higher rates of drug discontinuation due to disease progression (20% in TKI-naïve cohort and 42% in TKI-pretreated cohort) at the time of the DCO. EXP-5 and EXP-6 had similar rates for other reasons for drug discontinuation such as AEs, physician choice, and death.

Eighty-eight patients (9 from Phase 1 and 79 from Phase 2) met the pooling criteria for the integrated efficacy analysis prespecified in the SAP. **Error! Reference source not found.** describes the schema of constructing the integrated efficacy analysis set for NTRK+ solid tumor cohorts. FDA generally agrees with the Applicant's description of patient disposition in the integrated efficacy analysis set. FDA notes that the duration of follow-up calculated by the Applicant was defined as time from the first dose to the DCO date, which did not consider the disposition of patients. FDA adds that the median of duration of follow-up, estimated by the Kaplan-Meier method using OS data with reversed censoring status, was 17.1 months (range: 0.9, 46.3) in Pooled EXP-5 and 16.0 months (range: 0.8, 34.2) in Pooled EXP-6.

Figure 2: FDA Schema of Integrated Safety and Efficacy Analysis Sets, TRIDENT-1



Source: Figure 1.2.1.5-1 in Summary of Clinical Efficacy.

8.1.2.4. Protocol Violations/Deviations

Data:
Analysis of protocol deviations was conducted on the individual Phase 1 and Phase 2 portions of the TRIDENT-1 study.

In Phase 1 portion of the study, 21 (22.6%) patients reported an important deviation including overdose or misuse (13 [14.0%]), safety assessment deviations (4 [4.3%]), deviations to informed consent, lab or endpoint data, and prohibited comedication (2 [2.2%] subjects each). Note that per the Protocol Deviation Guidance Plan, the category of overdose or misuse included deviations associated with drug accountability (failure to return or complete diary, missing diary, etc.), failure to return medication dispensed at last visit, breaking capsules, or not taking capsules intact, along with overall dosing compliance. There were no reports of overdose during the conduct of the study.

In Phase 2 portion of the study, 63 (15.1%) patients reported at least 1 important deviation. The most commonly reported important deviation types (≥ 1% of all patients) included informed consent (7.0%), safety assessments (4.1), prohibited co-medication (1.7%), and overdose or misuse (1.4%). Note that the majority of deviations (> 80%) related to informed consent were due to delays in reconsenting on updated versions of the Informed Consent Form.

The Applicant's Position:
The important protocol deviations observed in TRIDENT-1 did not impact the primary endpoint, patient safety or the interpretation of the study results.

The FDA's Assessment:
FDA agrees with the Applicant's overall assessment of protocol deviations for all patients regardless of dose or gene alteration in the Phase 1 and Phase 2 parts of the TRIDENT-1 study. More specifically, of the patients who received the RP2D in Phase 1 (n=12), there were 5 (42%) with a reported important protocol deviation including 3 (25%) overdose/misuse, 1 (8%) safety assessment deviation, and 1 (8%) prohibited co-medication. In Phase 2, for just the 104 NTRK+ solid tumor patients, there were 11 (11%) with at least one important protocol deviation including 4 (4%) informed consent, 4 (4%) safety assessment deviation, 2 (2%) prohibited co-medication, 1 (1%) other and 1 (1%) study drug. FDA agrees that the reported deviations are unlikely to have significantly impacted the results of this study.

8.1.2.5. Table of Demographic Characteristics

Data:

Table 10: Applicant Key Demographics in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors (Efficacy Analysis Set)

	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)
Age (years)		
Mean	59.4 (14.24)	54.2 (16.50)
Median	60.5	58.0
Min, Max	25, 84	20, 81
Age Group, n (%)		
≥ 18 to < 65	24 (60.0)	30 (62.5)
≥ 65 to < 75	11 (27.5)	15 (31.3)
≥ 75	5 (12.5)	3 (6.3)
Sex, n (%)		
Female	24 (60.0)	23 (47.9)
Male	16 (40.0)	25 (52.1)
Race, n (%)		
Asian	21 (52.5)	12 (25.0)
White	10 (25.0)	31 (64.6)
Black or African American	2 (5.0)	1 (2.1)
Native Hawaiian or Other Pacific Islander	0	0
Not Reported	6 (15.0)	4 (8.3)
Ethnicity, n (%)		
Hispanic or Latino	2 (5.0)	0
Not Hispanic or Latino	35 (87.5)	44 (91.7)
Missing	3 (7.5)	4 (8.3)
Region		
US	8 (20.0)	17 (35.4)
Asia	19 (47.5)	8 (16.7)
Other[a]	13 (32.5)	23 (47.9)

Abbreviations: EXP = expansion cohort; max = maximum; min = minimum; NTRK = neurotrophin receptor kinase; TKI = tyrosine kinase inhibitor; US = United States.
Notes: Data cutoff date of 19-Dec-2022.
[a] Countries grouped to "Other" include Australia, Canada, Spain, France, United Kingdom, Italy, Poland.
Source: ISE Table 14.1.3.2n

The Applicant's Position:

The epidemiological data for patients with *NTRK*-positive solid tumors are extremely limited, with the prevalence of *NTRK* gene fusions varying greatly by age, cancer type, and histology

(O'Haire 2023; Solomon 2020; Rosen 2020; Forsythe 2020; Westphalen 2021). Prevalence rates appear to be higher in younger patients, consistent with other driver mutations, however, there currently is insufficient information to fully characterize the incidence of patients with *NTRK*-positive solid tumors by demographic characteristics (O'Haire 2023; Westphalen 2021).

In Pooled EXP-5, patients were younger (median age: 60.5; 60.0% age ≥ 18 to < 65), with a higher proportion of female (60.0%) and Asian (52.5%) patients. Representation by race and ethnic populations included under-represented groups of Black or African American (5.0%) and Hispanic or Latino (5.0%).

In Pooled EXP-6, patients were younger (median age: 58.0; 62.5% age ≥ 18 to < 65), with a similar proportion of male and female patients (male, 52.1%; female, 47.9%) and a higher proportion of White (64.6%) patients. Representation by race and ethnic populations included under-represented groups of Black or African American (2.1%).

Overall, the TKI-naïve and TKI-pretreated populations in TRIDENT-1 are considered diverse. While the demographics characteristics for patients with *NTRK*-positive solid tumors are not fully characterized in the real-world setting, the demographics of the *NTRK*-positive populations enrolled in TRIDENT-1 are similar to those enrolled for other TRK TKIs in clinical trials (e.g., larotrectinib [Vitrakvi® USPI 2023] and entrectinib [Rozlytrek® USPI 2023]).

The FDA's Assessment:
FDA agrees that NTRK+ solid tumors represent a very heterogenous group of tumors making it difficult to fully characterize the demographic characteristics. NTRK+ solid tumors appear to be more common in children with a prevalence of 1.3% vs. 0.3% in adults, and a peak incidence of 2.3% in children <5 years of age (Marchetti 2022). While adolescnet patients 12 years of age and older were eligible to enroll in the Phase 2 of TRIDENT-1, the youngest patient included in the primary efficacy analysis group was 20 years of age.

The majority of patients included in the primary efficacy analysis group in TRIDENT-1 were Asian (53% of EXP-5 and 25% of EXP-6), similar to the approval for entrectinib. TRIDENT-1, similar to the approval for larotrectinib, included a limited number of patients in underrepresented groups such as Black patients (5% in EXP-5 and 2% in EXP-6) and Hispanic patients (5% in EXP-5).

Note that one patient reported as "other" in the Pooled EXP-5 Cohort was not included in

Table 10: Applicant Key Demographics in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors (Efficacy Analysis Set)

Table 10.

8.1.2.6. Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 11: Applicant Key Baseline Disease Characteristics in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors (Efficacy Analysis Set)

	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)
Baseline ECOG Performance Status, n (%)		
0	18 (45.0)	19 (39.6)
1	22 (55.0)	29 (60.4)
Smoking Status, n (%)		
Current	3 (7.5)	2 (4.2)
Former	11 (27.5)	17 (35.4)
Never	21 (52.5)	25 (52.1)
Not Collected	5 (12.5)	4 (8.3)
Tumor Type, n (%)		
NSCLC	21 (52.5)	14 (29.2)
Salivary Gland Cancer	3 (7.5)	8 (16.7)
Sarcoma, Soft Tissue	3 (7.5)	6 (12.5)
Thyroid Cancer	5 (12.5)	4 (8.3)
Glioblastoma	1 (2.5)	3 (6.3)
Breast Cancer	2 (5.0)	1 (2.1)
Cholangiocarcinoma	1 (2.5)	2 (4.2)
Colorectal Cancer	1 (2.5)	2 (4.2)
Peripheral Nerve Sheath Tumor	1 (2.5)	2 (4.2)
Neuroendocrine Tumor	0 (0.0)	2 (4.2)
Pancreatic Cancer	0 (0.0)	2 (4.2)
Esophageal Cancer	1 (2.5)	0 (0.0)
Gallbladder Cancer	0 (0.0)	1 (2.1)
Head and Neck Cancer	1 (2.5)	0 (0.0)
Unknown Primary Cancer	0 (0.0)	1 (2.1)
Histology, n (%)		
Adenocarcinoma	23 (57.5)	25 (52.1)
Papillary Thyroid Carcinoma	4 (10.0)	1 (2.1)

	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	**TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)**
Glioblastoma	1 (2.5)	3 (6.3)
Sarcoma	1 (2.5)	3 (6.3)
Secretory Carcinoma	1 (2.5)	3 (6.3)
Squamous	3 (7.5)	1 (2.1)
Neuroendocrine	1 (2.5)	2 (4.2)
Spindle Cell Sarcoma	0 (0.0)	3 (6.3)
Fibrosarcoma	1 (2.5)	1 (2.1)
Angiosarcoma	1 (2.5)	0 (0.0)
Atypical Carcinoid	0 (0.0)	1 (2.1)
Cholangiocarcinoma	0 (0.0)	1 (2.1)
Endometrial Stromal Sarcoma	1 (2.5)	0 (0.0)
Follicular Carcinoma	0 (0.0)	1 (2.1)
Histiocytic Sarcoma	0 (0.0)	1 (2.1)
Insular Carcinoma	0 (0.0)	1 (2.1)
Large Cell Carcinoma	0 (0.0)	1 (2.1)
Malignant Peripheral Nerve Sheath Neoplasm	1 (2.5)	0 (0.0)
Papillary Thyroid Carcinoma	1 (2.5)	0 (0.0)
Unknown	1 (2.5)	0 (0.0)
Disease at Study Entry		
Metastatic	39 (97.5)	46 (95.8)
Locally Advanced	1 (2.5)	1 (2.1)
Missing	0	1 (2.1)
Brain Metastasis by BICR[a], n (%)		
Yes	9 (22.5)	12 (25.0)
No	31 (77.5)	36 (75.0)
Prior Therapy, n (%)		
TKI Therapy	0 (0.0)	48 (100.0)
Chemotherapy with/without Immunotherapy	25 (62.5)	33 (68.8)
Immunotherapy Alone	5 (12.5)	6 (12.5)
Other Targeted Therapy	9 (22.5)	13 (27.1)
Other Therapy	3 (7.5)	4 (8.3)
No Prior Therapy	12 (30.0)	0 (0.0)
Prior lines of systemic anticancer therapy		
Median (Min, Max)	1.00 (0.0, 4.0)	2.00 (1.0, 6.0)

	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)
0	12 (30.0)	0 (0.0)
1	16 (40.0)	11 (22.9)
2	9 (22.5)	15 (31.3)
≥ 3	3 (7.5)	22 (45.8)
Prior TRK TKI Therapy, n (%)		
Entrectinib	NA	24 (50.0)
Larotrectinib	NA	23 (47.9)
Selitrectinib	NA	5 (10.4)
Cabozantinib	NA	1 (2.1)
Vc004 With TRK Activity	NA	1 (2.1)
Resistance Mutations[b]		
Solvent Front	NA	25 (52.1)
Gatekeeper	NA	1 (2.1)
Activating	NA	0 (0.0)
Other	NA	1 (2.1)
Mutation negative	31 (77.5)	20 (41.7)
Mutation Status Unknown[c]	9 (22.5)	2 (4.2)

Abbreviations: BICR = Blinded Independent Central Review; ECOG = Eastern Cooperative Oncology Group; EXP = expansion cohort; max = maximum; min = minimum; NA = Not Applicable; NTRK = neurotrophin receptor kinas; RECIST = Response Evaluation Criteria in Solid Tumors; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.
Notes: Data cutoff date of 19-Dec-2022.
[a] *Brain metastasis present if target and/or non-target lesion selected in the brain at baseline and may include primary CNS tumors.*
[b] *Patients can be counted in more than one category*
[c] *Mutation Status Unknown includes no sample, QC failure, invalid sample/assay type (i.e., tested before the initial TKI)*
Source: ISE Table 14.1.3.2.n, Table 14.1.4.2.n, Table 14.1.7.2.n, Table 14.1.8.n.

The Applicant's Position:

Pooled EXP-5

Among the patients in Pooled EXP-5 (N = 40), the majority never smoked (52.5%) and had an ECOG performance status of 0 (45.0%) or 1 (55.0%) at study entry. Most patients (97.5%) had metastatic disease, with advanced disease reported in 2.5% at study entry. The most common tumor types were NSCLC (52.5%), Thyroid Cancer (12.5%), Salivary Gland Cancer (7.5%), and Soft Tissue Sarcoma (7.5%), with representation across 11 total tumor types. 9 (22.5%) patients had brain metastases at baseline as determined by BICR assessment. Most patients (70%) received prior systemic therapies.

Pooled EXP-6

Among the patients in Pooled EXP-6 (N = 48), the majority of patients never smoked (52.1%) and had an ECOG performance status of 1 (60.4%) at study entry. Most patients (95.8%) had

metastatic disease, with advanced disease reported in 2.1% at study entry. The most common tumor types were NSCLC (29.2%), Salivary Gland Cancer (16.7%), Soft Tissue Sarcoma (12.5%), and Thyroid Cancer (8.3%), with representation across 13 total tumor types. 12 (25.0%) patients had brain metastases at baseline, as determined by BICR assessment. Twenty-seven resistance mutations reported in 48 patients, including 25 (52.1%) patients with solvent front mutations at baseline. The majority of TKI-pretreated patients were pretreated with entrectinib (50.0%) followed by larotrectinib (47.9%), and 45.8% of patients had ≥ 3 prior systemic therapies.

Overall, the baseline disease characteristics were as expected for the patient populations enrolled per protocol for the TRIDENT-1 study. The baseline disease characteristics are generally representative of TKI-naïve and TKI-pretreated locally advanced or metastatic *NTRK*-positive solid tumor populations that would be treated in the clinic.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of baseline characteristics, though notes that papillary thyroid carcinoma is listed twice under "Histology" in Table 11.

The tumor types represented in the primary efficacy analysis population are consistent with the common tumor types that may harbor NTRK fusions such as NSCLC, soft tissue sarcoma, and breast cancer. As stated, certain (ultra-rare) adult histologies are associated with NTRK fusions (>90%) including mammary analogue secretory carcinoma (MASC) and secretory breast carcinoma. There were no patients with secretory breast carcinoma but four patients with MASC in the primary efficacy analysis population (1 in EXP-5 and 3 in EXP-6).

NTRK1 and NTRK3 fusions represent the most common NTRK fusions in solid tumors with ETV6-NTRK3 and TPM3-NTRK1 being the most common NTRK fusion partners. The primary efficacy analysis population exhibited the same trend as shown in **Error! Reference source not found.**. FDA identified 26 patients in the TKI-pretreated cohort (n=48) with resistance mutations at baseline, including 24 with solvent front mutations (SFM), one patient with both SFM and a gatekeeper mutation and one with another mutation.

Table 12: FDA NTRK Fusion Partners in Primary Efficacy Analysis Population, TRIDENT-1

Identified Molecular Alteration and Fusion Partner	EXP-5 N=40	EXP-6 N=48
NTRK1	**20 (50)**	**12 (25)**
TPM3-NTRK1	7 (18)	3 (6)
IRF2BP2-NTRK1	2 (5)	1 (2)
PEAR1-NTRK1	2 (5)	0
Unknown*	2 (5)	0
ATP2B2-IT2-NRK1	1 (2.5)	0

Identified Molecular Alteration and Fusion Partner	EXP-5 N=40	EXP-6 N=48
GOLGB1-NTRK1	1 (2.5)	0
LRRC71-NTRK1	1 (2.5)	0
SQSTM1-NTRK1	1 (2.5)	0
STRN3-NTRK1	1 (2.5)	0
TPR-NTRK1	1 (2.5)	0
TRIM33-NTRK1	1 (2.5)	0
LMNA-NTRK1	0	4 (8)
ATP1B1-NTRK1	0	1 (2)
GP2-NTRK1	0	1 (2)
PRDX1-NTRK1	0	1 (2)
SEL1-NTRK1	0	1 (2)
NTRK2	**2 (5)**	**3 (6)**
IL1RL2-NTRK2	1 (2.5)	0
LRRC71-NTRK2	1 (2.5)	0
BCR-NTRK2	0	1 (2)
ETV6-NTRK2	0	1 (2)
KANK2-NTRK2	0	1 (2)
NTRK3	**18 (45)**	**33 (69)**
ETV6-NTRK3	12 (30)	24 (50)
EML4-NTRK3	2 (5)	5 (10)
LRPPRC-NTRK3	1 (2.5)	0
RBPMS-NTRK3	1 (2.5)	1 (2)
TMED3-NTRK3	1 (2.5)	0
Multiple	1 (2.5)	1 (2)
SQSTM1-NTRK3	0	1 (2)
STRN3-NTRK3	0	1 (2)

Source: adsl.xpt
*NTRK1 with unknown partners

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

Patients were largely compliant with treatment throughout the study, as determined by the patient dosing diary and reflected by the overall relative dose intensity.

The median (range) duration of exposure to repotrectinib and number of treatment cycles in the Overall population who received at least one dose of repotrectinib (N = 519) was 5.42

months (range: 0.1, 66.6) and 6.0 cycles (range: 1, 73), respectively, with a median relative dose intensity of 94.80%.

The median duration of exposure to treatment and number of treatment cycles in TKI-naïve patients (Pooled EXP-5) was 11.5 months (range: 0.1, 41.3) and 13.5 (range: 1, 45), respectively, with a median relative dose intensity of 73.75%. The median duration of exposure to treatment and number of treatment cycles in TKI-pretreated patients (Pooled EXP-6) was 6.8 months (range: 0.6, 25.1) and 8.0 (range: 1, 28), respectively, with a median relative dose intensity of 94.75%.

Concomitant Medications
All concomitant medication and concurrent treatments (e.g., radiation therapy) were documented at Screening and at every clinic visit. Important protocol deviations of prohibited co-medication occurred in 2 (2.2%) patients and 7 (1.7%) patients in Phase 1 and Phase 2, respectively. Concomitant treatments administered were generally representative of those commonly prescribed to patients in the target population and did not impact patient safety or interpretability of the results.

Rescue Medication
Not applicable

The FDA's Assessment:
FDA agrees that deviations in treatment compliance or co-medications are unlikely to impact the overall efficacy and safety (deviations such as missed doses would be more likely to result in a lower response rate). In Phase 1 of TRIDENT-1, 21 (23%) patients who received repotrectinib at any dose level reported deviations in the Applicant's designated category of overuse or misuse of repotrectinib; however, there were no reports by the Investigators of overdose of repotrectinib. Deviations including prohibited co-medication occurred in 8 (9%) patients and 2 (2.2%) patients were noted to have a prohibited co-medication considered an important deviation. One important deviation, co-medication with ondansetron, occurred in a patient with NTRK+ solid tumor treated at the RP2D. The most common non-important co-medication was radiotherapy.

In Phase 2, "overdose or misuse" was reported in 7 (1.7%) patients of the total patient population (n=416); however, none occurred in the NTRK+ solid tumor patients. Deviations including prohibited co-medication in 13 (3.1%) patients and were considered important in 7 (1.7%) patients, of which 2 occurred in NTRK+ solid tumor patients. The most common co-medication was radiotherapy, occurring in 2 patients.

8.1.2.8. Efficacy Results – Primary Endpoint

Data:

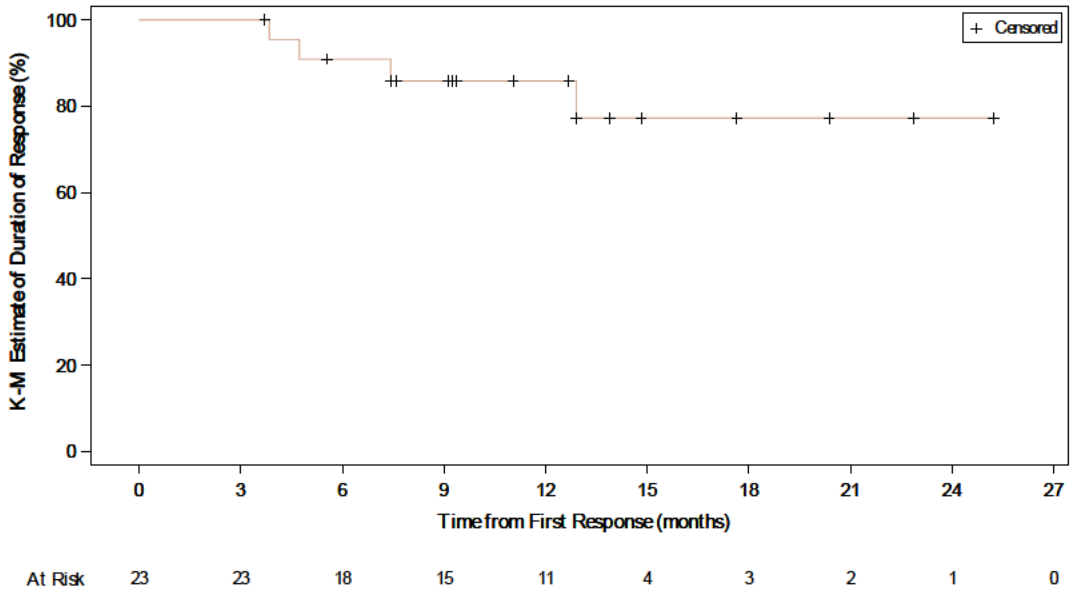
Table 13: Applicant Primary and Key Efficacy Endpoints (By BICR) in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors (Efficacy Analysis Set)

Key Efficacy Data	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)
Confirmed ORR, % (95% CI)	57.5 (40.9, 73.0)	50.0 (35.2, 64.8)
CR, n (%)	5 (12.5)	0 (0.0)
PR, n (%)	18 (45.0)	24 (50.0)
Median Time to Response, months (range)	1.77 (1.6, 11.0)	1.87 (1.7, 3.7)
Duration of Response (DOR)		
Events, n (%)	4 (17.4)	15 (62.5)
Median DOR, months (95% CI)	NE (NE, NE)	9.76 (7.36, 12.91)
DOR Landmark Analyses (Kaplan Meier), % (95% CI)[a]		
DOR ≥ 6 months	90.9 (78.9, 100.0)	69.5 (50.5, 88.4)
DOR ≥ 9 months	85.9 (71.0, 100.0)	57.9 (36.4, 79.4)
DOR ≥ 12 months	85.9 (71.0, 100.0)	38.6 (15.7, 61.5)

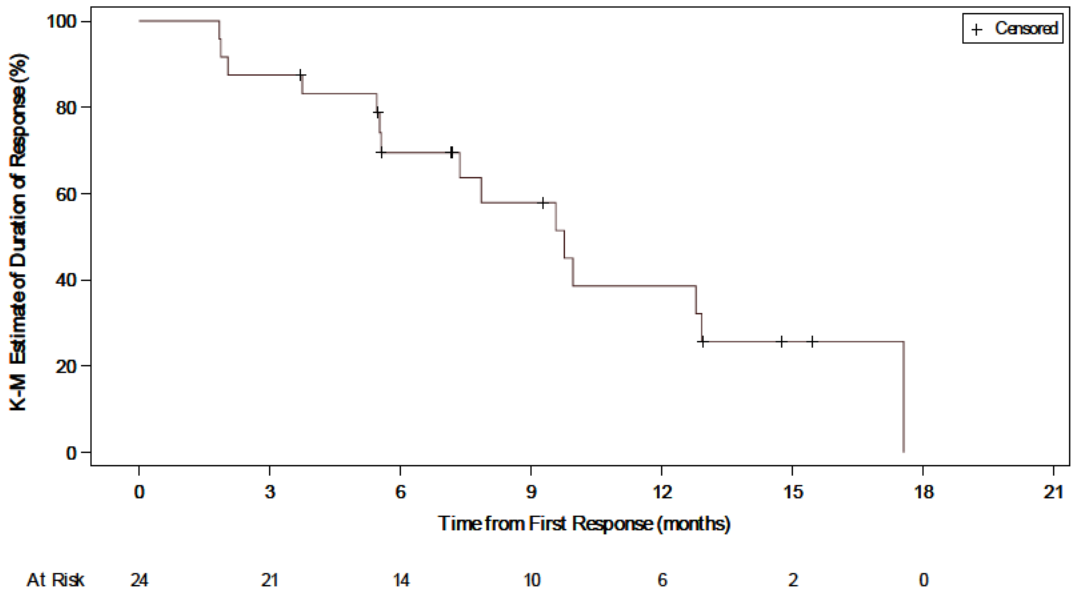
Abbreviations: BICR = Blinded Independent Central Review; BID = twice daily; CI = confidence interval; CR = complete response; DOR = duration of response; EXP = expansion cohort; NE = not estimable; NTRK = neurotrophin receptor kinase; ORR = objective response rate; PR = partial response; QD = once daily; TKI = tyrosine kinase inhibitor.
Notes: Data cutoff date of 19-Dec-2022.
All responding patients pooled from Phase 1 either started at or escalated to the repotrectinib dose of 160 mg QD/BID.
[a] Landmark analyses up to 24 month are reported in Module 5.3.5.3 ISE Table 14.2.1.1.n
Sources: ISE 14.2.1.1.n

Figure 3: Applicant Time-to-Event Analyses (Kaplan Meier): Duration of Response (by BICR) in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors

A. Pooled EXP-5 (N = 40)



B. Pooled EXP-6 (N = 48)



Abbreviations: BICR = blinded independent central review; EXP = expansion cohort; K-M = Kaplan Meier; NSCLC = non-small cell lung cancer; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; TKI = tyrosine kinase inhibitor.
Notes: Data cutoff date of 19-Dec-2022 with response assessment by BICR using RECIST v1.1.
The remaining patients at risk for each group are listed at the bottom of the figure.

Source: ISE Figure 14.2.3.1.n, Figure 14.2.3.2.n

The Applicant's Position:

Clinical meaningful benefits were seen with repotrectinib in patients with advanced or metastatic *NTRK*-positive solid tumors who were TRK TKI-naïve (Pooled EXP-5) or TRK TKI-pretreated (Pooled EXP-6). The data displayed above were evaluated by BICR after patients had the opportunity for at least 6 months of DOR follow-up to allow for adequate characterization of DOR.

Pooled EXP-5

In the pooled population of TKI-Naïve patients with *NTRK*-positive solid tumors (Pooled EXP-5, N = 40), treatment with repotrectinib demonstrated clinically meaningful efficacy through the following primary and key efficacy endpoints:

- Clinically meaningful anti-tumor activity, with a confirmed ORR by BICR of 57.5% (N = 23/40; 95% CI: 40.9, 73.0), including 12.5% (N = 5/40) CRs.
    - Of note, the lower bound of the ORR 95% CI exceeds the standard of care benchmark ORR point estimate of 35% pre-specified in the TRIDENT-1 protocol and SAP
- Rapid onset of response (median TTR = 1.77 months; range: 1.6, 11.0).
- Deep responses were observed, with 42.5% of patients having a reduction in the size of target lesions of at least 60% from baseline (refer to Table 14.2.7.1.n). Of note, the majority of patients showed a reduction in the size of target lesions from baseline.
- Median DOR was not estimable, with DOR ranging from 3.7+ to 25.2+ months.
- The percent of patients with an observed DOR ≥6 months, ≥9 months and ≥12 months was 78.3%, 65.2%, and 47.8%, respectively.
- Landmark DOR analyses (Kaplan Meier) showed that the probability of patients remaining in response at ≥ 6 months, ≥ 12 months, and ≥ 18 months was 90.9%, 85.9%, and 77.3%, respectively.
    - The median duration of treatment was 11.53 months (range: 0.1, 41.3+), with 21 (52.5%) of the 40 patients remaining on treatment at the time of data cutoff, including 19 (82.6%) of the 23 patients with confirmed responses.
    - Among the 15 (37.5%) patients with progression, 12 patients continued treatment beyond progression due to sustained clinical benefits; the median time on treatment post progression was 2.51 months (range: 0.4, 27.8).

Pooled EXP-6

In the pooled population of TKI-pretreated patients with *NTRK*-positive solid tumors (Pooled EXP-6, N = 48), treatment with repotrectinib demonstrated clinically meaningful efficacy through the following primary and key efficacy endpoints:

- Clinically robust activity, with an ORR by BICR of 50.0% (N = 24/48; 95% CI: 35.2, 64.8) in this heavily pretreated, pan-tumor population.
    - Of note, the lower bound of the ORR 95% CI exceeds the standard of care benchmark ORR point estimate of 10% pre-specified in the TRIDENT-1 protocol and SAP
- Rapid onset of response (median TTR = 1.87 months; range: 1.7, 3.7).
- Deep responses were observed, with 33.3% of patients having a reduction in the size of target lesions of at least 60% from baseline. Of note, the majority of patients (36 of 48) showed a reduction in the size of target lesions from baseline.
- An estimated median DOR of 9.76 months (95% CI: 7.36, 12.91), with DOR ranging from 1.8 to 17.5 months.
- The percent of patients with an observed DOR ≥6 months, ≥9 months and ≥12 months was 58.3%, 41.7%, and 25.0%, respectively.
- Landmark DOR analyses (Kaplan Meier) showed that the probability of patients remaining in response at ≥ 6 months and ≥ 12 months was 69.5% and 38.6%, respectively.
    - The median duration of treatment was 6.80 months (range: 0.6, 25.1+), with 12 (25.0%) of the 48 patients remaining on treatment at the time of data cutoff, including 12 (50.0%) of the 24 patients with confirmed responses.
    - Among the 31 (64.6%) patients with progression, 26 patients continued treatment beyond progression due to sustained clinical benefits; the median time on treatment post progression was 1.94 months (range: 0.1, 12.5).

The FDA's Assessment:

FDA generally agrees with the results of the primary endpoint presented by the Applicant. FDA notes that although the lower bound of the 95% CI of confirmed ORR exceeded the pre-specified threshold of 35% in Pooled EXP-5 and 10% in Pooled EXP-6. FDA does not consider statistical inferential procedures to evaluate treatment effects observed in a single-arm study.

The Applicant submitted updated efficacy data based on a data cutoff of October 15, 2023 with the submission of the Day 90 Safety Update, which provided an additional 10 months of DOR follow-up (total of 16 months DOR follow-up from the first post-baseline scan for responding patients). FDA identified there were multiple patients in the Pooled EXP-5 cohort with the best of response (BOR) assessed by BICR differed from the original efficacy data. Additional details were obtained through information requests (IR). The Applicant clarified that one patient's BOR changed from PR to SD due to adjudication change based on the DCO of October 15, 2023. One patient's BOR changed from SD to PR due to confirmation of PR after the original DCO. One patient's BOR changed from PR to CR due to deepening of response. For the two patients who

changed from SD to PR and PR to CR, respectively, FDA further assessed that the initial unconfirmed PR and CRs responses happened before the original DCO. Incorporating the BOR change of these three patients, the ORR assessed by BICR does not change in the Pooled EXP-5 cohort with 15% of patients achieving CR and 43% PR.

The updated median duration of follow-up was 27.3 months in Pooled EXP-5 and 25.0 months in Pooled EXP-6, estimated by the Kaplan-Meier method using OS data with reversed censoring status. For Pooled EXP-5, the updated median DOR was not estimable, with DOR ranging from 3.7+ to 43.9+ months. The percent of patients with an observed DOR ≥6 months and ≥12 months was 87% and 83%, respectively. For Pooled EXP-6, the updated median DOR was 9.9 months (95% CI: 7.4, 13.0). The percent of patients with an observed DOR ≥6 months and ≥12 months was 71% and 42%, respectively.

The reported magnitude of ORR in both cohorts is sufficiently compelling to support clinical benefit in patients with NTRK-fusion positive tumors. Approximately 13% of patients in the TKI-naïve group experienced complete radiographic disappearance of their tumors. The durability was supportive although longer in the TKI-naïve cohort.

8.1.2.9. Data Quality and Integrity

The Applicant's Position:
The study was performed following GCP and all local regulations, and there are no concerns regarding data integrity and submission quality.

All data for the pivotal TRIDENT-1 study are entered into a validated database managed by the Applicant. The present database lock occurred once quality assurance procedures were completed. All procedures for the handling and analysis of data are conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

With the emergence of COVID-19 during the trial, a record of patients who tested positive was maintained, including information about date/time of test collection, any study visits not performed, any dose interrupted or missed, any MRI or CT assessments not performed as well as EOT, TEAEs related to COVID-19, study discontinuation, or death due to reason attributable to COVID-19. As the use of vaccines was not a restriction for this study, enrolled and potential adult clinical study patients were allowed to receive the COVID-19 vaccine with no impact on their eligibility or ability to remain on study drug.

The Applicant conducted the clinical studies according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, the Applicant undertakes a GCP audit program. Audits

are performed by (b) (4) that operates independently of the study monitors. The audits within a clinical program are aimed at study documentation, Investigator sites, and CSRs. The audit program, together with the Applicant's internal quality control procedures, provide reassurance that study conclusions are based on valid procedures for data management and analysis, and that the clinical study program is carried out in accordance with GCP guidelines.

The FDA's Assessment:

FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a complete review of the efficacy of repotrectinib in patients with NTRK+ solid tumors. FDA issued information requests during the review cycle to obtain clarification and additional information regarding data (e.g., sources of data and additional datasets for the CARE study) included in the NDA, and all requests were addressed appropriately.

8.1.2.10. Efficacy Results – Secondary and other relevant endpoints

Data:

Table 14: Applicant Key Secondary Efficacy Endpoints (By BICR) in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors (Efficacy Analysis Set)

Key Secondary Efficacy Data	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5) (N = 40)	TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6) (N = 48)
CBR (CR + PR + SD), % (95% CI)	80.0 (64.4, 90.9)	75.0 (60.4, 86.4)
Median Duration of Treatment, months (range)	11.53 (0.1, 41.3)	6.80 (0.6, 25.1)
Progression-Free Survival (PFS)		
Events, n (%)	18 (45.0)	35 (72.9)
Median PFS, months (95% CI)	NE (5.52, NE)	7.36 (3.88, 9.72)
PFS Landmark Analyses (Kaplan Meier), % (95% CI) [b]		
PFS ≥ 6 months	61.3 (46.0, 76.7)	53.2 (38.5, 67.9)
PFS ≥ 9 months	58.7 (43.1, 74.2)	41.1 (26.4, 55.8)
PFS ≥ 12 months	55.7 (39.9, 71.5)	21.6 (7.7, 35.5)
Overall Survival (OS)		
Death, n (%)	13 (32.5)	23 (47.9)
Median OS, months (95% CI)	NE (18.53, NE)	19.12 (9.56, 25.72)
IC-ORR, % (n/N) [a]	100 (2/2)	100 (3/3)

Abbreviations: BICR = Blinded Independent Central Review; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; EXP = expansion cohort; IC-ORR = intracranial objective response rate; ISE = Integrated Summary of Efficacy; NE = not

evaluable; NTRK = neurotrophin receptor kinase; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease; TKI = tyrosine kinase inhibitor.
Notes: Data cutoff date of 19-Dec-2022.
[a] IC-ORR was evaluated in Phase 2 of the TRIDENT-1 study. Of the 35 TKI-naïve patients from Phase 2, 2 patients had measurable brain disease at baseline by BICR; of the 44 TKI-pretreated patients from Phase 2, 3 patients had measurable brain disease at baseline by BICR.
[b] Landmark analyses up to 24 months are reported in ISE Table 14.2.3.1.n
Sources: ISE Table 14.1.6.2.n, Table 14.2.1.1.n, Table 14.2.3.1.n, Table 14.2.6.1.n; TRIDENT-1 Phase 2 CSR Addendum 01 Table 14.2.3.5

Table 15: Applicant Summary of Efficacy Data (by BICR) by Tumor Type: TKI-Naïve NTRK-Positive Solid Tumors (Pooled EXP-5)

Tumor Type	Patients (N)	ORR (CR + PR),		DOR Min, Max (months)
		n (%)	(95% CI)	
NSCLC	21	13 (61.9)	38.4, 81.9	3.7+, 22.9+
Thyroid Cancer	5	4 (80.0)	28.4, 99.5	4.7, 25.2+
Salivary Gland Cancer	3	3 (100.0)	29.2, 100.0	9.1+, 20.4+
Sarcoma, Soft tissue	3	1 (33.3)	0.8, 90.6	5.6+
Peripheral Nerve Sheath Tumor	1	PR	NA	12.9+
Other[a]	2	PR, SD	NA	13.9+
Glioblastoma	1	SD	NA	NA
Cholangiocarcinoma	1	PD	NA	NA
Colorectal cancer	1	SD	NA	NA
Breast Cancer	2	PD, PD	NA	NA

Abbreviations: BICR = Blinded Independent Central Review; CI = confidence interval; CR = complete response; DOR = duration of response; EXP = expansion; Max = maximum; Min = minimum; NA = not applicable; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ORR = objective response rate; PR = partial response; TKI = tyrosine kinase inhibitor.
Notes: 95% CIs are calculated using the Clopper-Pearson Exact method. 95% CIs are only included when N > 2 patients.
Data Cutoff Date: 19-Dec-2022.
[a] Includes: esophageal cancer and head and neck cancer.
Source: ISE Table 14.2.1.10.n

Table 16: Applicant Summary of Efficacy Data (by BICR) by Tumor Type: TKI-Pretreated NTRK-Positive Solid Tumors (Pooled EXP-6) - Efficacy Analysis Set

Tumor Type	Patients (N)	ORR (CR + PR)		DOR Min, Max (Months)
		n (%)	95% CI	
NSCLC	14	6 (42.9)	17.7, 71.1	1.9, 12.9+
Salivary Gland Cancer	8	7 (87.5)	47.3, 99.7	3.7, 15.4+
Sarcoma, Soft tissue	6	1 (16.7)	0.4, 64.1	5.6

Tumor Type	Patients (N)	ORR (CR + PR)		DOR Min, Max (Months)
		n (%)	95% CI	
Thyroid Cancer	4	2 (50.0)	6.8, 93.2	2.0, 9.6
Glioblastoma	3	1 (33.3)	0.8, 90.6	14.8+
Cholangiocarcinoma	2	PR, PD	NA	1.8
Colorectal cancer	2	PR, SD	NA	17.5
Peripheral Nerve Sheath Tumor	2	PR, PR	NA	3.7+, 5.5
Neuroendocrine Tumor	2	PR, PR	NA	5.5, 7.2+
Pancreatic Cancer	2	PD, PD	NA	NA
Other[a]	2	SD, PD	NA	NA
Breast Cancer	1	PR	NA	5.5+

Abbreviations: BICR = Blinded Independent Central Review; CI = confidence interval; CR = complete response; DOR = duration of response; EXP = expansion; Max = maximum; Min = minimum; NA = not applicable; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ORR = objective response rate; PR = partial response; TKI = tyrosine kinase inhibitor.
Notes: 95% CIs are calculated using the Clopper-Pearson Exact method. 95% CIs are only included when N > 2 patients.
Data Cutoff Date: 19-Dec-2022.
[a] Includes: gallbladder cancer and unknown primary.
Source: ISE Table 14.2.1.10.n.

The Applicant's Position:

Pooled EXP-5

In the pooled population of TKI-Naïve patients with *NTRK*-positive solid tumors (Pooled EXP-5, N = 40), clinically meaningful efficacy demonstrated with the key efficacy endpoints described above were further supported by key secondary efficacy endpoints (Table 14 and Table 15):

- Objective responses observed across a wide variety of tumor histologies, fusion partners, and subgroups.
- Median PFS was not estimable, with PFS ranging from 0.0+ to 40.4+ months. Landmark PFS analyses showed that the probability of patients remaining progression-free at ≥ 6 months, ≥ 12 months, and ≥ 18 months was 61.3%, 55.7%, and 50.7%, respectively.
- Median OS was not estimable. There was a high level of censoring due to the small number of deaths.

- CBR by BICR of 80% (95% CI: 64.4, 90.9).
- Intracranial activity (IC-ORR) was observed, with a confirmed IC-ORR in both (2/2) patients, and the observed DOR was 7.4+ and 12.8+ months in the 2 patients. Both patients were ongoing study treatment at the time of data cutoff.

Pooled EXP-6

In the pooled population of TKI-pretreated patients with *NTRK*-positive solid tumors (Pooled EXP-6, N = 48), clinically meaningful efficacy demonstrated with the key efficacy endpoints described above were further supported by key secondary efficacy endpoints (Table 14 and Table 16):

- Objective responses observed across a wide variety of tumor histologies, fusion partners, and subgroups.
- An estimated median PFS of 7.36 months (95% CI: 3.88, 9.72), with PFS ranging from 0.8 to 19.4 months. Landmark PFS analyses showed that the probability of patients remaining progression-free at ≥ 6 months and ≥ 12 months was 53.2% and 21.6%, respectively.
- Median OS of 19.12 months (95% CI: 9.56, 25.72).
- CBR by BICR of 75.0% (95% CI: 60.4, 86.4)
- Clinical activity observed in patients reported with SFMs at baseline, a recognized resistance mechanism to other TRK TKIs (ORR 60% [95% CI: 38.7, 78.9]).
- Intracranial activity (IC-ORR), with a confirmed IC-ORR in all (3/3) patients and observed DOR ranging from 6 to 11 months.
    - ORR of 43.5% (95% CI: 23.2, 65.5) in patients pretreated with larotrectinib and 54.2% (95% CI: 32.8, 74.4) in patients pretreated with entrectinib.

The FDA's Assessment:

FDA generally agrees with the results of secondary and other relevant endpoints described above. However, FDA notes that CBR is not an established efficacy endpoint and will not be used for labeling claims (a drug's effect on "stable disease", a component of CBR, cannot be adequately estimated in a single-arm trial). In addition, the time-to-event endpoints such as PFS and OS are not interpretable in a single-arm trial.

Repotrectinib demonstrated activity in 5 patients with CNS metastases at baseline as assessed by BICR. FDA notes that 1 out of 2 TKI-naïve and 2 out of 3 TKI-pretreated patients received radiotherapy to the brain more than 2 months prior to study entry.

8.1.2.11. Dose/Dose Response

The Applicant's Position:

Data on dose response are presented in Section 6.3.2.1 (Clinical Pharmacology).

The FDA's Assessment:

All patients included in the primary efficacy analysis population in TRIDENT-1 were treated at the RP2D. Refer to Section 6.3.2 for more information.

8.1.2.12. Durability of Response

Data:
The duration of response data are presented in Section 748.1.2.8.

The Applicant's Position:
See Applicant's Position presented in Section 8.1.2.8, including description of durability of response.

The FDA's Assessment:
FDA agrees with the Applicant's position based on DOR as presented in Section 8.1.2.8 with the DCO of December 19, 2022. Durability of response was measured by DOR. The mDOR in EXP-5 was not estimable ranging from 3.7+ to 25.2+ months and in EXP-6 9.8 months (95% CI: 7.4, 12.9) ranging from 1.8 to 17.5 months.

Updated DOR data was included in the 90-day safety update with a DCO of October 15, 2023. The updated mDOR in EXP-5 was not estimable, with DOR ranging from 3.7+ to 43.9+ months. The percent of patients with an observed DOR ≥6 months and ≥12 months was 87% and 83%, respectively. For EXP-6, the updated median DOR was 9.9 months (95% CI: 7.4, 13.0). The percent of patients with an observed DOR ≥6 months and ≥12 months was 71% and 42%, respectively.

Although cross-study comparison has limitations (particularly given that the distribution of tumors differed in the studies), the mDOR was similar for TKI-naïve patients who received larotrectinib (32.9 months [95% CI: 14.8, NE] ranging from 1.6+ to 50.6+ months) and was not reached for entrectinib ranging from 2.8 to 27.8+ months. Repotrectinib showed activity with durable responses in TKI-naïve and TKI-pretreated patients. Refer to FDA's assessment in Section 8.1.2.8.

8.1.2.13. Persistence of Effect

Data:
Persistence of efficacy was primarily measured by DOR. PFS and OS were also assessed and considered supportive. The data from the pivotal TRIDENT-1 study are presented above.

The Applicant's Position:
In pooled EXP 5 (TKI-Naïve *NTRK*-positive solid tumor population), the estimated median DOR (Kaplan Meier) was not estimable (range: 3.7+ to 25.2+ months), with landmark analyses at

≥ 12 months showing a survival probability of 85.9% (95% CI: 71.0, 100.0). In pooled EXP 6 (TKI-pretreated *NTRK*-positive solid tumor patients), the estimated median DOR (Kaplan Meier) was 9.76 months (95% CI: 7.36, 12.91), with landmark analyses at ≥ 6 months and ≥ 9 months showing survival probabilities of 69.5% (95% CI: 50.5, 88.4) and 57.9% (95% CI: 36.4, 79.4), respectively.

Although the interpretation of PFS and OS is limited for a single-arm study, persistence of efficacy has been observed with these secondary endpoints and is considered clinically supportive.

In pooled EXP 5, median PFS was not estimable (range: 0.0+ to 40.4+ months), with landmark analyses showing that the probability of patients remaining progression-free at ≥ 12 months was 55.7% (95% CI: 39.9, 71.5). In pooled EXP 6, median PFS was 7.36 months (95% CI: 3.88, 9.72), with landmark analyses showing that the probability of patients remaining progression free at ≥ 6 months and ≥ 9 months was 53.2% (95% CI: 38.5, 67.9) and 41.1% (95% CI: 26.4, 55.8), respectively.

In pooled EXP-5 median overall survival was not estimable at the time of the data cutoff date. In pooled EXP-6, median overall survival was 19.12 (95% CI: 9.56, 25.72).

The FDA's Assessment:

Refer to FDA's assessment in Section 8.1.2.8 for details on DOR with DCO December 19, 2022, with additional data on updated DOR with DCO October 15, 2023. FDA notes that the analyses of PFS and OS are considered exploratory in single-arm trials. No reliable conclusions can be made based on these results without comparison to contemporarily randomized control patients.

8.1.2.14. Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Patient reported outcomes were assessed in Phase 2 of the pivotal TRIDENT-1 study. Full details for analyses are provided in a separate SAP. The PROs were assessed using self-administered validated questionnaires: the EORTC QOL core questionnaire (QLQ-C30) and lung cancer module (QLQ-LC13). All PRO analyses are considered descriptive in nature. In interpreting change in QLQ-C30 and LC13 results, based on the literature (Osoba 1998), a 10-point change from baseline in an item or domain is considered clinically meaningful within-patient change.

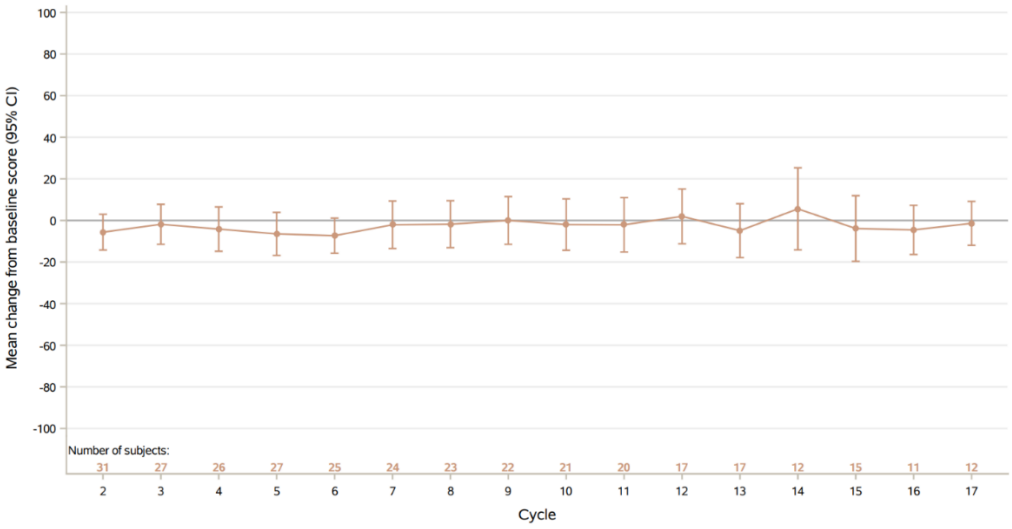
A summary of the PRO results overall and at Cycle 6 and Cycle 12 are described in the tables that follow for TRK TKI-naïve (EXP-5) and TRK TKI-pretreated (EXP-5) groups.

The FAS population used for the PRO analyses included 35 patients with *NTRK*-positive solid tumors who were TKI-naïve (EXP-5) and 44 patients with *NTRK*-positive solid tumors who were TKI-pretreated (EXP-6), all of whom were dosed as of 19-Apr-2022.

TKI-Naïve NTRK-positive Solid Tumors (EXP-5)

Completion rates for the QLQ-C30 were high for each visit timepoint. The overall completion rate at Baseline, Cycle 6, and Cycle 12 was 100%, 96.3% and 89.5%, respectively. Evaluability rates were 100% for all visits. Overall, the mean change from baseline in EORTC-QLQ-C30 GHS/QOL score in TRK TKI-naïve- (Figure 4: Applicant Mean Change from Baseline in EORTC-QLQ-C30 GHS/QOL Score in TRK TKI-Naïve Patients by Cycle (Full Analysis Set)Figure 4) patients remained stable over time at each cycle. The majority of TRK TKI-naïve patients reported stable or improved responses in GHS/QOL. The majority of participants had improved or stable responses in the EORTC QLQ-C30 symptom scales.

Figure 4: Applicant Mean Change from Baseline in EORTC-QLQ-C30 GHS/QOL Score in TRK TKI-Naïve Patients by Cycle (Full Analysis Set)



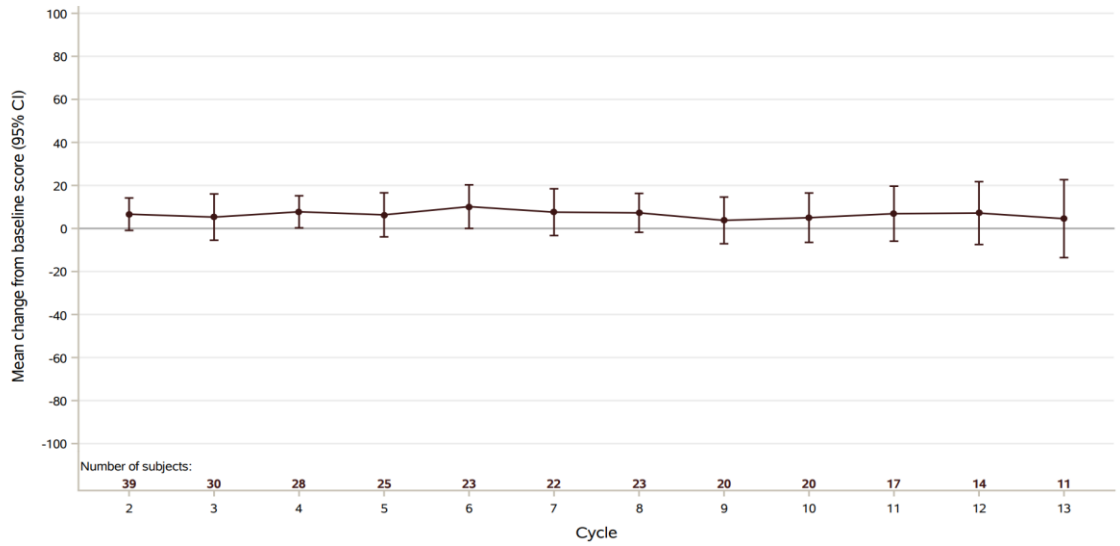
Abbreviations: CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; GHS = Global Health Status; QLQ-C30 = quality of life core questionnaire; QOL = quality of life; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.
Source: TRIDENT-1 Phase 2 CSR Addendum 01 Appendix 16.4, Figure 1.2.1.1

TKI-pretreated NTRK-positive Solid Tumors (EXP-6)

Completion rates for the QLQ-C30 were high for each visit timepoint. The overall completion rate at Baseline, Cycle 6, and Cycle 12 was 97.7%, 95.8% and 93.3%, respectively. Evaluability rates were 100% for all visits. Overall, the mean change from baseline in EORTC-QLQ-C30 GHS/QOL score in TRK TKI-pretreated (Figure 5) patients remained stable over time at each cycle. The majority of TRK TKI-pretreated patients reported stable or improved responses in

GHS/QOL. The majority of participants had improved or stable responses in all EORTC QLQ-C30 symptom scales.

Figure 5: Applicant Mean Change from Baseline in EORTC-QLQ-C30 GHS/QOL Score in TRK TKI-Pretreated Patients by Cycle (Full Analysis Set)



Abbreviations: CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; GHS = Global Health Status; QLQ-C30 = quality of life core questionnaire; QOL = quality of life; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.
Source: TRIDENT-1 Phase 2 CSR Appendix 16.4 Figure 1.2.1.2

The Applicant's Position:

The EORTC QLQ-C30 GHS/QOL and functioning scales were stable through the first year on treatment in both the TKI-naïve and TKI-pretreated groups. Meaningful improvements (at least 10 points decrease in mean change from baseline) up to Cycle 12 were observed in the EORTC QLQ-C30 symptoms scales Pain and Insomnia for both TKI-naïve and TKI-pretreated groups. Consistent worsening in Constipation was observed over time in the TKI-naïve group.

With less than half of the *NTRK*-positive solid tumors patients not experiencing a deterioration event, the median TDD for the EORTC QLQ-C30 GHS/QOL was 17.48 months for the TKI-naïve group and 13.11 months for the TKI-pretreated group. The median TFI for the EORTC QLQ-C30 GHS/QOL was not reached in both groups. The median TFI for the Physical Functioning was not reached in either TKI-naïve or TKI-pretreated groups.

Although the HRQOL analyses do not support formal statistical inferences, based on the currently available data presented here in addition to the efficacy and safety results, the analyses suggest that repotrectinib may be a promising treatment option for patients with

advanced *NTRK*-positive solid tumors and, while maintaining QOL, provides a high tumor response rate and landmark duration of response.

The FDA's Assessment:
In the Phase 2 part of TRIDENT-1, NTRK+ NSCLC patients were required to complete EORTC QOL-C30 and QLQ-LC13 questionnaires at screening, prior to the first dose of repotrectinib on Cycle 1 Day 1, pre-dose on Day 1 of each subsequent treatment cycle thereafter, and at the End of Treatment. NTRK+ solid tumors were only required to complete the EORTC-QLQ-C30 module with the same schedule.

FDA agrees with the Applicant's description regarding completion rates of QLQ-C30. However, FDA adds that for late cycles there were very few patients who were on study during those cycles. For the TKI-naïve cohort (EXP-5), the available data rates (number of patients with valid questionnaire assessment/number of randomized patients) of QLQ-C30 at Baseline, Cycle 6, and Cycle 12 were 100%, 74%, and 49%, respectively. For the TKI-pretreated cohort (EXP-6), the available data rates of QLQ-C30 at Baseline, Cycle 6, and Cycle 12 were 98%, 52%, and 29%, respectively.

FDA notes multiple issues with the Applicant's PRO analyses. First, PROs from TRIDENT-1 are challenging to interpret due to the small PRO sample size in EXP-5 and EXP-6 and the open-label, single-arm design of the trial. Second, PRO time-to-deterioration endpoints are difficult to interpret due to multiple potential issues including adequacy of the deterioration definition, how intercurrent events are handled, and missing data in late cycles. Third, use of global health status results (e.g., lack of deterioration in GHS) is not acceptable as evidence of tolerability, as non-disease and non-treatment related factors could influence this score. The Applicant did not utilize specific patient-reported symptom or side effect impact items assess important tolerability considerations such as dizziness, taste changes, and visual disturbance. Lastly, assessment of PROs in a tissue agnostic setting is challenging because different tumor types have different cardinal symptoms that should be assessed differently. Use of a NSCLC specific measure alone is insufficient to capture patient generated data across multiple tumor types.

In summary, FDA considers the PRO analyses exploratory and conclusions on tolerability and efficacy cannot be made based on the available PRO data.

8.1.2.15. Additional Analyses Conducted on the Individual Trial

Data:

Comparison of Results of Subpopulations

Table 17: Applicant Summary of Key Subgroup Analysis of Efficacy (By BICR) in TKI-Naïve (Pooled EXP-5) and TKI-Pretreated (Pooled EXP-6) Patients with NTRK-positive Solid Tumors (Efficacy Analysis Set)

	TKI-Naïve *NTRK*-positive Solid Tumors (Pooled EXP-5)		TKI-Pretreated *NTRK*-positive Solid Tumors (Pooled EXP-6)	
Subgroup	**N**	**ORR n (%) [95% CI]**	**N**	**ORR n (%) [95% CI]**
Baseline Brain Metastasis per BICR[a]				
Yes	9	6 (66.7) [29.9, 92.5]	12	5 (41.7) [15.2, 72.3]
No	31	17 (54.8) [36.0, 72.7]	36	19 (52.8) [35.5, 69.6]
Region				
US	8	2 (25.0) [3.2, 65.1]	17	6 (35.3) [14.2, 61.7]
Asia	19	12 (63.2) [38.4, 83.7]	8	5 (62.5) [24.5, 91.5]
Other	13	9 (69.2) [38.6, 90.9]	23	13 (56.5) [34.5, 76.8]
Race				
Asian	21	13 (61.9) [38.4, 81.9]	12	7 (58.3) [27.7, 84.8]
Black or African	2	0 (0.0) [0.0, 84.2]	1	1 (100.0) [2.5, 100.0]
White	10	6 (60.0) [26.2, 87.8]	31	12 (38.7) [21.8, 57.8]
Other	1	0 (0.0) [0.0, 97.5]	0	NA
Not Reported	6	4 (66.7) [22.3, 95.7]	4	4 (100.0) [39.8, 100.0]
Age				
≥ 18 to < 65	24	15 (62.5) [40.6, 81.2]	30	20 (66.7) [47.2, 82.7]
≥ 65 to < 75	11	6 (54.5) [23.4, 83.3]	15	4 (26.7) [7.8, 55.1]
≥ 75	5	2 (40.0) [5.3, 85.3]	3	0 (0.0) [0.0, 70.8]
SFM at Baseline				
Yes	NA	NA	25	15 (60.0) [38.7, 78.9]
Prior TRK TKI treatment				
Larotrectinib	NA	NA	23	10 (43.5) [23.2, 65.5]
Entrectinib	NA	NA	24	13 (54.2) [32.8, 74.4]

Abbreviations: BICR = Blinded Independent Central Review; EXP = expansion cohort; NA = not applicable; NTRK = neurotrophic tyrosine receptor kinase; ORR = objective response rate; RECIST = Response Evaluation Criteria in Solid Tumors; SFM = solvent-front mutation; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase .

Notes: Data cutoff date of 19-Dec-2022.

[a] *Brain metastasis present if target and/or non-target lesion selected in the brain at baseline and may include primary CNS tumors.*

Sources: ISE Table 14.2.1.2.n, Table 14.2.1.4.n, Table 14.2.1.5.n, Table 14.2.1.8.n, Table 14.2.1.11.n, Table 14.2.1.12.n.

The Applicant's Position:

To examine the consistency of treatment effect for repotrectinib on efficacy endpoints, prespecified subgroup analyses were conducted by demographic and baseline risk factors including age, sex, race, region, brain metastasis at baseline, SFMs at baseline and prior TKI

treatment. As the study was not powered to detect statistical differences between the subgroups, and given the small sample size in each subgroup, the results should be interpreted with caution.

In Pooled EXP-5 and EXP-6, although there were some variations in confirmed ORR and median DOR across the subgroups, which was expected given the small number of patients, confirmed clinical activity was observed across all subgroup populations with a substantial overlap in the 95% CIs across subgroups (Table 17). Notably, of the 48 patients in Pooled EXP-6, 25 (52.1%) patients were reported with an SFM at baseline of which 15 achieved confirmed responses for a confirmed ORR of 60.0% (95% CI: 38.7, 78.9). Patients also responded irrespective of which TKI was administered as prior line. Subgroup analyses of PFS, TTR, CBR and OS were also performed with no notable differences observed.

The FDA's Assessment:

FDA agrees with the results of the prespecified subgroup analysis described by the Applicant. FDA also conducted subgroup analyses by NTRK fusion (**Error! Reference source not found.**) and by NTRK fusion partners (**Error! Reference source not found.** and **Error! Reference source not found.**). Given the small sample sizes in the subgroups, efficacy results in subpopulations should be interpreted with caution. Consistent with the known incidence of NTRK fusion subtypes and fusion partners, fusion types NTRK1 and NTRK3, and fusion partners ETV6-NTRK3 and TPM3-NTRK1 were the most identified in the patient population.

Table 18: FDA Efficacy Results by NTRK Fusion Type Subgroup, TRIDENT-1

NTRK Fusion	TKI-Naïve (Pooled EXP-5) (N=40)		TKI-Pretreated (Pooled EXP-6) (N=48)	
	N	ORR by BICR % (95% CI)	N	ORR by BICR % (95% CI)
NTRK 1	20	50 (27, 73)	12	8 (0.2, 38)
NTRK 2	2	0 (0, 84)	3	33 (0.8, 91)
NTRK 3	18	72 (47, 90)	33	67 (48, 82)

Abbreviations: BICR = Blinded Independent Central Review; EXP = expansion cohort; NTRK = neurotrophic tyrosine receptor kinase; ORR = objective response rate; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.
Source: FDA analysis of sponsor submitted datasets (ADEFF, ADSL) as of the data cutoff on Dec-19-2022.

Table 19: FDA Efficacy Results by NTRK Fusion Partner in TKI-naïve Patients, TRIDENT-1

***NTRK* Partner**	**Subjects (N=40)**	**ORR by BICR**		**DOR**
		n (%)	**95% CI**	**Range (Months)**
ETV6-NTRK3	12	9 (75)	(43, 95)	4.7, 31.4+
TPM3-NTRK1	7	5 (71)	(29, 96)	3.8, 23.1+
EML4-NTRK3	2	Missing, PR	NA	14.8+

***NTRK* Partner**	**Subjects (N=40)**	**ORR by BICR**		**DOR**
		n (%)	**95% CI**	**Range (Months)**
IRF2BP2-NTRK1	2	PR, PR	NA	3.7+, 20.3+
PEAR1-NTRK1	2	Missing, PD	NA	NA
Unknown	2	PD, SD	NA	NA
ATP2B2-IT2-NTRK1	1	SD	NA	NA
GOLGB1-NTRK1	1	SD	NA	NA
IL1RL2-NTRK2	1	SD	NA	NA
LRPPRC-NTRK3	1	SD	NA	NA
LRRC71-NTRK1	1	Missing	NA	NA
Multiple	1	PR	NA	28.6+
RBPMS-NTRK3	1	PR	NA	34.3+
SLC28A3-NTRK2	1	PD	NA	NA
SQSTM1-NTRK1	1	PR	NA	15.7+
STRN3-NTRK1	1	PR	NA	23.9+
TMED3-NTRK3	1	PD	NA	NA
TPR-NTRK1	1	PR	NA	43.9+
TRIM33-NTRK1	1	CR	NA	17.8+

Abbreviations: BICR = Blinded Independent Central Review; DOR = Duration of Response; EXP = expansion cohort; NA = Not Applicable; NTRK = neurotrophic tyrosine receptor kinase; ORR = objective response rate; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase;
Source: FDA analysis of sponsor submitted datasets (ADEFF, ADSL) as of the data cutoff on Oct-15-2023.
Note: + denotes ongoing response.

Table 20: FDA Efficacy Results by NTRK Fusion Partner in TKI-pretreated Patients, TRIDENT-1

***NTRK* Partner**	**Subjects (N=48)**	**ORR**		**DOR**
		n (%)	**95% CI**	**Range (Months)**
ETV6-NTRK3	24	16 (67)	(45, 84)	1.8, 26.5+
EML4-NTRK3	5	4 (80)	(28, 99)	1.9, 12.9
LMNA-NTRK1	4	1 (25)	(0.6, 81)	5.6
TPM3-NTRK1	3	0 (0)	(0, 71)	NA
ATP1B1-NTRK1	1	PD	NA	NA
BCR-NTRK2	1	SD	NA	NA
ETV6-NTRK2	1	NE	NA	NA
GP2-NTRK1	1	PD	NA	NA
IRF2BP2-NTRK1	1	Missing	NA	NA
KANK2-NTRK2	1	PR	NA	23.5
Multiple	1	PD	NA	NA
PRDX1-NTRK1	1	Missing	NA	NA
RBPMS-NTRK3	1	PD	NA	NA
SEL1L-NTRK1	1	PD	NA	NA
SQSTM1-NTRK3	1	PR	NA	5.5
STRN3-NTRK3	1	PR	NA	11.1

Abbreviations: BICR = Blinded Independent Central Review; DOR = Duration of Response; EXP = expansion cohort; NTRK =

neurotrophic tyrosine receptor kinase; ORR = objective response rate; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase;
Source: FDA analysis of sponsor submitted datasets (ADEFF, ADSL) as of the data cutoff on Oct-15-2023.
Note: + denotes ongoing response.

FDA subgroup analysis of response by NTRK fusion and fusion partner demonstrated that response was highest in NTRK3 fusions (ORR 72% [n=18] in TKI-naïve and 67% [n=33] in TKI-pretreated) compared to NTRK1 fusions (ORR 50% [n=20] in TKI-naïve and 8% [n=12] in TKI-pretreated). The two most common NTRK fusion partners in the TKI-naïve group were ETV6-NTRK3 and TPM3-NTRK1 with an ORR of 75% (9/12) and 71% (5/7), respectively. The two most common NTRK fusion partners in the TKI-pretreated group were ETV6-NTRK3 and EML4-NTRK3 with an ORR of 67% (16/24) and 80% (4/5), respectively. The remaining fusion partners occurred in less than 5 patients each. It is important to note that no inferences can be made on the efficacy of repotrectinib in specific NTRK fusions or fusion partners given the small sample sizes.

FDA also adds that 26 TKI-pretreated patients had a resistance mutation at baseline, including 24 with SFMs (NTRK1^{G595R} and NTRK3$^{G623L/R/E/V}$), one with both an SFM and gatekeeper mutation (NTRK1^{F589L}), and one with another mutation (NTRK1^{G667C}). Of the 25 TKI-pretreated patients with SFMs at baseline, ORR was 60% (95% CI: 39, 79). Of the 20 TKI-pretreated patients without a resistance mutation at baseline, ORR was 45% (95% CI: 23, 68). Two patients had unknown mutation status at baseline. The presence of resistance mutations in the TKI-pretreated patients is likely a contributor to the lower ORR in the EXP-6. Repotrectinib shows activity against resistance mutations, particularly SFMs, though data should be interpreted with caution given small sample sizes. There is limited or no data for activity of repotrectinib in other resistance mutations.

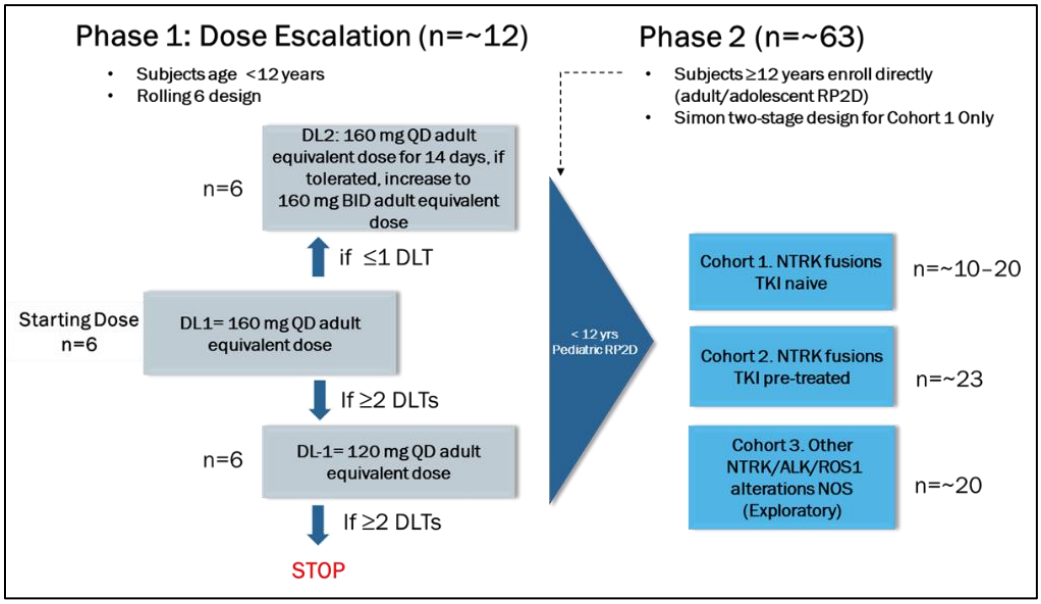
Not all patients treated at the RP2D were titrated up to 160 mg BID (refer to Section 8.2.2.1). Of the 21 TKI-naive patients and 41 TKI -pretreated patients titrated up to 160 mg BID, ORR was 62% (95% CI: 38, 82) and 51% (95% CI: 35, 67), respectively. Of the 14 TKI-naïve patients and 3 TKI-pretreated patients who did not meet criteria to increase to 160 mg BID, ORR was 64% (95% CI: 35, 87) and 67% (95% CI: 9, 99), respectively. The remaining 9 patients were enrolled in Phase 1 and did not have the option to titrate up to 160 mg BID, including 5 TKI-naïve and 4 TKI-pretreated patients. Acknowledging sample sizes of patients who remained on 160 mg QD or were titrated up to 160 mg BID are small, ORR was similar across these groups.

8.1.3. Supportive Study for Efficacy - Pediatric CARE Study (TPX-0005-07)

8.1.3.1. Trial Design (CARE Study)

The Applicant's Description:
Basic Study Design

Figure 6: Applicant Schema of Phase 1/2 Study CARE



Abbreviations: ALK = anaplastic lymphoma kinase; BID = twice daily; DL = dose level; DLT = dose-limiting toxicity; NOS = not otherwise specified; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; QD = once daily; TKI = tyrosine kinase inhibitor; TRK = tropomyosin receptor kinase.

CARE (TPX-0005-07) is an ongoing, Phase 1/2, open-label, single-arm, multicenter, multicohort study to evaluate the safety, tolerability, PK, and efficacy of repotrectinib in pediatric, adolescent, and young adult (up to 25 years of age) patients with advanced or metastatic solid tumors with *ALK*, *ROS1*, or *NTRK* alterations. The pediatric CARE study was initiated in November 2019.

The study included a Phase 1 dose escalation, MTD/RP2D determining part and a Phase 2 part (Figure 6). Enrollment of patients into Phase 1 and Phase 2 occurred concurrently by age as follows:

- Patients < 12 years old were initially enrolled in Phase 1 to determine the pediatric RP2D for this age group and patients ≥12 years old enrolled in Phase 2.
- Following the determination of the pediatric RP2D, all patients ≤ 25 years old were then enrolled directly into Phase 2 of the study.

Enrollment into the Phase 1 dose escalation part is complete. Enrollment into Phase 2 of the study is currently ongoing. A total of 26 patients were enrolled across Phase 1 and Phase 2 of the CARE study as of the cutoff date (19-Dec-2022) and are included in this sNDA.

Patients were required to have a Lansky (<16 years) or Karnofsky (≥ 16 years) score of at least 50 and measurable disease per RECIST v 1.1 or RANO criteria. Patients with a primary CNS tumor or CNS metastases were required to be neurologically stable on a stable or decreasing dose of steroids for at least 14 days prior to enrollment. Identification of *NTRK1-3* gene fusions in tumor specimens was prospectively determined in local laboratories using NGS, PCR or FISH tests. All *NTRK* gene fusion positive tumors by local FISH testing required prospective central laboratory confirmation using an analytically validated NGS test.

The objectives of the Phase 1 portion of the study were to evaluate the safety and tolerability at different dose levels of repotrectinib, to estimate the MTD or MAD, and to select the pediatric RP2D/schedule of repotrectinib administered to pediatric and young adult patients with advanced or metastatic malignancies harboring *ALK*, *ROS1*, or *NTRK*1-3 alterations.

The objective of the Phase 2 portion of the study is to determine the antitumor activity of repotrectinib in pediatric and young adult patients with advanced or metastatic malignancies harboring *ALK*, *ROS1*, or *NTRK*1-3 alterations.

Preliminary efficacy results from the CARE study as of the data cutoff date of 19-Dec-2022 are descriptive and include interim ORR results for repotrectinib in pediatric patients with *NTRK*-altered solid malignancies to support the TRIDENT-1 efficacy results. Efficacy analysis population sets are described in Table 21.

Table 21: Applicant Definitions of Efficacy Analysis Population Sets (CARE)

***NTRK* Efficacy Evaluable Set (N = 6)**	All enrolled *NTRK* patients who received at least one dose of study treatment, have documentation of measurable disease at baseline per central reviewer, and have started treatment at least 8 months prior to the data cutoff date (had the opportunity to have 6 months of follow-up for tumor assessment after first post-baseline scan).
Modified *NTRK* Efficacy Evaluable Set (N = 13)	All enrolled *NTRK* patients who received at least one dose of study treatment, have documentation of measurable disease at baseline per central reviewer, and at least one post baseline assessment.

Trial location

This study is being conducted at 28 sites globally, including the US, Canada, Australia, Taiwan, South Korea, and Singapore.

The FDA's Assessment:

The CARE study was intended to support the efficacy results of the TRIDENT-1 study, particularly adolescent patients 12 years of age and older because the primary efficacy analysis population from the TRIDENT-1 study did not enroll any patients 12 years of age or older. The CARE study is still ongoing with study completion expected (b) (4). FDA notes that the

modified NTRK efficacy evaluable set was not pre-specified in the integrated summary of efficacy (ISE) SAP. The analyses using this analysis set will be considered exploratory.

8.1.3.2. Efficacy Results (CARE Study)

Data:

Table 22: Applicant Overall Response and Associated Efficacy Endpoints for NTRK-Positive Patients by BICR - NTRK Efficacy Evaluable Set (CARE Study)

	TKI-Naïve			TKI-Pretreated		
	< 12 yrs old (N = 0)	≥ 12 yrs old (N = 2)	Total (N = 2)	< 12 yrs old (N = 4)	≥ 12 yrs old (N = 0)	Total (N = 4)
Best Overall Response, n (%)						
CR	0	1 (50.0)	1 (50.0)	0	0	0
PR	0	0	0	1 (25.0)	0	1 (25.0)
SD	0	0	0	0	0	0
PD	0	1 (50.0)	1 (50.0)	3 (75.0)	0	3 (75.0)
ORR (CR + PR), n (%)	NA	1 (50.0)	1 (50.0)	1 (25.0)	NA	1 (25.0)
(95% CI)	NA	1.3, 98.7	1.3, 98.7	0.6, 80.6	NA	0.6, 80.6
Duration of Response (months)						
Events, n (%)	NA	0	0	1 (100.0)	NA	1 (100.0)
Censored, n (%)	NA	1 (100.0)	1 (100.0)	0	NA	0
Min, Max	NA	7.6+, 7.6+	7.6+, 7.6+	9.2, 9.2	NA	9.2, 9.2

Abbreviations: CI = confidence interval; CR = complete response; Max = maximum; Min = minimum; NA = not applicable; NTRK = neurotrophin receptor kinase; ORR = objective response rate; PR = partial response; SD = stable disease.
Note: Percentages are based on the number of patients in the NTRK Efficacy Evaluable Set.
95% CIs for ORR are based on Clopper-Pearson Exact method.
'+' indicates a censored value.
Source: Table 7.1-1 and Table 7.1-2 of the CARE Ad Hoc Report, Module 5.3.5.4.

Table 23: Applicant Overall Response and Associated Efficacy Endpoints for NTRK-Positive Patients by BICR - Modified NTRK Efficacy Evaluable Set (CARE Study)

	TKI-Naïve (N=5)	TKI-Pretreated (N=8)
Best Overall Response, n (%)		
CR	1 (20.0)	0
PR	1 (20.0)	1 (12.5)
SD*	1 (20.0)	4 (50.0)
PD	2 (40.0)	3 (37.5)
ORR (CR + PR), n (%)	2 (40.0)	1 (12.5)
(95% CI)	5.3, 85.3	0.3, 52.7

	TKI-Naïve (N=5)	TKI-Pretreated (N=8)
Duration of Response (months)		
Events, n	0	1 (100.0)
Censored, n	2 (100.0)	0
Min, Max	3.7+, 7.6+	9.2, 9.2

Abbreviations: CI = confidence interval; CR = complete response; Max = maximum; Min = minimum; NA = not applicable; NTRK = neurotrophin receptor kinase; ORR = objective response rate; PR = partial response; SD = stable disease.
Percentages are based on the number of patients in the Modified NTRK Efficacy Evaluable Set.
Notes: Modified NTRK Efficacy Evaluable Set includes all enrolled NTRK patients who received study treatment, had a baseline tumor assessment with documentation of measurable disease per central reviewer, and at least one post baseline assessment.
95% CIs for ORR are based on Clopper-Pearson Exact method.
'+' indicates a censored value
'' 1 TKI-naïve patient and 2 TKI-pretreated patients had 1 post-baseline scan with a timepoint response of PR and is considered BOR of SD.*
Source: Table 7.1-3 of the CARE Ad Hoc Report, Module 5.3.5.4.

The Applicant's Position:

Preliminary Efficacy Data

The adequacy of the CARE study data package to support the proposed sNDA indication was discussed at the pre-sNDA meeting with FDA (Ref ID 5261887). Thirteen *NTRK*-positive pediatric patients (1 year to 15 years old) were included in the efficacy analysis from the CARE study with measurable disease and at least one post-baseline scan. Of these, 5 were TRK TKI-naïve (3 CNS tumors and 2 solid tumors) and 8 had received prior TRK TKI therapy (3 CNS tumors and 5 solid tumors).

Of the 5 TKI-naïve patients (Table 23), 1 CR was observed in a 13-year-old patient with soft tissue sarcoma (DOR of 7.6+ months) and 1 PR in a 14-year-old patient with CNS tumor (DOR of > 3.6 months). In addition, an unconfirmed ongoing PR was observed in a 6-year-old with CNS tumor.

Of the 8 TKI-pretreated patients, a PR was observed in a 7-year-old patient with high-grade glioma (DOR of 9.2 months). In addition, unconfirmed ongoing PRs were observed in 2 patients with soft tissue sarcoma aged 4 and 15 years, respectively. Disease stabilization was also observed in a 5-year-old patient with soft tissue sarcoma and a 4-year-old patient with CNS tumor at the time of data cut-off.

In a subpopulation of efficacy evaluable patients as predefined in the SAP for CARE (i.e., centrally confirmed measurable disease with at least 6 months of follow-up from their first post baseline scan) (Table 22), 2 of 6 patients achieved confirmed responses (1 CR [TKI-naïve] and 1 PR [TKI-pretreated]).

Overall, the preliminary efficacy data from the CARE study supports the efficacy observed in adults, with responses reported in both the TKI-naïve and TKI-pretreated settings. This is expected considering the mechanism of action of repotrectinib (Section 2.2) and given that *NTRK* fusions are tumor-agnostic and age-independent predictive biomarkers for this patient population (Zhao 2021).

The FDA's Assessment:
FDA clarifies that of the 26 patients enrolled in the CARE study at the time of sNDA submission, 16 had NTRK+ solid tumors, of which 6 were efficacy evaluable with centrally confirmed measurable disease with at least 6 months of follow-up from their first post-baseline scan. Two patients, both 12-17 years of age, were TKI-naïve with one patient with a CR (ORR 50%; 95% CI: 1, 99). Four patients were TKI-pretreated, all less than 12 years of age, with 1 patient with a partial response (ORR 25%; 95%: CI 0.6, 81). Preliminary efficacy data from the CARE study is limited and therefore may not be used to adequately assess the efficacy of repotrectinib in pediatric patients with NTRK+ solid tumors.

8.1.4. Integrated Review of Effectiveness

The FDA's Assessment:
The efficacy evaluation for this sNDA is based on the analysis of 40 TKI-naïve (pooled EXP-5) and 48 TKI-pretreated (pooled EXP-6) patients with NTRK+ solid tumors that were locally advanced or metastatic.

The primary evidence of effectiveness of repotrectinib is established by the demonstration of a clinically meaningful, durable ORR in the primary analysis population from the TRIDENT-1 study. The confirmed ORR by BICR per RECIST v1.1 was 58% (95% CI: 41, 73) for the pooled EXP-5 cohort with a median DOR not estimable (range 3.7+, 43.9+) and 83% of responders with a response duration of ≥12 months. The confirmed ORR by BICR per RECIST v1.1 was 50% (95% CI: 35, 65) for the pooled EXP-6 cohort with a median DOR of 9.9 months (95% CI: 7.4, 13.0) and 42% of responders with a response duration of ≥ 12 months. Median DORs are reported based on the data cutoff date of October 15, 2023.

In addition, durable responses were observed in patients with resistance mutations and a limited number of patients with measurable CNS metastases. Among TKI-naïve patients, 2 had measurable CNS metastases at baseline as assessed by BICR and responses in intracranial tumors were observed in both (100%) of these patients. Among the TKI-pretreated patient, 3 had measurable CNS metastases at baseline as assessed by BICR and responses in intracranial tumors were observed in all three (100%) of these patients. Twenty-six of the TKI-pretreated patients had a resistance mutation at baseline, of which 25 were SFMs. Responses were observed in 15 (ORR 60%; 95% CI: 39, 79) of these patients.

The totality of data suggests response rates with clinically meaningful magnitude and durability in patients 12 years of age and older with locally advanced or metastatic NTRK+ solid tumors in the TKI-naïve and TKI-pretreated populations. Subgroup analyses also indicate activity in patients with CNS metastases and in patients with resistance mutations following prior TKI therapy; however, these subgroup analyses are considered exploratory. Results should be interpreted with caution given the small samples sizes in the subgroups and no definitive conclusions can be drawn from these analyses.

8.1.5. Assessment of Efficacy Across Trials

The Applicant's Position:
Efficacy was assessed based on data from the single, pivotal clinical trial TRIDENT-1 presented in Section 8.1.2, with efficacy from CARE study in pediatrics presented as supportive in Section 8.1.3.2.

The FDA's Assessment:
FDA agrees with Applicant's position.

8.1.6. Integrated Assessment of Effectiveness

Data:
Integrated data from the pivotal TRIDENT-1 study to support efficacy claims are presented above in Section 8.1.2. Supporting data from the pediatric CARE study are presented in Section 8.1.3.2.

The Applicant's Position:
In TRIDENT-1 and CARE, cumulative data across >100 TKI-naïve and TKI-pretreated adult and pediatric patients with *NTRK*-positive tumors, with a mean duration of follow up of 18 to 20 months (adults, TRIDENT-1), have demonstrated clinically meaningful response rates, including intracranial responses, and impressive durability of response irrespective of tumor type and inclusive of patients with CNS disease.

TRK TKI-Naïve
In patients who were TKI-naïve (majority received 1-3 prior lines of non-targeted therapy), the confirmed ORR per BICR was 58% (95% CI: 41, 73) with the lower end of the 95% CI above the standard of care benchmark ORR point estimate of 35% described in the protocol and SAP. The magnitude of efficacy observed with repotrectinib in the *NTRK*-positive TKI-naïve solid tumor population is comparable to current targeted therapies approved under accelerated approval, i.e., larotrectinib and entrectinib (Table 24), with encouraging landmark DOR analyses where a probability of patients remaining in response at ≥ 6 and ≥ 12 months was 90.9% and 85.9%, respectively. Intracranial activity (IC-ORR) was observed, with a confirmed IC-ORR in all (2/2)

subjects with brain metastases at baseline per BICR and the observed DOR being 7.4+ and 12.8+ months. Both subjects were ongoing with study treatment as of DCO. Clinical efficacy was also observed in the pediatric TKI-naïve population with *NTRK*-positive solid tumors, as demonstrated in the preliminary CARE results (see Section 8.1.3.2).

Importantly, *NTRK1-3* fusions appear to be distributed in different proportions across solid tumors, with the highest prevalence being *NTRK3* gene fusions in salivary gland (36.8%) followed by breast (14.7%), soft tissue sarcoma (13.7%), and relatively low incidence in NSCLC (2.1%) (Westphalen 2021). In addition, across patients treated with *NTRK* gene fusions, *NTRK3* have been the most sensitive to TRK inhibition therapy with *NTRK1-2* being more difficult to treat (Vitrakvi® USPI 2023; Rozlytrek® USPI 2023). This is particularly relevant in the characterization and difference in responses noted with TRK TKIs. Responses seen with repotrectinib are observed agnostic of fusion partner or tumor types but in the E-R efficacy analysis, the probability of achieving ORR was significantly higher in patients with *NTRK3* than those with *NTRK1-2* gene fusions. Among the *NTRK* solid tumor patients enrolled in TRIDENT-1, NSCLC patients comprised approximately 40% of enrolled patients followed by salivary gland (12.5%), soft tissue sarcoma (10.2%) and breast tumors (3.4%). Lower prevalence of *NTRK3* gene fusions in the highest enrolled tumor type in TRIDENT-1 could potentially explain the difference in response rate observed between repotrectinib and that observed with larotrectinib wherein similarly high response rates were observed with *NTRK3* gene fusions and tumor types with high prevalence of *NTRK3* gene fusions were enrolled (salivary gland 21.8%, soft tissue sarcoma 20%) compared to NSCLC (7.5%) (Vitrakvi® USPI 2023).

Table 24: Applicant Efficacy of Repotrectinib (Pooled EXP-5) and Historical Benchmarks in TKI-Naïve NTRK-Positive Solid Tumors

NTRK+ Solid Tumors, TKI-Naïve	Repotrectinib (Pooled EXP-5) (Includes Primary CNS and Adults Only)	Larotrectinib[a] (Vitrakvi USPI) (Includes Primary CNS, Adults and Pediatrics)	Larotrectinib[b] (Vitrakvi SmPC) (Includes Primary CNS, Adults, and Pediatrics)	Larotrectinib[b] (Vitrakvi SmPC) (Adult Only Subpopulation)	Entrectinib[c] (Rozlytrek USPI) (Includes Primary CNS and Adults Only)	Entrectinib[d] (Rozlytrek SmPC) (Includes Primary CNS and Adults Only)
Key Efficacy Data	**N=40**	**N=55**	**N=313**	**N=178**	**N=54**	**N=150**
ORR, % (95% CI)	58 (41, 73)	75 (61, 85)	61 (55, 66)	58 (-)	59 (45, 72)	61 (53, 69)
CR, %	13	25	20	-	13	17
Pathological CR[e], %	-	-	4	-	-	-
PR, %	45	49	37	-	46	45
DOR						
Median DOR, months (95% CI)	NE (NE, NE)	32.9 (14.8, NE)	41.5 (-)	-	-	20 (13.2, 31.1)
DOR Range, months	3.7+, 25.2+	1.6+, 50.6+	0.0+, 65.4+	-	2.8, 47.8+	-
DOR Landmark Analyses (Kaplan Meier), % (95% CI)						
DOR ≥ 6 months	90.9 (78.9, 100.0)	-	-	-	-	83 (75, 91)
DOR ≥ 12 months	85.9 (71.0, 100.0)	-	79 (-)	-	-	66 (56, 76)
IC-ORR, % (n/N)	100 (2/2)	-	22 (9/41)	-	75 (3/4)	69 (9/13)

Abbreviations: BICR = Blinded Independent Central Review; BID = twice daily; CI = confidence interval; CR = complete response; DOR = duration of response; EXP = expansion cohort; IC-ORR = intracranial objective response rate; NE = not estimable; NR = not reported; NTRK = neurotrophin receptor kinase; PR = partial response; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; SmPC = Summary of Product Characteristics; TKI = tyrosine kinase inhibitor; USPI = United States Package Insert.
Notes: All responding patients pooled from Phase 1 either started at or escalated to the repotrectinib dose of 160 mg QD/BID.
A "-" is included if information was not available/not reported
[a] *Vitrakvi® USPI 2023; best overall response was determined by BICR using RECIST v1.1.*

[b] *Vitrakvi SmPC 2023; best overall response was determined by BICR using RECIST v1.1.*
[c] *Rozlytrek® USPI 2023; best overall response was determined by BICR using RECIST v1.1.*
[d] *Rozlytrek SmPC 2023; best overall response was determined by BICR using RECIST v1.1.*
[e] *A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on post-surgical pathology evaluation. The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v.1.1.*

TRK TKI-Pretreated

There are currently no approved TRK targeted therapies for *NTRK*-positive patients who have progressed after prior TRK TKIs, with palliative therapy typically being offered to these heavily pretreated patients (Xu 2022). Considering the results in Pooled EXP-6 and the lack of approved TRK TKIs in this setting, repotrectinib has also demonstrated clinically meaningful benefits in TKI-pretreated patients with *NTRK*-positive solid tumors through:

- Clinically robust activity, with an ORR by BICR of 50.0% (N = 24/48; 95% CI: 35.2, 64.8) in this heavily pretreated, pan-tumor population.
- Rapid onset of response (median TTR = 1.87 months; range: 1.68, 3.71).
- Objective responses observed across a wide variety of tumor histologies, fusion partners, and subgroups.
- Deep responses were observed, with 33.3% of patients having a reduction in the size of target lesions of at least 60% from baseline. Of note, the majority of patients showed a reduction in the size of target lesions from baseline.
- An estimated median DOR of 9.76 months (95% CI: 7.36, 12.91), with DOR ranging from 1.8 to 17.5 months. Landmark DOR analyses (Kaplan Meier) showed that the probability of patients remaining in response at ≥ 6 months and ≥ 12 months was 69.5% and 38.6%, respectively.
    - The median duration of treatment was 6.80 months (range: 0.6, 25.1+), with 12 (25.0%) of the 48 patients remaining on treatment at the time of data cutoff, including 12 (50.0%) of the 24 patients with confirmed responses.
    - Among the 31 (64.6%) patients with progression, 26 patients continued treatment beyond progression due to sustained clinical benefits; the median time on treatment post progression was 1.94 months (range: 0.1, 12.5).
- An estimated median PFS of 7.36 months (95% CI: 3.88, 9.72), with PFS ranging from 0.8 to 19.4 months. Landmark PFS analyses showed that the probability of patients remaining progression-free at ≥ 6 months and ≥ 12 months was 53.2% and 21.6%, respectively.
- Median OS of 19.12 months (95% CI: 9.56, 25.72).
- CBR by BICR of 75.0% (95% CI: 60.4, 86.4)
- Notably, clinical activity was observed in patients reported with SFMs at baseline, a recognized resistance mechanism to other *NTRK* TKIs (ORR 60% [95% CI: 38.7, 78.9]).
- Intracranial activity (IC-ORR), with a confirmed IC-ORR in all (3/3) patients and observed DOR ranging from 6 to 11 months.
- ORR of 43.5% (95% CI: 23.2, 65.5) in patients pretreated with larotrectinib and 54.2% (95% CI: 32.8, 74.4) in patients pretreated with entrectinib.
- Clinical efficacy was also observed in the initial pediatric TKI-pretreated population with *NTRK* rearrangements, as demonstrated in the CARE preliminary results (see Section 8.1.3.2).

The FDA's Assessment:

This application was supported by the integrated efficacy analysis of 88 patients with an NTRK

gene fusion enrolled in the pivotal TRIDENT-1 study. For the 40 patients who were TKI-naïve, the ORR assessed by BICR was 58% (95% CI: 41, 73), and 15% TKI-naïve patients experienced a CR. Among the 23 TKI-naïve patients who responded, the mDOR was not reached (range: 3.7+ to 43.9+ months) and 87% of the patients experienced responses of at least six months. For the 48 patients who were TKI-pretreated, the ORR assessed by BICR was 50% (95% CI: 35, 65). Among the 24 TKI-pretreated patients who responded, the mDOR was 9.9 months (95% CI: 7.4, 13.0 months; range: 1.8 to 26.5+ months) and 71% patients experienced responses of at least six months. mDORs are reported based on the DCO date of October 15, 2023.

FDA agrees with the Applicant that the efficacy results demonstrate a clinically meaningful antitumor activity of repotrectinib in both TKI-naïve and TKI-pretreated patients with NTRK+ solid tumors. The effectiveness of repotrectinib was also demonstrated across prespecified subgroups, including patients with CNS metastases and resistance mutations, and supported by sustained durability of response.

Due to the small sample size enrolled in both EXP-5 and EXP-6, there is uncertainty regarding the magnitude of the treatment effect of repotrectinib in any one histologic subtype of solid tumors with an activating NTRK rearrangement. Under a PMR, the Applicant will conduct an analysis of patients from ongoing or planned (b) (4) trials to verify and describe the clinical benefit of repotrectinib, including a sufficient number of patients evaluated to more precisely characterize the response and durability of response for a spectrum of patients with different TKI-naïve and TKI-pretreated tumor types. Due to the rarity of all solid tumors that harbor an NTRK rearrangement, a randomized trial to verify the benefit is not feasible.

The Applicant's Table 24 also shows efficacy results for approvals outside the US for entrectinib and larotrectinib; however, FDA has not reviewed these data and would not consider these results as part of the overall risk: benefit assessment. Furthermore, given differences in patients enrolled (e.g., tumor types and fusion partners), comparisons of results across different drugs are not appropriate.

8.2. Review of Safety

The Applicant's Position:

The overall safety profile assessed in the pivotal TRIDENT-1 study in the Overall population (N = 519), the subpopulation receiving at least 1 dose of repotrectinib at the RP2D (N = 426), and the subpopulations of *ROS1*-positive NSCLC patients (N = 320) and *NTRK*-positive solid tumor patients (N = 104) receiving at least 1 dose of repotrectinib at the RP2D demonstrated that the safety profile was manageable and that repotrectinib was generally well tolerated. The TEAEs that were reported with repotrectinib were monitorable, manageable, and resolved with standard symptomatic measures, and/or dose modifications or discontinuation depending on severity. Long-term treatment with repotrectinib (> 12 months) showed no evidence of

increased/cumulative toxicity. Preliminary safety data from the pediatric CARE study (N =26 pediatric patients) demonstrated a comparable safety profile with that reported in adults.

The proposed Safety population for the NTRK sNDA follows the safety presentation in the initial NDA for *ROS1*-postive NSCLC and was deemed acceptable by FDA at the pre-sNDA meeting (Ref ID 5261887).

The FDA's Assessment:

FDA agrees with the Applicant's description of the TRIDENT-1 safety subpopulations. FDA's approach for safety focused on patients with NTRK+ solid tumors and ROS1+ NSCLC who received at least one dose of repotrectinib at the RP2D (n=426), and on the population of patients with NTRK+ solid tumors who received at least one dose of repotrectinib at the RP2D (n=104) in the TRIDENT-1 study. FDA clarifies that the RP2D population also contains data from two additional patients (n=2), including a patient with centrally discordant ROS1+ NSCLC and a patient with ROS1+ pancreatic cancer. FDA did not conduct any specific safety analyses on the overall population (n=519) which included patients with advanced solid tumors harboring an NTRK, ROS, or ALK alteration at multiple dose levels of repotrectinib. In addition, the Applicant submitted a 90-day safety update which was reviewed and verified to identify any new safety signals.

From this point of the review forward, FDA will refer to the RP2D subpopulation (n=426) as "RP2D population" and the NTRK+ subpopulation (n=104) as "RP2D NTRK+ population".

8.2.1. Safety Review Approach

Data:

The number of patients treated with repotrectinib in the primary analysis set is presented in Table 25.

Table 25: Applicant Number of Patients Treated with Repotrectinib in the Primary Analysis Set

Study/ISS	Phase/Indication	Design	Patients Treated[a]
TRIDENT-1 Phase 1 and midazolam DDI substudy	Phase 1; adults with advanced solid tumors	Open-label, dose escalation (3+3), PK, efficacy, and safety study	103
TRIDENT-1 Phase 2	Phase 2; adults and youth with advanced solid tumors	Open-label, multicohort, global registrational, efficacy and safety study	341
ISS	Phase 1 and Phase 2 of TRIDENT-1	Integrated safety:	Overall Population: 519

Study/ISS	Phase/Indication	Design	Patients Treated[a]
		Phase 1 and Phase 2 of TRIDENT-1	RP2D Subpopulation: 426
			ROS1-positive NSCLC Treated at the RP2D Subpopulation: 320
			NTRK-positive Solid Tumor Treated at the RP2D Subpopulation: 104

Abbreviations: DDI = drug-drug interaction; CDISC = Clinical Data Interchange Standards Consortium; ISS = integrated summary of safety; NTRK = neurotrophin receptor kinase; PK = pharmacokinetic; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose.
[a] Number of patients treated is based on a data cutoff date of 19-Dec-2022.

The Applicant's Position:

Integrated safety data to support the use of repotrectinib for the treatment of adult patients with locally advanced or metastatic *NTRK*-positive solid tumors comprised pooled results of 519 patients (Safety Analysis Set) from Phase 1 and Phase 2 of the pivotal TRIDENT-1 study and includes all patients who received at least 1 dose of repotrectinib. Data are also presented for subpopulations of patients treated at the RP2D (N = 426), patients with *ROS1*-positive NSCLC treated at the RP2D (N = 320), and patients with *NTRK*-positive solid tumors treated at the RP2D (N = 104), which includes those patients likely to benefit from treatment with repotrectinib based on the RP2D.

Data considered supportive by other clinical studies in cancer patients include the preliminary safety data from the pediatric monotherapy study CARE (TPX-0005-07), from patients that received at least one dose of repotrectinib (N = 26), Phase 1 patients < 12 years of age (N = 10), and Phase 2 patients 12 to 25 years of age (N = 16). Since patients enrolled in the CARE study are distinctly different in their baseline disease characteristics, disease histology, prior therapy, and on-study treatment in comparison to the population enrolled for the *NTRK*-positive cohorts on the TRIDENT-1 study, the Applicant did not integrate CARE with the pivotal study TRIDENT-1 for the integrated safety analysis and described the preliminary data separately. No new safety-related concerns from pediatric patients have been identified. The safety data for the CARE study are briefly described in Section 8.2.9.3.

Safety and tolerability are assessed based on extent of exposure, treatment compliance, AEs, clinical laboratory data, physical examinations, vital signs, ECG parameters, ECHO/MUGA scan, pregnancy, concomitant medications and procedures, survival follow-up, and death reports.

All AEs reported during the AE reporting period (inclusive AEs after the first dose of repotrectinib through the 28-day period after receipt of the last dose of study drug) were

considered TEAEs. Assessment of TEAEs includes type, incidence, severity (graded by the CTCAE, v4.03), timing, seriousness, and relatedness. Adverse events were assessed at every clinic visit.

Complete physical examination, neurological examination, ECOG/Lansky/Karnofsky performance scale assessment, extensive clinical laboratory assessments (hematology, chemistry, coagulation, urinalysis, serum pregnancy tests [for WOCBP] and hypogonadism blood samples [male patients only]) and vital signs (body temperature, blood pressure, heart rate, respiratory rate, pain level [0 to 10], body weight, and height) provided a complete assessment of safety and tolerability in the study.

The FDA's Assessment:

Refer to Section 8.2.1 regarding FDA's approach to the safety analysis. FDA completed a comprehensive analysis and review of safety datasets and patient narratives submitted by the Applicant from TRIDENT-1 and CARE. The number of patients was sufficient to characterize both common and uncommon adverse events; however, the single-arm nature of the trials limited the ability to attribute AEs to the drug versus underlying patients' tumors or other co-morbidities. The assessments conducted as part of the TRIDENT-1 study allowed for a reasonable characterization of AEs, except fractures and pediatric growth (which will be further assessed in the post-market settings).

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

Data:

Table 26: Applicant Extent of Exposure of Study Drug (Safety Analysis Set) (TRIDENT-1)

Characteristic	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[i]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Treatment duration (months)[a]				
Mean (SD)	9.18 (10.013)	8.78 (8.127)	8.94 (8.435)	8.32 (7.186)
Median	5.42	5.54	5.54	5.73
Min, max	0.1, 66.6	0.1, 36.5	0.2, 36.5	0.1, 30.1
Patients treated by month, n (%)				

Characteristic	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[i]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
1	519 (100.0)	426 (100.0)	320 (100.0)	104 (100.0)
2	468 (90.2)	388 (91.1)	289 (90.3)	97 (93.3)
3	395 (76.1)	334 (78.4)	253 (79.1)	79 (76.0)
4	347 (66.9)	298 (70.0)	222 (69.4)	74 (71.2)
5	294 (56.6)	253 (59.4)	189 (59.1)	63 (60.6)
6	272 (52.4)	235 (55.2)	177 (55.3)	57 (54.8)
> 6	238 (45.9)	203 (47.7)	151 (47.2)	51 (49.0)
> 12	143 (27.6)	120 (28.2)	92 (28.8)	28 (26.9)
> 15	109 (21.0)	89 (20.9)	70 (21.9)	19 (18.3)
> 18	81 (15.6)	63 (14.8)	49 (15.3)	14 (13.5)
Patients treated by cycle[b], n (%)				
1	519 (100.0)	426 (100.0)	320 (100.0)	104 (100.0)
2	471 (90.8)	392 (92.0)	292 (91.3)	98 (94.2)
3	404 (77.8)	343 (80.5)	257 (80.3)	84 (80.8)
4	361 (69.6)	309 (72.5)	231 (72.2)	76 (73.1)
5	314 (60.5)	272 (63.8)	202 (63.1)	68 (65.4)
6	284 (54.7)	245 (57.5)	185 (57.8)	59 (56.7)
> 6	249 (48.0)	213 (50.0)	160 (50.0)	52 (50.0)
> 12	154 (29.7)	130 (30.5)	98 (30.6)	32 (30.8)
> 15	118 (22.7)	98 (23.0)	76 (23.8)	22 (21.2)
> 18	98 (18.9)	78 (18.3)	63 (19.7)	15 (14.4)
Number of treatment cycles[c]				
Mean (SD)	10.4 (10.88)	10.0 (8.84)	10.1 (9.17)	9.6 (7.83)
Median	6.0	6.5	6.5	6.5
Min, max	1, 73	1, 40	1, 40	1, 33
Treated at RP2D and titrated to 160 mg BID, n (%)[d]				
Yes[e]	363 (69.9)	363 (85.2)	276 (86.3)	85 (81.7)
No[f]	60 (11.6)	60 (14.1)	43 (13.4)	17 (16.3)
NA[g]	3 (0.6)	3 (0.7)	1 (0.3)	2 (1.9)
NA-Phase 1	93 (17.9)	0	0	0
Cumulative dose on study (mg)				
Mean (SD)	62908.13 (72214.750)	63070.05 (64463.352)	65471.63 (67877.842)	56030.38 (52920.127)
Median	34880.00	40480.00	41360.00	36940.00
Min, max	160.0, 559360.0	160.0, 329600.0	480.0, 329600.0	160.0, 225280.0

Characteristic	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[i]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Relative dose intensity (%)[h]				
Mean (SD)	88.76 (54.697)	79.81 (23.528)	80.79 (22.984)	76.84 (25.013)
Median	94.80	91.90	93.10	84.15
Min, max	13.3, 707.8	13.3, 103.8	18.5, 103.8	13.3, 101.1

Abbreviations: BID = twice daily; DCO = data cutoff; ISS = Integrated Summary of Efficacy; NA = not applicable; NSCLC = non-small cell lung cancer; NTRK = ; QD = once daily; ROS1 = ; RP2D = recommended Phase 2 dose; SD = stable disease.

[a] *Treatment duration (months) for repotrectinib is calculated as (date of last dose – date of first dose + 1)/ 30.4375. For patients who are still on drug as of the data cut-off date, the data cut-off date is used as the date of last dose.*

[b] *A patient is treated during a cycle if they have been administered at least one dose within the specified cycle.*

[c] *Number of cycles is the duration of treatment divided by the length of a cycle (28 days) and then increased to the next integer.*

[d] *The RP2D is 160 mg QD for 14 days followed by 160 mg BID. NA = patients were not on treatment for at least 14 days. NA-Phase 1 = patients in Phase 1 did not have the option to titrate at day 14.*

[e] *Yes = Treated at the RP2D (160 mg QD for 14 days followed by 160 mg BID).*

[f] *No = Started at 160 mg QD, did not titrate up to 160 mg BID.*

[g] *NA = started at 160 mg QD, did not reach titration at the time of DCO.*

[h] *Relative Dose Intensity (%) is defined as (cumulative dose on study (in mg) divided by expected cumulative dose on study) x 100 where expected cumulative dose is defined as the starting dose times number of days on treatment. The expected cumulative dose is adjusted for patients who received a lead-in dose and for patients starting at BID dosing who are required to take study drug QD on the first day.*

[i] *RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).*

Sources: ISS Table 14.1.6.1.1, Table 14.1.6.1.2

The Applicant's Position:

The median (range) duration of exposure to repotrectinib in the Overall population was 5.42 (0.1, 66.6) months, and the extent of exposure was generally consistent across safety populations. A median relative dose intensity of 94.8% is suggestive of good overall compliance with study treatment. The majority (54.7%) of all patients received up to 6 cycles of treatment and 154 (29.7%) ≥ 12 cycles, which supports long-term tolerability of repotrectinib.

Treatment-emergent AEs leading to discontinuation of study drug were reported for < 10% of patients in the Overall population; TEAEs were typically reported at very low incidences (≤ 2 patients). The most frequently reported TEAEs leading to dose reduction (> 2% of patients) were dizziness, ataxia, blood creatine phosphokinase increased, and muscular weakness. Treatment-emergent AEs leading to dose interruption were reported at low incidences (≤ 5% of patients); those reported in > 5% patients were dizziness, dyspnea, and muscular weakness. These results suggest repotrectinib was manageable, tolerable, and TEAEs generally resolved with symptomatic measures.

The FDA's Assessment:

FDA generally agrees with the summary of overall exposure to repotrectinib in the RP2D population and RP2D NTRK+ population. FDA did not verify the data for the overall safety population (n=519) that included patients at different doses and with other gene alterations.

The RP2D is defined as receiving repotrectinib 160 mg QD for 14 days followed by an increase to 160 mg BID. Patients must have met the following criteria on 160 mg QD prior to increasing to 160 mg BID: no evidence of Grade ≥3 treatment-related AE; unmanageable Grade ≥2 dizziness, ataxia, or paresthesia; or Grade ≥3 clinically significant laboratory abnormalities.

The median duration of exposure to repotrectinib in the RP2D population was 5.5 (range: 0.1, 36.5) months and the median number of cycles 6.5 (range: 1, 40). The median relative dose intensity of 92%. Approximately half (58%) of all patients received up to 6 cycles of treatment and 31% received >12 cycles. The majority (85%) of patients received 160 mg QD followed by 160 mg BID. Due to not meeting above criteria, 14% of patients who received repotrectinib were not titrated up to 160 mg BID and 1% of patients were not on treatment for at least 14 days.

The median (range) duration of exposure to repotrectinib and number of treatment cycles in the RP2D NTRK+ population was 5.7 (0.1, 30.1) months and 6.5 (1, 33) cycles, respectively, with a median relative dose intensity of 84%. Approximately half (57%) of all patients received up to 6 cycles of treatment and 31% received >12 cycles. The majority (82%) of patients were treated with 160 mg QD followed by 160 mg BID. Due to not meeting above criteria, 16% of patients who received repotrectinib were not titrated to 160 mg BID and 2% of patients were not on treatment at least 14 days.

8.2.2.2. Relevant characteristics of the safety population:

Data:

Table 27: Applicant Key Demographic Characteristics of the Study Population (Safety Analysis Set) (TRIDENT-1)

Characteristic	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[e]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Age (years)				
Mean	55.0	55.4	55.1	56.3
Standard deviation	13.14	13.05	12.19	15.49

Characteristic	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[e]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Median	56.0	57.0	56.0	59.0
Min, max	18, 93	18, 93	27, 93	18, 84
Age Group, n (%)[a]				
≥ 18 to < 65	392 (75.5)	319 (74.9)	252 (78.8)	66 (63.5)
≥ 65 to < 75	97 (18.7)	81 (19.0)	51 (15.9)	29 (27.9)
≥ 75	30 (5.8)	26 (6.1)	17 (5.3)	9 (8.7)
Sex, n (%)				
Female	300 (57.8)	251 (58.9)	198 (61.9)	51 (49.0)
Male	219 (42.2)	175 (41.1)	122 (38.1)	53 (51.0)
Race, n (%)				
Asian	237 (45.7)	199 (46.7)	157 (49.1)	41 (39.4)
White	231 (44.5)	183 (43.0)	137 (42.8)	46 (44.2)
Black or African American	15 (2.9)	12 (2.8)	9 (2.8)	3 (2.9)
Native Hawaiian or Other Pacific Islander	3 (0.6)	2 (0.5)	2 (0.6)	0
American Indian or Alaska Native	1 (0.2)	1 (0.2)	1 (0.3)	0
Other	4 (0.8)	1 (0.2)	0	0
Not reported	25 (4.8)	25 (5.9)	11 (3.4)	14 (13.5)
Unknown	3 (0.6)	3 (0.7)	3 (0.9)	0
Ethnicity, n (%)				
Hispanic or Latino	15 (2.9)	13 (3.1)	11 (3.4)	2 (1.9)
Not Hispanic or Latino	491 (94.6)	400 (93.9)	303 (94.7)	95 (91.3)
Missing	13 (2.5)	13 (3.1)	6 (1.9)	7 (6.7)
Region, n (%)				
US	164 (31.6)	100 (23.5)	75 (23.4)	23 (22.1)
Asia	195 (37.6)	167 (39.2)	132 (41.3)	35 (33.7)
Other[b]	160 (30.8)	159 (37.3)	113 (35.3)	46 (44.2)
Baseline ECOG performance status[c], n (%)				
0	181 (34.9)	152 (35.7)	112 (35.0)	39 (37.5)
1	337 (64.9)	273 (64.1)	207 (64.7)	65 (62.5)
Missing	1 (0.2)	1 (0.2)	1 (0.3)	0
Smoking status, n (%)				
Current smoker	11 (2.1)	11 (2.6)	5 (1.6)	6 (5.8)
Former smoker	136 (26.2)	136 (31.9)	97 (30.3)	39 (37.5)
Never smoked	269 (51.8)	269 (63.1)	210 (65.6)	59 (56.7)
Not collected[d]	103 (19.8)	10 (2.3)	8 (2.5)	0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ISS = Integrated Summary of Safety; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; US = United States.

Notes: Percentages are based on the number of patients in the Safety Analysis Set.

[a] *Age in years is calculated based on the number of years between the informed consent date and the birth date.*

[b] *Countries grouped to 'Other' include: Australia, Belgium, Canada, Germany, Denmark, Spain, France, United Kingdom, Hungary, Italy, Netherlands, Poland.*

[c] *ECOG Performance Status (0 = Fully Active to 5 = Dead)*

[d] *Smoking status was not collected during Phase 1 of TRIDENT-1.*

[e] *RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).*

Sources: ISS Table 14.1.3.1.1, Table 14.1.3.1.2

Table 28: Applicant Disease History of Study Population (Safety Analysis Set) (TRIDENT-1)

Characteristic	Overall Population (N = 519)	RP2D Populations		
		RP2D Population (N = 426)[e]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Brain metastasis per BICR[b], n (%)				
Yes	147 (28.3)	118 (27.7)	97 (30.3)	21 (20.2)
Brain metastasis per Investigator[b], n (%)				
Yes	182 (35.1)	145 (34.0)	123 (38.4)	21 (20.2)
Stage at study entry, n (%)				
III	11 (2.1)	11 (2.6)	7 (2.2)	4 (3.8)
IIIB	13 (2.5)	12 (2.8)	11 (3.4)	1 (1.0)
IV	494 (95.2)	402 (94.4)	302 (94.4)	98 (94.2)
Missing	1 (0.2)	1 (0.2)	0 (0.0)	1 (1.0)
Resistance mutation[c], n (%)				
Solvent front	76 (14.6)	61 (14.3)	35 (10.9)	26 (25.0)
Gatekeeper	5 (1.0)	4 (0.9)	2 (0.6)	2 (1.9)
Activating	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Other	16 (3.1)	11 (2.6)	9 (2.8)	2 (1.9)
Mutation Negative	340 (65.5)	294 (69.0)	233 (72.8)	61 (58.7)
Mutation Status Unkown[d]	86 (16.6)	60 (14.1)	43 (13.4)	15 (14.4)
Number of Lines Prior Systemic Therapy, n (%)				
Median (Min, Max)	1.00 (0.0, 12.0)	1.00 (0.0, 8.0)	1.00 (0.0, 8.0)	2.00 (0.0, 5.0)
0	98 (18.9)	97 (22.8)	82 (25.6)	15 (14.4)
1	175 (33.7)	159 (37.3)	127 (39.7)	31 (29.8)
2	141 (27.2)	118 (27.7)	85 (26.6)	32 (30.8)
≥3	105 (20.2)	52 (12.2)	26 (8.1)	26 (25.0)
Type of prior systemic therapy[c], n (%)				
TKI	344 (66.3)	275 (64.6)	213 (66.6)	61 (58.7)

Characteristic	Overall Population (N = 519)	RP2D Populations		
		RP2D Population (N = 426)[e]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Chemotherapy with/without immunotherapy	238 (45.9)	158 (37.1)	96 (30.0)	61 (58.7)
Immunotherapy alone	29 (5.6)	13 (3.1)	3 (0.9)	10 (9.6)
Other targeted therapy	68 (13.1)	38 (8.9)	15 (4.7)	23 (22.1)
Other therapy	12 (2.3)	9 (2.1)	2 (0.6)	7 (6.7)
No prior therapy taken	98 (18.9)	97 (22.8)	82 (25.6)	15 (14.4)

Abbreviations: BICR = Blinded Independent Central Review; ISS = Integrated Summary of Safety; Max = maximum; Min = minimum; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; RECIST = Response Evaluation Criteria in Solid Tumors; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; TKI= tyrosine kinase inhibitor.
Notes: Percentages are based on the number of patients in the Safety Analysis Set.
[a] *Reported in more than 1 patient.*
[b] *Brain metastasis present if target and/or non-target lesion selected in the brain at baseline and may include primary CNS tumors..*
[c] *Patients can be counted in more than one category.*
[d] Mutation Status Unknown includes no sample, QC failure, invalid sample/assay type (i.e., tested before the initial TKI).
[e] *RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).*
Sources: ISS Table 14.1.4.1.1, Table 14.1.4.1.2, Table 14.1.7.1.1, Table 14.1.7.1.2

The Applicant's Position:

Demographic characteristics of patients in the RP2D population, and subset of the RP2D population comprising *ROS1*-positive NSCLC patients and *NTRK*-positive patients treated at the RP2D, were broadly consistent with those found in the Overall population. The Overall population has adequate regional representation, with 31% of patients being enrolled from the US.

Overall, the median age (56.0 years), higher proportion of females (57.8%), high proportion of never smokers (51.8%), and incidence of CNS disease (28.3% by BICR; 35.1% by Investigator) at baseline are consistent with the anticipated characteristics of patients with *ROS1*-positive NSCLC and *NTRK*-positive solid tumors that would be treated in the clinic (Chevallier 2021; Gendarme 2022; Ou 2019).

Representation by race and ethnic populations were also as expected and generally representative of the *ROS1*-positive NSCLC and *NTRK*-positive solid tumor patient populations, including a higher proportion of Asian patients (45.7%) and under-represented groups of Black or African American (2.9%), Native Hawaiian or Other Pacific Islanders (0.6%), and Hispanic or Latino (3.4%), which have been reported at a prevalence ranging from 0 to 2.5% in the real-world setting in *ROS1*-positive NSCLC (Chevallier 2021; Costa 2021; Shi 2022; Liang 2014;

Villanueva 2022; Zheng 2020). While the real-world demographics characteristics for patients with *NTRK*-positive solid tumors are not as well characterized as those with *ROS1*-positive NSCLC, the demographics of the *NTRK*-positive populations enrolled in TRIDENT-1 are similar to those enrolled for other TRK TKIs in clinical trials (e.g., larotrectinib [Vitrakvi® USPI 2023] and entrectinib [Rozlytrek® USPI 2023]).

The FDA's Assessment:
FDA agrees with the Applicant's position that the demographic characteristics are generally similar between the RP2D population and RP2D NTRK+ population. The RP2D NTRK+ population was more heavily pretreated (25% with 3 or more prior lines of systemic therapy) compared to the RP2D population (12% with 3 or more prior lines of systemic therapy). There are few reports in the literature regarding the racial and ethnic backgrounds of patients with NTRK+ solid tumors. In one report, there was a higher NTRK prevalence in patients with primarily East Asian ancestry (0.46%, p = 0.015) compared to South Asian (0.37%), American (0.34%), European (0.29%) or African (0.32%) (Wilson, et al 2019).

8.2.2.3. Adequacy of the safety database:

The Applicant's Position:
The population studied in TRIDENT-1 is representative of the *NTRK*-positive solid tumor population; as supported by the study population's demographic, disease, and other baseline characteristics, described above. The patient sample size (N = 519) and duration of exposure to repotrectinib together with evaluation of TEAEs from time of the first dose of repotrectinib through the 28-day period after receipt of the last dose, and the routine clinical and laboratory evaluations performed in the study, were sufficient to evaluate the safety and tolerability of repotrectinib in the proposed indication.

The FDA's Assessment:
The RP2D population in TRIDENT-1 was adequate to assess the safety, including demographics, disease, and other baseline characteristics. The data submitted, including narratives, were well-organized and of adequate quality to perform a comprehensive review of the safety of repotrectinib. Several information requests (IRs) were sent to the Applicant during the review of safety to confirm data, request additional data, request alternative presentations of safety data, or clarify minor discrepancies. Specifically, IRs were sent requesting additional information about patient deaths which is detailed in Section 8.2.4.1.

FDA clarifies that the safety analysis population included in the repotrectinib USPI will be the RP2D population (n=426) that includes ROS1+ NSCLC and NTRK+ solid tumors. This allows for a more precise assessment of AEs that may occur at a lower incidence. Safety data from the CARE study was reviewed but was not included in the overall safety database due to differences in study design and population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

8.2.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
All procedures for the handling and analysis of data were conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

No issues were identified regarding the integrity and quality of the safety data included in this NDA.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.3.2. Categorization of Adverse Event

The Applicant's Position:
AEs were graded according to the NCI CTCAE version 4.03 and coded to PT and SOC using the MedDRA version 25.0 or higher. In TRIDENT-1, all AEs reported during the AE reporting period (inclusive AEs after the first dose of repotrectinib through the 28-day after receipt of the last dose of study drug) are considered TEAEs. AESIs include medical concepts comprised of composite PTs, which are assessed to determine clinical relevance in the target patient population (refer to Section 8.2.4.5 for further detail).

The FDA's Assessment:
In general, FDA agrees with the Applicant's description of AE grading and use of preferred and group terms. Discrepancies in grouping of AE terms and PTs were discussed with the Applicant during labeling negotiations and FDA elected to maintain consistency with those agreed upon during the review for the ROS1+ NSCLC indication. Refer to Section 8.2.4.5 for details of the agreed upon PTs. In this application TEAEs were inclusive of AEs after the first dose of repotrectinib through 30 days after receipt of the last dose of study drug. FDA agrees with the Applicant's position on medical concepts regarding AESIs in Section 8.2.4.5.

8.2.3.3. Routine Clinical Tests

The Applicant's Position:
In Phase 1 of the TRIDENT-1 study, blood chemistry, hematology, coagulation parameters, and urine analysis were analyzed by the local laboratory. In Phase 2, blood chemistry, hematology, coagulation parameters, and urine analysis were analyzed by a central laboratory except for China sites where the parameters were analyzed at the local laboratory. Investigators could

also perform additional local laboratory tests for the purpose of planning treatment administration, dose modification, or following AEs.

The FDA's Assessment:

FDA agrees with the Applicant's position on routine clinical tests. The schedule of events per the TRIDENT-1 protocol includes a complete blood count and complete chemistry assessment during screening, on Days 1, 8, 15 of Cycle 1, on Days 1 and 15 of Cycle 2, and Day 1 of subsequent cycles. The chemistry panel consisted of relevant labs such as: uric acid, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and creatine phosphokinase.

Per the protocol, patients were promptly evaluated with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. Patients and caregivers were advised of the risk of CNS adverse reactions with repotrectinib, including not driving or using machines if they were experiencing a CNS adverse reaction.

8.2.4. Safety Results

In the Overall safety population of TRIDENT-1, TEAEs were reported for 99.2% of patients with treatment-related TEAEs reported for 94.6% of patients. TEAEs with fatal outcome were reported in 5.0% of patients; none were assessed by the Investigator as treatment-related. SAEs were reported for 36.6% of patients and were primarily driven by disease under study with 7.9% of patients with SAEs assessed by the Investigator as treatment-related. Inspection of individual event preferred terms for SAEs (all causality), shows these were typically reported at low incidences (< 2%). The pattern in reported CTCAE grade ≥ 3 TEAEs was similar to that reported for SAEs (i.e., individual event preferred terms [all causality]) and were typically reported at low incidences [< 2%]). Less than 10% of patients discontinued study treatment due to a reported TEAE. Dose modifications due to reported TEAEs occurred in 52.8% of patients, with 34.7% requiring repotrectinib dose reduction and 46.8% interruption of repotrectinib.

Table 29: Applicant Overall Summary of TEAEs (Safety Analysis Set) (TRIDENT 1)

		RP2D Subpopulations		
TEAEs by Event Category	**Overall Population (N = 519)**	**RP2D Population (N = 426)[a]**	***ROS1*-positive NSCLC Treated at RP2D Population (N = 320)**	***NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)**
Patients with TEAEs, n (%)				
All Patients with TEAEs	515 (99.2)	422 (99.1)	318 (99.4)	102 (98.1)

TEAEs by Event Category	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[a]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Leading to Discontinuation of Study Drug	45 (8.7)	31 (7.3)	23 (7.2)	8 (7.7)
Leading to Dose Modifications	274 (52.8)	242 (56.8)	178 (55.6)	63 (60.6)
Leading to Dose Reduction	180 (34.7)	163 (38.3)	112 (35.0)	50 (48.1)
Leading to Drug Interruption	243 (46.8)	213 (50.0)	158 (49.4)	54 (51.9)
SAEs	190 (36.6)	147 (34.5)	106 (33.1)	41 (39.4)
Grade ≥ 3 TEAEs	269 (51.8)	216 (50.7)	156 (48.8)	59 (56.7)
Fatal TEAEs	26 (5.0)	19 (4.5)	13 (4.1)	6 (5.8)
Patients with TRAEs, n (%)				
All Patients with TRAEs	491 (94.6)	409 (96.0)	306 (95.6)	101 (97.1)
Leading to Discontinuation of Study Drug	17 (3.3)	14 (3.3)	11 (3.4)	3 (2.9)
Leading to Dose Modifications	204 (39.3)	186 (43.7)	131 (40.9)	54 (51.9)
Leading to Dose Reduction	165 (31.8)	149 (35.0)	100 (31.3)	48 (46.2)
Leading to Drug Interruption	165 (31.8)	150 (35.2)	107 (33.4)	42 (40.4)
Treatment-Related SAEs	41 (7.9)	38 (8.9)	24 (7.5)	14 (13.5)
Grade ≥ 3 TRAEs	134 (25.8)	122 (28.6)	86 (26.9)	36 (34.6)
Fatal TRAEs	0	0	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events v4.03; ISS = Integrated Summary of Safety; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; SAE = Serious Adverse Event; TEAE = Treatment-Emergent Adverse Event; TRAE = Treatment-Related Adverse Event.

Percentages are based on the number of patients in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 25.0. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. A patient is counted once for each type of event reported. For maximum grade, a patient is counted once based on the maximum grade identified for the specified event type. Leading to Dose Modification includes adverse events that led to dose reduction or drug interruption.

[a] *RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).*

Sources: ISS Table 14.3.1.1.1 and Table 14.3.1.1.5

8.2.4.1. Deaths

Data:

Table 30: Applicant TEAEs with a Fatal Outcome (Safety Analysis Set) (TRIDENT-1)

System Organ Class Preferred Term	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[a]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Patients with TEAEs with fatal outcome	26 (5.0)	19 (4.5)	13 (4.1)	6 (5.8)
Cardiac disorders	6 (1.2)	3 (0.7)	2 (0.6)	1 (1.0)
Cardiac arrest	4 (0.8)	2 (0.5)	1 (0.3)	1 (1.0)
Cardiac failure	1 (0.2)	1 (0.2)	1 (0.3)	0
Cardio-respiratory arrest	1 (0.2)	0	0	0
Infections and infestations	6 (1.2)	4 (0.9)	2 (0.6)	2 (1.9)
Pneumonia	3 (0.6)	2 (0.5)	0	2 (1.9)
Pneumonia aspiration	2 (0.4)	2 (0.5)	2 (0.6)	0
Sepsis	1 (0.2)	0	0	0
General disorders and administration site conditions	6 (1.2)	5 (1.2)	4 (1.3)	1 (1.0)
Death	3 (0.6)	3 (0.7)	3 (0.9)	0
Sudden death	2 (0.4)	1 (0.2)	1 (0.3)	0
Sudden cardiac death	1 (0.2)	1 (0.2)	0	1 (1.0)
Respiratory, thoracic and mediastinal disorders	6 (1.2)	5 (1.2)	4 (1.3)	1 (1.0)
Dyspnoea	2 (0.4)	2 (0.5)	2 (0.6)	0
Respiratory failure	2 (0.4)	1 (0.2)	0	1 (1.0)
Hypoxia	2 (0.4)	2 (0.5)	2 (0.6)	0
Blood and lymphatic system disorders	1 (0.2)	1 (0.2)	1 (0.3)	0
Disseminated intravascular coagulation	1 (0.2)	1 (0.2)	1 (0.3)	0
Nervous system disorders	1 (0.2)	1 (0.2)	0	1 (1.0)
Tremor	1 (0.2)	1 (0.2)	0	1 (1.0)

Abbreviations: ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; NTRK = neurotrophin receptor kinase; NSCLC = non-small cell lung cancer; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; TEAE = Treatment-Emergent Adverse Event.

Notes: Percentages are based on the number of patients in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 25.0. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment-emergent. System organ classes are sorted in order of descending total frequency; preferred terms are sorted similarly within their associated system organ classes.

[a] *RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).*

Sources: ISS Table 14.3.1.19.1, Table 14.3.1.19.5

The Applicant's Position:

At the time of data cutoff date (19-Dec-2022), 26 (5.0%) patients were reported with TEAEs with a fatal outcome in the Overall population. The rate of fatal TEAEs of the Overall population was consistent with the RP2D population, *ROS1*-positive NSCLC Treated at RP2D population, and *NTRK*-positive NSCLC Treated at RP2D population. There were no reported TEAEs with a fatal outcome assessed as treatment related by the Investigator. All other deaths were attributed to progressive disease by the Investigator. Overall, the deaths reported across the repotrectinib clinical program are consistent with the seriousness, complications and/or progression of the underlying malignancy (Nichols 2012), and life-threatening nature of disease under investigation.

The FDA's Assessment:

FDA generally agrees with the Applicant's overall summary of TEAEs among the RP2D population and the NTRK+ solid tumors. FDA did not assess the overall population. Withdrawal from study therapy due to TEAEs was similar between the RP2D population and NTRK+ populations, occurring in 7% and 8% of patients, respectively. In the RP2D population, Grades 3-4 TEAEs were observed in 51% of patients, and similarly, in the NTRK+ population, Grades 3-4 TEAEs occurred in 57% of patients.

FDA does not agree with the Applicant's position regarding on-study deaths, however, these deaths all occurred in the ROS1+ NSCLC indication from the previous approval. FDA analysis of Grade 5 TEAEs differed from the Applicant's assessment. The Applicant stated that 19 (4.5%) patients had a TEAE with a fatal outcome including cardiac arrest (n=2), death (n=3), hypoxia (n=2), pneumonia (n=2), pneumonia aspiration (n=2), cardiac failure (n=1), disseminated intravascular coagulation (n=1), dyspnea (n=2), respiratory failure (n=1), sudden cardiac death (n=1), sudden death (n=1), and tremor (n=1). After FDA reviewed the patient narratives for all deaths, FDA requested clarification and additional information (b) (4) for the AEs of death and sudden death to make a determination of cause. The additional information provided by the Applicant allowed FDA to confirm that these four deaths were due to disease progression. Based on this, FDA determined that Grade 5 TEAEs occurred in 3.5% and 5.8% of the RP2D population and NTRK+ populations, respectively.

A brief summary of all on-study deaths is provided in **Error! Reference source not found.**. Four of these 19 patients reported death (n=3) or sudden death (n=1) as their fatal TEAE.

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Table 31: FDA Grade 5 TEAEs, TRIDENT-1

Patient ID	Disease	AE Term	Study Day of Event
Phase 1			
(b) (6)	NSCLC	Hypoxia	85
Phase 2			
(b) (6)	ROS1+ NSCLC	Death	49

Patient ID	Disease	AE Term	Study Day of Event
(b) (6)	NSCLC	Death	21
	NSCLC	Death	110
	ROS1+ NSCLC	Sudden Death	83
	ROS1+ NSCLC	Dyspnea	28
	NTRK+ solid tumor	Pneumonia	281
	ROS1+ NSCLC	Pneumonia aspiration	220
	ROS1+ NSCLC	Pneumonia aspiration	35
	ROS1+ NSCLC	Hypoxia	156
	NTRK+ solid tumor	Tremor	117
	ROS1+ NSCLC	Cardiac failure	54
	ROS1+ NSCLC	Dyspnea	241
	NTRK+ solid tumor	Cardiac arrest	18
	ROS1+ NSLC	DIC	147
	NTRK+ solid tumor	Pneumonia	4
	ROS1+ NSCLC	Cardiac arrest	23
	NTRK+ solid tumor	Respiratory failure	56
	NTRK+ solid tumor	Sudden cardiac death	47

Source: Clinical Study Report, NDA 218213
Abbreviations: DIC: Disseminated intravascular coagulation; NSCLC: non-small cell lung cancer

Below are detailed narratives of four patients that had AEs of death and sudden death (b) (4)

(b) (6): This was a 70-year-old man with ROS1+ NSCLC who had previously received a TKI and had a history of coronary artery stent insertion, COPD and congestive cardiac failure. The patient received repotrectinib for 49 days until discontinuing due to death. The reported cause of death was “death”. Given the context provided in the narrative, FDA considers this death likely related progression of underlying comorbidities or disease.

(b) (6): This was a 63-year-old woman with ROS1+ NSCLC with ECG findings of inferior wall myocardial infarction of indeterminate age at baseline. The patient received repotrectinib for 21 days until discontinuing due to death. The reported cause of death was “death.” Given the context provided in the narrative, FDA considers this death likely related to progression of underlying cardiac comorbidities or respiratory failure secondary to disease progression.

(b) (6): This was a 56-year-old woman with NTRK+ NSCLC who had previously received a TKI and received repotrectinib for 110 days until the event of death. The reported cause of death was “death”. Given the context provided in the narrative, FDA considers this death likely related to disease progression.

(b) (6): This was a 55-year-old woman with ROS1+ NSCLC who had previously received a TKI and had a history of DVT. The patient received repotrectinib at the RP2D for 83 days until she experienced sudden death in the setting of worsening cough and dyspnea in the preceding week. Preliminary autopsy did not reveal a pulmonary embolism. Given the context provided in the narrative, FDA considers this death likely related to disease progression.

8.2.4.2. Serious Adverse Events

Data:

Table 32: Applicant Treatment-Emergent Serious Adverse Events in > 2 Patients by SOC and PT (Safety Analysis Set) (TRIDENT-1)

System Organ Class[a] Preferred Term	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[b]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Patients with at least one SAE	190 (36.6)	147 (34.5)	106 (33.1)	41 (39.4)
Respiratory, thoracic and mediastinal disorders	66 (12.7)	51 (12.0)	41 (12.8)	10 (9.6)
Dyspnoea	18 (3.5)	13 (3.1)	11 (3.4)	2 (1.9)
Pleural effusion	15 (2.9)	12 (2.8)	11 (3.4)	1 (1.0)
Hypoxia	13 (2.5)	11 (2.6)	10 (3.1)	1 (1.0)
Pulmonary embolism	8 (1.5)	6 (1.4)	4 (1.3)	2 (1.9)
Pneumonitis	6 (1.2)	6 (1.4)	5 (1.6)	1 (1.0)
Respiratory failure	6 (1.2)	4 (0.9)	2 (0.6)	2 (1.9)
Infections and infestations	58 (11.2)	43 (10.1)	25 (7.8)	18 (17.3)
Pneumonia	28 (5.4)	21 (4.9)	11 (3.4)	10 (9.6)
Sepsis	6 (1.2)	3 (0.7)	2 (0.6)	1 (1.0)
Urinary tract infection	4 (0.8)	2 (0.5)	1 (0.3)	1 (1.0)
Pneumonia aspiration	3 (0.6)	3 (0.7)	3 (0.9)	0
Nervous system disorders	33 (6.4)	23 (5.4)	17 (5.3)	6 (5.8)
Syncope	6 (1.2)	6 (1.4)	3 (0.9)	3 (2.9)
Dizziness	5 (1.0)	3 (0.7)	1 (0.3)	2 (1.9)
Cerebrovascular accident	4 (0.8)	1 (0.2)	1 (0.3)	0
General disorders and administration site conditions	19 (3.7)	16 (3.8)	11 (3.4)	5 (4.8)
Pyrexia	7 (1.3)	6 (1.4)	3 (0.9)	3 (2.9)
Death	3 (0.6)	3 (0.7)	3 (0.9)	0

System Organ Class[a] Preferred Term	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[b]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Cardiac disorders	16 (3.1)	11 (2.6)	8 (2.5)	3 (2.9)
Pericardial effusion	5 (1.0)	4 (0.9)	4 (1.3)	0
Cardiac arrest	4 (0.8)	2 (0.5)	1 (0.3)	1 (1.0)
Gastrointestinal disorders	15 (2.9)	11 (2.6)	5 (1.6)	6 (5.8)
Abdominal pain	3 (0.6)	3 (0.7)	2 (0.6)	1 (1.0)
Nausea	3 (0.6)	1 (0.2)	1 (0.3)	0
Musculoskeletal and connective tissue disorders	14 (2.7)	10 (2.3)	7 (2.2)	3 (2.9)
Muscular weakness	6 (1.2)	5 (1.2)	3 (0.9)	2 (1.9)
Blood and lymphatic system disorders	10 (1.9)	8 (1.9)	6 (1.9)	2 (1.9)
Anaemia	6 (1.2)	5 (1.2)	3 (0.9)	2 (1.9)
Injury, poisoning and procedural complications	9 (1.7)	7 (1.6)	6 (1.9)	1 (1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (1.5)	5 (1.2)	4 (1.3)	1 (1.0)
Vascular disorders	7 (1.3)	5 (1.2)	4 (1.3)	1 (1.0)
Metabolism and nutrition disorders	5 (1.0)	4 (0.9)	3 (0.9)	1 (1.0)
Hyponatraemia	3 (0.6)	3 (0.7)	3 (0.9)	0
Renal and urinary disorders	5 (1.0)	4 (0.9)	4 (1.3)	0
Hepatobiliary disorders	4 (0.8)	1 (0.2)	0	1 (1.0)
Investigations	3 (0.6)	2 (0.5)	1 (0.3)	1 (1.0)

Abbreviations: ISS = integrated summary of safety; MedDRA = Medical Dictionary for Regulatory Activities ; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; PT = preferred term; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; SAE = Serious Adverse Event; SOC = system organ class; TEAE = treatment-emergent adverse event.

Notes: Percentages are based on the number of patients in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 25.0. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. System organ classes are sorted in order of descending total frequency; preferred terms are sorted similarly within their associated system organ classes.

[a] The selection criterion of > 2 patients used in this table has been applied at the SOC level for the Overall Population. The incidence of all TEAEs within a SOC may reach the required threshold of > 2 patients, whilst all PTs within a SOC occur at incidences of < 2 patients, explaining the absence of any PTs for those SOCs.

[b] RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).

Sources: ISS Table 14.3.1.11.1, Table 14.3.1.11.5

The Applicant's Position:

In the Overall population of TRIDENT-1, the most frequently reported SAEs (reported in > 5% of patients) at the SOC level were Respiratory, thoracic and mediastinal disorders (12.7%),

Infections and infestations (11.2%), and Nervous system disorders (6.4%). The most frequently reported SAEs (> 2% of patients) in the Overall population were pneumonia (5.4%), dyspnea (3.5%), pleural effusion (2.9%) and hypoxia (2.5%). Similar to the assessment of death, overall, the pattern and frequency of SAEs reported in the overall population are also consistent with the seriousness, complications and/or progression of the underlying malignancy and life-threatening nature of the disease under investigation.

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of treatment-emergent SAEs in the RP2D population. In the RP2D population and RP2D NTRK+ population, SAEs occurred in 35% and 39% of patients, respectively. The most common SAEs (≥2%) in the RP2D population were pneumonia GT (6%), dyspnea (3.1%), pleural effusion (2.8%), and hypoxia (2.6%). Pneumonia GT included pneumonia, pneumonia aspiration, lower respiratory tract infection, pneumonia viral, pneumonia bacterial, lower respiratory tract infection bacterial, and pneumonia klebsiella. FDA identified 27 of 426 (6%) patients with the GT pneumonia and 21 of 426 (4.9%) using the PT pneumonia. The most frequent SAEs (≥2%) in the RP2D NTRK+ population was the GT pneumonia (10%) syncope (2.9%), and pyrexia (2.8%).

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 33: Applicant TEAEs Leading to Discontinuation of Study Drug in > 2 Patients (Safety Analysis Set) (TRIDENT-1)

System Organ Class Preferred Term	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[a]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Patients with TEAEs leading to discontinuation of study drug	45 (8.7)	31 (7.3)	23 (7.2)	8 (7.7)
Grade 1	1 (0.2)	1 (0.2)	1 (0.3)	0
Grade 2	12 (2.3)	7 (1.6)	5 (1.6)	2 (1.9)
Grade 3	18 (3.5)	13 (3.1)	11 (3.4)	2 (1.9)
Grade 4	3 (0.6)	3 (0.7)	2 (0.6)	1 (1.0)
Grade 5	11 (2.1)	7 (1.6)	4 (1.3)	3 (2.9)
Respiratory, thoracic, and mediastinal disorders	16 (3.1)	12 (2.8)	9 (2.8)	3 (2.9)
Dyspnoea	4 (0.8)	3 (0.7)	2 (0.6)	1 (1.0)

System Organ Class Preferred Term	Overall Population (N = 519)	RP2D Subpopulations		
		RP2D Population (N = 426)[a]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Pneumonitis	4 (0.8)	4 (0.9)	3 (0.9)	1 (1.0)
Nervous system disorders	6 (1.2)	4 (0.9)	3 (0.9)	1 (1.0)
General disorders and administration site conditions	5 (1.0)	4 (0.9)	2 (0.6)	2 (1.9)
Cardiac disorders	3 (0.6)	3 (0.7)	2 (0.6)	1 (1.0)
Infections and infestations	3 (0.6)	1 (0.2)	1 (0.3)	0
Metabolism and nutrition disorders	3 (0.6)	1 (0.2)	1 (0.3)	0
Musculoskeletal and connective tissue disorders	3 (0.6)	3 (0.7)	3 (0.9)	0
Muscular weakness	3 (0.6)	3 (0.7)	3 (0.9)	0

Abbreviations: ISS = integrated summary of safety; MedDRA = Medical Dictionary for Regulatory Activities ; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; TEAE = Treatment-Emergent Adverse Event.
Notes: Percentages are based on the number of patients in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 25.0. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. System organ classes are sorted in order of descending total frequency; preferred terms are sorted similarly within their associated system organ classes.
[a] *RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).*
Sources: ISS Table 14.3.1.6.1, Table 14.3.1.6.5

The Applicant's Position:

In the Overall population, TEAEs leading to discontinuation of study drug were reported for 8.7% of patients and were consistent with the RP2D, *ROS1*-positive NSCLC treated at RP2D, and *NTRK*-positive solid tumor treated at the RP2D Populations. Discontinuations were largely driven (3.1%) by respiratory events likely secondary to underlying disease and/or progression or required per protocol dose modification guidelines. Although dizziness was the most frequently reported TEAE, there were no treatment discontinuations reported due to dizziness suggesting a clinically manageable course of the events including implementation of dose modifications.

The FDA's Assessment:

FDA agrees with the Applicant's summary of treatment discontinuations in the RP2D population and RP2D NTRK+ population. Permanent discontinuation of repotrectinib due to an AE occurred in 7% of patients in the RP2D population. AEs that required treatment discontinuation in ≥0.5% of patients in the RP2D population included pneumonitis (0.9%), dyspnea (0.7%), and muscular weakness (0.7%). All other adverse reactions occurred in <0.5% of patients.

8.2.4.4. Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

In the Overall population, TEAEs leading to interruption of study drug were reported for 46.8% of patients and were consistent between the RP2D, *ROS1*-positive NSCLC treated at RP2D, and *NTRK*-positive solid tumors treated at the RP2D populations, respectively. Individual TEAE PTs in the Overall population were typically reported at low incidences (≤ 5% of patients). The most frequently reported TEAEs leading to dose interruption (> 2% patients) were dizziness (8.5%), dyspnea (6.0%), muscular weakness (5.0%), ataxia (3.3%), pneumonia (3.3%), blood creatine phosphokinase increased (2.9%), and anemia (2.7%). Dose reductions were driven largely by on-target TRK-related CNS toxicities (18.9%) and muscular disorders (4.8%), allowing patients to continue on treatment and derive clinical benefit while optimally balancing toxicity. Respiratory events were associated with 3.9% of dose reductions. The most frequently reported TEAEs leading to dose reduction (> 2% patients) were dizziness (10.2%), ataxia (5.0%), muscular weakness (3.9%), and blood creatine phosphokinase increased (2.3%).

The FDA's Assessment:

As previously stated, FDA did not confirm the safety data in the overall population. In the RP2D population, dosage interruptions due to an adverse reaction occurred in 50% of patients who received repotrectinib. AEs requiring dosage interruption in ≥2% of patients included dizziness (9%), dyspnea (6%), muscular weakness (6%), ataxia (5%), pneumonia (5%), peripheral neuropathy (4.7%), anemia (3.1%), and vomiting (2.1%).

In the RP2D population, dosage reductions due to an AE occurred in 38% of patients. AEs requiring dosage reduction in ≥2% of patients included dizziness (12%), ataxia (8%), muscular weakness (4.5%), peripheral neuropathy (2.8%), and cognitive impairment (2.1%).

8.2.4.5. Significant Adverse Events

Adverse Events of Special Interest

Data:

Table 34: Applicant Treatment-Emergent Adverse Events of Special Interest in > 2 Patients by Medical Concept (Safety Analysis Set) (TRIDENT-1)

Adverse Event of Special Interest (AESI)[a]	Overall Population	RP2D Subpopulation		
	All Causality (N = 519)	RP2D Population (N = 426)[a]	*ROS1*-positive NSCLC Treated at RP2D Population (N = 320)	*NTRK*-positive Solid Tumors Treated at RP2D Population (N = 104)
Patients with at least one AESI	489 (94.2)	403 (94.6)	305 (95.3)	96 (92.3)
Medical Concept Term				
Ataxia	137 (26.4)	121 (28.4)	89 (27.8)	31 (29.8)
Cognitive disorders	116 (22.4)	105 (24.6)	76 (23.8)	29 (27.9)
Dizziness	333 (64.2)	275 (64.6)	206 (64.4)	68 (65.4)
Dysgeusia	289 (55.7)	242 (56.8)	176 (55.0)	64 (61.5)
Hepatic enzyme elevation	127 (24.5)	118 (27.7)	96 (30.0)	22 (21.2)
Mood disorders	32 (6.2)	25 (5.9)	20 (6.3)	5 (4.8)
Muscular weakness	101 (19.5)	85 (20.0)	70 (21.9)	13 (12.5)
Paraesthesia	197 (38.0)	167 (39.2)	128 (40.0)	39 (37.5)
Peripheral sensory neuropathy	98 (18.9)	83 (19.5)	63 (19.7)	19 (18.3)
Pneumonitis	15 (2.9)	13 (3.1)	9 (2.8)	4 (3.8)
QT prolongation	5 (1.0)	5 (1.2)	4 (1.3)	1 (1.0)
Skeletal fractures	15 (2.9)	10 (2.3)	8 (2.5)	2 (1.9)
Sleep disorders	79 (15.2)	75 (17.6)	53 (16.6)	22 (21.2)
Vision disorders	69 (13.3)	56 (13.1)	38 (11.9)	18 (17.3)

Abbreviations: AESI = adverse event of special interest; EOSI = event of special interest; ISS = integrated summary of safety; MedDRA = Medical Dictionary for Regulatory Activities ; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; PT = preferred term; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; SAP = statistical analysis plan; TEAE = treatment-emergent adverse event.

Notes: Percentages are based on the number of patients in the Safety Analysis Set. AESIs are presented here by grouped Medical Concepts; individual PTs contributing to each medical concept are further described in M2.7.4. and the SAP based on cross functional review of higher-level terms and preferred terms.

[a] RP2D (N=426) consists of the ROS1-positive NSCLC Treated at RP2D Population (N = 320), NTRK-positive Solid Tumors Treated at RP2D Population (N = 104), and Others Treated at the RP2D population (N = 2).

Sources: ISS Table 14.3.1.31.1, Table 14.3.1.51.1

The Applicant's Position:

The AESI selection for the repotrectinib safety assessment was multi-factorial, taking into consideration the toxicities observed in the preclinical data; the frequent, severe, and serios AEs reported in the clinical data, potential neurologic effects associated with TRK inhibition, and reported adverse events listed for TKIs that are similar drugs-in-class for *ROS1*-positive and *NTRK*-positive tumors. The following AESIs were identified and assessed for repotrectinib as pre-defined in the SAP: Ataxia, Cognitive Disorders, Dizziness, Dysgeusia, Mood Disorders, Sleep Disorders, Paresthesia, Peripheral sensory neuropathy, Muscular Weakness, Hepatic Enzyme

Elevations, Pneumonitis, QT prolongation, Skeletal Fractures, and Vision Disorders. Medical Concepts containing grouped medical terms were provided when appropriate.

The most frequently reported AESIs by Medical Concept (all causality) in the Overall population were primarily CNS effects consistent with those reported with TRK inhibition (Drilon 2020); CNS AESIs are discussed further in Section 8.2.5.1. The median time to first event onset for the most frequently reported AESIs (≥ 10% of patients) in the Overall population was typically within the first month of study treatment, irrespective of causality.

- Dizziness was the most frequently reported AESI (Medical Concept, 64.2% of patients); Grade 3 dizziness was reported in 16 (3.1%) patients. The median (range) time to onset for dizziness events was 7 days (1 day to 526 days). Dose reduction was required in 10.6% of patients and 8.9% required dose interruption of repotrectinib due to reported dizziness. No patients discontinued repotrectinib due to reported dizziness.
- Skeletal Fractures, as a Medical Concept, were reported in 15 (2.9%) of patients in the Overall population with the most common site of fracture occurring in the foot (5 [1%] patients). Most fractures were mild-to-moderate in severity. None of the skeletal fractures were considered treatment-related. Most patients did not require a dose modification and none led to discontinuation of study drug. Most patients reported with a fracture had an underlying risk factor that included a history of bone metastases, hypophosphatemia, osteoporosis, osteoarthritis, prior fractures, unwitnessed falls, visual impairment, and adverse events of relevance on study (e.g., dizziness, cognitive disorders, ataxia, and falls) that preceded the skeletal fracture. A review of these cases did not identify any direct causal relationship between skeletal fractures and repotrectinib.
    - Serious Skeletal Fractures, as a Medical Concept, were reported in 5 (1.0%) patients with one event each of ankle, fibula, pathological, rib, and spinal compression fracture.
- No clinically meaningful cardiac toxicity or cardiac dysrhythmias were reported including evidence of QT prolongation
- No reported cases of tumor lysis syndrome (TLS)
- No reported cases of drug-induced liver injury (DILI)
- No reported cases of serious or sight threatening vision disorders; the majority of events were low grade in severity.
    - Of the patients with ocular events (13.3%) reported, 70% of patients were reported with at least one confounding or risk factor identified, however, these risk factors did not likely influence the initiation or continuation of repotrectinib.

AESIs leading to discontinuation of study drug were infrequent (14 [2.7%] patients), with pneumonitis (4 [0.8%] patients), cognitive disorders (4 [0.8%]), and muscular weakness (3 [0.6%]) being the only Medical Concepts where any AESI PT was reported in > 1 patient. To mitigate against worst grade events, measures were implemented to allow for prophylactic management of toxicities, e.g., dizziness with medication such as meclizine or other antihistamines at the Investigator's discretion. In addition, dose management guidance for

toxicities by severity was provided to Investigators to allow for dose interruption and dose reductions in support of drug tolerability and patient compliance.

Serious AESIs and grade ≥ 3 AESIs were reported for 5.6% and 11.8% of patients, respectively; in both event categories, the individual event PTs were typically reported at very low incidences (< 1% of patients). There were no AESIs with fatal outcome. The most frequently reported serious AESIs (≥ 2 patients) in the Overall population, summarized by Medical Concept, were pneumonitis (6 [1.2%] patients), muscular weakness (6 [1.2%]), skeletal fractures (5 [1.0%]), dizziness (5 [1.0%]), and cognitive disorders (4 [0.8%]). The most frequently reported grade ≥ 3 treatment-related AESIs (≥ 1% of patients) in the Overall population, summarized by Medical Concept, were dizziness (16 [3.1%]), hepatic enzyme elevation (11 [2.1%]), muscular weakness (9 [1.7%]), and peripheral sensory neuropathy (6 [1.2%]).

There were no important differences in the incidence of Medical Concept terms across the RP2D subpopulations when compared to the Overall population.

The FDA's Assessment:

FDA did not assess the AESIs in the overall population; however, FDA conducted a review of the AESIs in the RP2D population and agrees with the Applicant's assessment. FDA did not identify any new AESIs during the review of this application. AESIs previously identified for repotrectinib were ataxia, cognitive disorders, dizziness, dysgeusia, hepatic enzyme elevation, mood disorders, muscular weakness, paresthesia, pneumonitis, peripheral sensory neuropathy, QT prolongation, skeletal fractures, sleep disorders, and vision disorders. The grouped terms used to analyze the RP2D population are listed in **Error! Reference source not found.**.

Table 35: FDA Group Terms for AESIs, TRIDENT-1

Grouped Term	MedDRA Search Terms
Ataxia	ataxia, gait disturbances, balance disorder, coordination abnormal and cerebellar ataxia
Cognitive Impairment	memory impairment, disturbance in attention, cognitive disorder, confusional state, amnesia, delirium, aphasia, attention deficit hyperactivity disorder, depressed level of consciousness, delusion, hallucinations, mental disorder, mental status change, altered state of consciousness, and neurological decompensation
Dizziness	dizziness, vertigo, dizziness postural, dizziness exertional, and vertigo positional
Mood disorders	Affect lability, Affective disorder, Aggression, Agitated depression, Agitation, Anxiety, Anxiety disorder, Depressed mood, Depression, Euphoric mood, Irritability, Mania, Mood altered, Mood

Grouped Term	MedDRA Search Terms
	swings, Persistent depression disorder, Personality change, Personality disorder, Psychomotor retardation, Stress, Suicidal ideation
Myalgia	myalgia, musculoskeletal pain, myositis, musculoskeletal discomfort
Peripheral sensory neuropathy	Neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy, dysesthesia, paresthesia, hypoesthesia, hyperesthesia
Pneumonitis	Interstitial lung disease, pneumonitis
Skeletal fractures	Fractures: Acetabulum, Ankle, Foot, Rib, Spinal Compression, Sternal
Sleep disorders	somnolence, insomnia, hypersomnia, sleep disorder, narcolepsy, sleep apnea syndrome, snoring
Vision disorders	vision blurred, dry eye, visual impairment, visual field defect, cataract, conjunctivitis, eye pain, photophobia, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, color blindness, diplopia, eye hematoma, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, night blindness, ophthalmic herpes zoster

Source: Summary of Clinical Safety Table 1.1.3.2-1 and FDA Grouped Terms

The following FDA assessment of AESIs are based on the RP2D population.

Central nervous system AEs were observed in patients receiving repotrectinib. Dizziness occurred in 65% of patients with dose interruption required in 9% and dose reduction in 11% of patients. The GT Ataxia occurred in 28% of patients with interruption occurring in 5% and dose reduction in 8% of patients. One (0.2%) patient permanently discontinued repotrectinib due to ataxia. Cognitive disorders occurred in 25% of patients and required dose reduction in 2.1%, dose interruption in 2%, and permanent discontinuation in 0.5% of patients. Mood disorders occurred in 6% of patients and required dose interruption and reduction in 0.2% of patients each. Sleep disorders occurred in 18% of patients and required dose interruption in 0.7% and dose reduction in 0.2% of patients.

Muscular weakness was reported in 20% of patients with 2% having Grade 3 or 4, and 1.2% reported as an SAE. Dose interruption occurred in 6%, dose reduction in 4.5%, and permanent discontinuation in 0.7% of patients. Myalgia with increase blood creatine phosphokinase (CPK) has been identified as an AESI by the Applicant during the ROS1+ NSCLC review. In the RP2D population, myalgia occurred in 13% of patients with Grade 3 occurring in 0.7% of patients.

Four patients (0.9%) required dose interruption due to myalgia. Concurrent increase in CPK occurred in 3.7% of patients, requiring dose interruption for one (0.2%) patient. No events of rhabdomyolysis were observed.

Skeletal fractures were observed in patients receiving repotrectinib and have been reported with other TKI therapies including larotrectinib and entrectinib. Narrative summaries were reviewed for the RP2D population. Some fractures occurred at sites of disease or prior radiation site. Fractures occurred in 2.3% of patients. Fractures involved the ribs (0.5%); feet (0.5%); and spine, acetabulum, sternum, and ankles in 0.2% of patients each. Additional data submitted from the CARE study in pediatric and young adult patients noted skeletal fractures occurring in 2 (8%) of 26 evaluable patients; one 12-year-old patient (ankle/foot) who fell off their skateboard and one 10-year-old patient (tibial stress fracture) with unknown mechanism of injury, both requiring dose interruption. Neither patient was noted to have a pathological fracture or prior radiation to the fracture site.

Interstitial lung disease (ILD)/pneumonitis occurred in 3.1% of patients with Grade 3 ILD/pneumonitis occurring in 1.2% of patients. ILD occurred in 0.2% and pneumonitis in 2.8% of patients. Dose interruption was required in 1.4%, dose reduction in 0.5%, and permanent discontinuation in 1.1% of patients.

FDA reviewed patient narratives and searched the safety datasets for terms related to or possibly contributing to liver toxicity. Increased aspartate aminotransferase (AST) occurred in 41% of patients and increased alanine transaminase (ALT) occurred in 38% of patients, including Grade 3 or 4 increased ALT occurring in 3.3%, and increased AST in 2.9% of patients. The median time to onset of increased ALT or AST was 15 days (range: 1 day to 1.9 years). Dose interruptions or reductions occurred in 2.8% and 1.2% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.5% of patients.

For the above AESIs, based on review of the Applicant's data, patient narratives, and considering other findings such as the safety profile of other drugs in class, FDA considered these events likely to be at least possibly related to repotrectinib and met the criteria to be included in the Warnings and Precautions section of the product label for repotrectinib. It must be noted that attribution of AEs to the study drug is challenging to the open-label, single-arm design of the study as no comparator arm was used.

Vision disorders were reported in patients receiving repotrectinib. FDA analyzed the safety dataset and patient narratives to inform this review. Vision disorders were reported in 12% of patients, including Grade 3 or 4 occurring in 0.5% of patients. Vision disorder preferred terms observed in the safety dataset occurring >1% included vision blurred (3.8%), visual impairment (1.9%) and dry eye (1.2%). There was one Grade 3 visual impairment and one Grade 3 ophthalmic herpes zoster. The majority of vision disorder preferred terms included in the grouped term "vision disorders" were all reported as low grade. Dose interruption occurred for

1.2%, dose reduction for 0.2% and permanent discontinuation for 0.2% (color blindness) of patients. Vision disorders were not included in the Warnings and Precautions section of the USPI for repotrectinib based on the review of the ROS+ NSCLC indication. FDA review of the safety data for vision disorders for the current indication does not support inclusion in Warnings and Precautions (e.g., based on severity of findings). FDA notes a PMR was issued in the approval letter for the ROS1+ NSCLC indication to further investigate the potential safety signal for vision disorders for repotrectinib.

AESIs of all grades are tabulated in **Error! Reference source not found.** below comparing the RP2D population to the RP2D NTRK+ population.

Table 36: FDA AESIs for the RP2D Population and RP2D NTRK+ Population, TRIDENT-1

Group Term	RP2D population N=426 n (%)	RP2D NTRK+ population N=104 n (%)
Dizziness	65	65
Ataxia	28	11
Cognitive impairment	25	28
Sleep disorders	18	22
Myalgia	13	15
Vision disorders	12	15
Mood disorders	6	6
ILD/pneumonitis	3.1	3.8
Skeletal fractures	2.3	1.9

Source: adae.xpt

Considering these AESIs, the risk: benefit ratio was favorable for repotrectinib for the treatment of NTRK+ solid tumors.

8.2.4.6. Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 37 summarizes the ADRs identified for repotrectinib that were reported in ≥ 10% of patients in the Overall population.

Table 37: Applicant Adverse Drug Reactions in the Overall Population (in ≥ 10% of Patients) and RP2D Subpopulations (Safety Analysis Set) (TRIDENT-1)

Adverse Reaction System Organ Class Grouped/Preferred Term	Overall Population (N=519)		RP2D Subpopulation (N=426)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Nervous system disorders				
Dizziness[a]	333 (64.2)	16 (3.1)	275 (64.6)	12 (2.8)
Dysgeusia[b]	274 (52.8)	0	228 (53.5)	0
Peripheral neuropathy[c]	250 (48.2)	7 (1.3)	207 (48.6)	6 (1.4)
Ataxia[d]	137 (26.4)	2 (0.4)	121 (28.4)	2 (0.5)
Cognitive disorders[e]	116 (22.4)	4 (0.8)	105 (24.6)	4 (0.9)
Headache[f]	98 (18.9)	1 (0.2)	81 (19.0)	0
Gastrointestinal disorders				
Constipation	195 (37.6)	1 (0.2)	162 (38.0)	1 (0.2)
Nausea	106 (20.4)	5 (1.0)	85 (20.0)	3 (0.7)
Vomiting	70 (13.5)	5 (1.0)	53 (12.4)	5 (1.2)
Diarrhoea	69 (13.3)	3 (0.6)	60 (14.1)	3 (0.7)
Respiratory, thoracic and mediastinal disorders				
Dyspnoea[g,*]	164 (31.6)	36 (6.9)	128 (30.0)	27 (6.3)
Cough[h]	102 (19.7)	1 (0.2)	77 (18.1)	1 (0.2)
General disorders and administration site conditions				
Fatigue[i]	160 (30.8)	7 (1.3)	127 (29.8)	5 (1.2)
Edema[j]	76 (14.6)	2 (0.4)	65 (15.3)	2 (0.5)
Musculoskeletal and connective tissue disorders				
Muscular weakness	101 (19.5)	9 (1.7)	85 (20.0)	8 (1.9)
Myalgia[k]	67 (12.9)	3 (0.6)	54 (12.7)	3 (0.7)
Pain in extremity	54 (10.4)	1 (0.2)	42 (9.9)	0
Metabolism and nutritional				
Increased weight	74 (14.3)	13 (2.5)	67 (15.7)	11 (2.6)
Eye disorders				
Vision disorders[l]	63 (12.1)	2 (0.4)	52 (12.2)	2 (0.5)

Abbreviations: ADR = adverse drug reaction; ISS = Integrated Summary of Safety; NSCLC = non-small cell lung cancer; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose.

Notes:

** Includes two patients with ROS1-positive NSCLC reported with Grade 5 dyspnea.*

[a] Includes terms dizziness, vertigo, dizziness postural, dizziness exertional, vertigo positional.

[b] Includes terms dysgeusia, ageusia, anosmia, hypogeusia.

[c] Includes terms neuralgia, neuropathy peripheral, peripheral sensory neuropathy, dysesthesia, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, hyperesthesia.

[d] Includes terms ataxia, gait disturbance, balance disorder, cerebellar ataxia.

[e] Includes terms memory impairment, disturbance in attention, cognitive disorder, confusional state, amnesia, attention deficit hyperactivity disorder, delirium, altered state of consciousness, aphasia, delusion, depressed level of consciousness, hallucination, mental status changes, neurological decompensation.
[f] Includes terms headache, migraine, tension headache
[g] Includes terms dyspnea and dyspnea exertional.
[h] Includes terms productive cough, cough, and upper-airway cough syndrome.
[i] Includes terms fatigue and asthenia.
[j] Includes terms generalized edema, periorbital edema, localized edema, face edema, edema peripheral, edema, eye edema, scrotal edema.
[k] Includes terms myalgia, myositis, musculoskeletal discomfort, musculoskeletal pain.
[l] Includes terms vision blurred, dry eye, visual impairment, visual field defect, cataract, conjunctivitis, eye pain, photophobia, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, color blindness, diplopia, eye hematoma, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, night blindness, ophthalmic herpes zoster.
Sources: ADRs reported for All Grades as Grouped Terms, please refer to ISS Table 14.3.1.31.1.f11 (Overall Population) and Table 14.3.1.51.1.1.f11 (RP2D Populations). For ADRs reported for All Grades as ungrouped PTs, Table 14.3.1.2.1 (Overall Population) and Table 14.3.1.2.5 (RP2D Populations). ADRs Grade ≥ 3, Table 14.3.1.38.1.f11 (Grouped Terms in the Overall Population), Table 14.3.1.58.1.f11 (Grouped Terms in the RP2D Population), for ungrouped PTs Table 14.3.1.17.1 (Overall Population), and Table 14.3.1.17.5 (RP2D Population).

The Applicant's Position:

Adverse drug reactions were determined by evaluating TEAEs across the Overall population. For labeling purposes, ADRs are also presented for the RP2D Population. The following considerations were used for determination of an ADR:

- TEAEs were assessed quantitatively and qualitatively as having a possible causal drug-event relationship.
- TEAEs that were assessed as related to alternative etiologies were excluded.
- PT grouped/cluster terms representing medical concepts were used when applicable to better inform the prescriber with useful information about the drug.
  - The PT grouped/clustered terms presented in
  -
  -
  - Table 37 were proposed by the FDA DO2 during review of the initial repotrectinib ROS1 NSCLC NDA and consistent with the repotrectinib US label (Augtyro™ 2023); these terms are defined in the table footnotes.
- Laboratory AEs were included as ADR if evidence supported a possible causal association.

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Table 37 summarizes the ADRs identified for repotrectinib that were reported in ≥ 10% of patients in the Overall population.

Fall (4.2%) and skeletal fractures (2.9%) are TEAEs reported in < 10% of patients in the Overall safety population however they are considered clinically relevant and included as ADRs.

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The pattern of ADRs (

Table 37) reported in the RP2D Population was similar to the Overall population. As the RP2D population represents the patients expected to be treated in the clinic at the indicated dose, the Applicant proposes to support labeling with the ADRs presented in

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Table 37 for the RP2D population (N = 426).

The FDA's Assessment:

FDA did not verify the data for the overall population (n=519) but generally agrees with the Applicant's summary of common adverse reactions in the RP2D population with clarifications. FDA notes that additional TEAEs in ≥10% of patients, differing from Applicant

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Table 37, were GT pneumonia (11%) and decreased appetite (11%) as shown in **Error! Reference source not found.**.

Notably, several group terms were agreed upon between the Applicant and FDA during the FDA's analysis of TEAEs during the ROS1+ NSCLC indication and maintained for consistency in the proposed indication. These include peripheral neuropathy, dizziness, ataxia, cognitive impairment, and vision disorders. Refer to **Error! Reference source not found.** for FDA's analysis including pneumonia GT and decreased appetite which is included in Section 6 of product labeling.

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Table 38: FDA TEAEs Occurring in >10% on Patients in the RP2D Population, TRIDENT-1

Adverse Reaction[1]	RP2D population N=426	
	All Grades (%)	Grade 3 or 4 (%)
Nervous System Disorders		
Dizziness[a]	65	2.8
Dysgeusia[b]	54	0

Adverse Reaction[1]	RP2D population N=426	
	All Grades (%)	Grade 3 or 4 (%)
Peripheral neuropathy[c]	49	1.4
Ataxia[d]	28	0.5
Cognitive impairment[e]	25	0.9
Headache[f]	19	0
Gastrointestinal Disorders		
Constipation	38	0.2
Nausea	20	0.7
Diarrhea	14	0.7
Vomiting	12	1.2
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[g]	30	6
Cough[h]	18	0.2
Pneumonia[i]	11	6
General Disorders		
Fatigue[j]	30	1.2
Edema[k]	15	0.5
Decreased appetite	11	0.2
Musculoskeletal and Connective Tissue Disorders		
Muscular weakness	20	2
Myalgia[l]	13	0.7
Metabolism and Nutritional		
Increased weight	16	3
Eye Disorders		
Vision disorders[m]	12	0.5

Source: adae.xpt

[1] Based on NCI CTCAE v4.03

[a] Includes terms dizziness, vertigo, dizziness postural, dizziness exertional, vertigo positional

[b] Includes terms dysgeusia, ageusia, anosmia, hypogeusia

[c] Includes terms neuralgia, neuropathy peripheral, peripheral sensory neuropathy, dysesthesia, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, hyperesthesia

[d] Includes terms ataxia, gait disturbance, balance disorder, cerebellar ataxia and coordination abnormal

[e] Includes terms memory impairment, disturbance in attention, cognitive disorder, confusional state, amnesia, attention deficit hyperactivity disorder, delirium, altered state of consciousness, aphasia, delusion, depressed level of consciousness, hallucination, mental status changes, neurological decompensation

[f] Includes terms headache, migraine, tension headache

[g] Includes terms dyspnea and dyspnea exertional

[h] Includes terms productive cough, cough, and upper-airway cough syndrome

[l] Includes terms pneumonia, pneumonia aspiration, lower respiratory tract infection, pneumonia viral, pneumonia bacterial, lower respiratory tract infection bacterial, pneumonia klebsiella

[j] Includes terms fatigue and asthenia

[k] Includes terms generalized edema, periorbital edema, localized edema, face edema, edema peripheral, edema, eye edema, scrotal edema

l Includes terms myalgia, myositis, musculoskeletal discomfort, musculoskeletal pain

[m] Includes terms vision blurred, dry eye, visual impairment, visual field defect, cataract, conjunctivitis, eye pain, photophobia, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, color blindness, diplopia, eye hematoma, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, night blindness, ophthalmic herpes zoster

FDA agrees with the Applicant's summary of clinically relevant adverse reaction. Additional clinically relevant adverse reactions occurring in <10% of patients were pyrexia (9%) and fall (3.8%). In general, the most important adverse reactions were described above. For some of the adverse events, attribution in the single-arm trial can be especially difficult (e.g., fatigue, dyspnea in patients with lung cancer, nausea) to assess in a patient population with advanced cancer.

8.2.4.7. Laboratory Findings

Data:

Table 39: Applicant Laboratory Abnormalities (≥ 20%) of Patients Worsening from Baseline (Safety Analysis Set) (TRIDENT-1)

Laboratory Abnormality Finding	Overall Population (N = 519)			RP2D Population (N = 426)		
	Denominator[a]	All Grades (%)	Grade 3-4 (%)	Denominator[a]	All Grades (%)	Grade 3-4 (%)
Hematology						
Hemoglobin, Low*	508	398 (78.4)	45 (8.9)	415	326 (78.6)	35 (8.4)
Lymphocytes, Low*	506	228 (45.1)	62 (12.3)	413	176 (42.6)	(b) (4)
(b) (4)						
Neutrophils (Low)	505	154 (30.5)	38 (7.5)	412	140 (34.0)	36 (8.7)
Coagulation						
Prothrombin Intl. Normalized Ratio (High)	502	129 (25.7)	0	412	99 (24.0)	0
Activated Partial Thromboplastin Time (High)	494	123 (24.9)	2 (0.4)	404	106 (26.2)	1 (0.3)
Chemistry						
Creatine Kinase (High)	402	247 (61.4)	26 (6.5)	402	247 (61.4)	26 (6.5)

Laboratory Abnormality Finding	Overall Population (N = 519)			RP2D Population (N = 426)		
	Denominator[a]	All Grades (%)	Grade 3-4 (%)	Denominator[a]	All Grades (%)	Grade 3-4 (%)
Gamma Glutamyl Transferase (High)	242	121 (50.0)	33 (13.6)	233	116 (49.8)	31 (13.3)
Aspartate Aminotransferase (High)	513	203 (39.6)	13 (2.5)	420	171 (40.7)	12 (2.9)
Alanine Aminotransferase (High)	515	187 (36.3)	15 (2.9)	422	162 (38.4)	14 (3.3)
Sodium (High)	516	167 (32.4)	1 (0.2)	423	141 (33.3)	1 (0.2)
Glucose (High)	514	160 (31.1)	12 (2.3)	422	111 (26.3)	10 (2.4)
(b) (4)						
Alkaline Phosphatase (High)	515	152 (29.5)	14 (2.7)	422	121 (28.7)	9 (2.1)
Phosphate (Low)	511	131 (25.6)	34 (6.7)	419	92 (22.0)	25 (6.0)
Creatinine (High)	516	129 (25.0)	4 (0.8)	-	-	-
(b) (4)						
Urate (High)	513	114 (22.2)	51 (9.9)	421	97 (23.0)	50 (11.9)
Potassium (High)	516	105 (20.4)	5 (1.0)	423	92 (21.8)	3 (0.7)

Abbreviations: CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; RP2D = recommended Phase 2 dose
Notes: Baseline values are defined as the last measurement on or before the date of the first dose. All visits (scheduled and unscheduled) are used for this analysis. Percentages are based on the number of patients in the Safety Analysis Set.
** Refers to the low (or high) end of the parameter graded with CTCAE version 4.03.*
[a] Denominator is the number of patients who have both baseline and postbaseline results for each analyte.
Sources: ISS Table 14.3.5.3, Table 14.3.5.4

The Applicant's Position:

Abnormalities in clinical laboratory parameters reported in ≥ 20% of patients in the Overall population for hematology and clinical chemistry are presented in Table 39. Other laboratory abnormalities reported in ≥ 10% patients in the Overall safety population which are not

included in Table 39, but considered clinically relevant included blood creatine phosphokinase increased (14.8%).

The abnormalities in clinical laboratory parameters (Table 39) in the RP2D subpopulations were similar to the Overall population. As the RP2D population represents the patients expected to be treated in the clinic at the indicated dose, the Applicant proposes to support labeling with the laboratory abnormalities presented in Table 39 for the RP2D population (N = 426).

Overall, analysis of the laboratory parameters did not suggest any safety concerns with dosing of repotrectinib as the reported events were generally consistent with those found in an advanced cancer patient population with metastatic sites of disease, primarily were low grade in severity, and infrequently led to repotrectinib dose interruption, dose reduction, and dose discontinuation.

The FDA's Assessment:
FDA did not verify the shifts in laboratory abnormalities worsening from baseline in the overall population but agrees with the Applicant's those occurring in the RP2D population and that they are similar to those in the RP2D NTRK+ population.

In the RP2D NTRK+ population, the most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, decreased leukocytes, increased ALT, decreased neutrophils, increased gamma glutamyl transferase, increased alkaline phosphatase, increased urate, increased magnesium, and decreased phosphate.

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Error! Reference source not found., which is included in Section 6 (Adverse Reactions) of the product labeling, summarizes select laboratory abnormalities worsening from baseline that occurred in ≥20% of patients in TRIDENT-1. (b) (4) was removed from the Applicant's table given low patient numbers and no occurrences of Grade 3 or 4 events. An IR was sent on May 24, 2024 to clarify the denominators used for various laboratory results.

Table 40: FDA Lab Shift Table Worsening from Baseline (>20%), TRIDENT-1

Laboratory Abnormality[1]	Repotrectinib N=426	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased hemoglobin	79	8.4
Decreased lymphocytes	43	10
Decreased neutrophils	34	9

Laboratory Abnormality[1]	Repotrectinib N=426	
	All Grades (%)	Grade 3 or 4 (%)
Increased activated partial thromboplastin time	26	0.3
Increased INR	24	0
Chemistry		
Increased creatine phosphokinase	61	7
Increased gamma glutamyl transferase	50	13
Increased aspartate aminotransferase	41	2.9
Increased alanine aminotransferase	38	3.3
Increased sodium	33	0.2
Increased alkaline phosphatase	29	2.1
Increased glucose	26	2.4
Increased urate	23	12
Decreased phosphate	22	6
Increased potassium	22	0.7
Decreased glucose	20	0.2

Source: adlb.xpt, ISS Table 14.3.5.4

1 Based on NCI CTCAE v4.03

2 The denominator used to calculate the rate varied from 233 to 423 based on the number of patients with a baseline value and at least one post-treatment value.

Hyperuricemia was observed in patients receiving repotrectinib. An analysis of hyperuricemia and blood uric acid increased in the AE and laboratory datasets were performed to identify patients with hyperuricemia and evaluate for any cases of potential tumor lysis syndrome (TLS). In the RP2D population based on the ADAE dataset, 21 of 426 patients (5%) experienced hyperuricemia reported as an AE, and 0.7% of patients experienced Grade 3 or 4 hyperuricemia. In the RP2D NTRK+ population, hyperuricemia occurred in 8% of patients, all of which were Grade 1. The majority of these AEs (18 of 21, or 86% of events) were Grade 1, meaning the patient had an elevation of uric acid with no physiologic consequence. Grade 3 and 4 hyperuricemia events were reported in 3 of 21 events. There was one Grade 4 event (not reported as an SAE); this patient did not require urate lowering medications. One patient without pre-existing gout required urate-lowering medication. One (0.2%) patient required a dose reduction occurred. There were no reported cases of TLS.

Overall laboratory abnormalities observed from TRIDENT-1 and analyzed during the review of this application shared similar findings with other TKIs. The RP2D and RP2D NTRK+ populations were similar in observed laboratory abnormalities.

8.2.4.8. Vital Signs

Data:

An outlier analysis in vital signs was examined for the Overall population. Systolic and diastolic elevations meeting outlier values were reported in 17.0% and 15.6% of patients, respectively, and for decreases, 6.6% and 9.2% of patients, respectively. Decreases or increases in pulse (bpm) meeting outlier values were reported in 2.3% and 17.1% of patients, respectively; outlier values for temperature (°C) were reported in < 5% of patients.

The Applicant's Position:
Analysis of the vital signs' parameters did not suggest any safety concerns with dosing of repotrectinib.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.4.9. Electrocardiograms (ECGs)

Data:
A dedicated cardiac safety analysis was performed in the initial repotrectinib NDA (NDA 218213). No new data are provided in the current submission.

The Applicant's Position:
Analysis of the ECG parameters did not suggest any cardiac safety concerns with the dosing of repotrectinib. Repotrectinib had no reported clinically meaningful effects on heart rate, PR interval, or QRS duration. There were no clinically meaningful effects on QTc based on the results of the primary concentration-QTc analysis as well as the by-time point, time averaged, and categorical outlier analyses.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.4.10. QT

Data:
Concentration-QTc analysis was performed in the initial repotrectinib NDA (NDA 218213). No new data are provided in the current submission.

The Applicant's Position:
Concentration-QTc analysis did not suggest any cardiac QTc safety concerns with dosing of repotrectinib.

The FDA's Assessment:
FDA agrees with the Applicant's position. The Applicant considered QT prolongation as an AESI

during the review of the ROS+ NSCLC application given the safety signal seen with other TKIs. In the RP2D population, QT prolongation GT occurred in 1.4% of patients, all of which were Grades 1 or 2. There were no events of torsade de pointes.

8.2.4.11. Immunogenicity

The Applicant's Position:
Not applicable.

The FDA's Assessment:
This section is not applicable for this small molecule drug.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. CNS Effects

Data:
In the Overall population (N = 519), dizziness (including dizziness, vertigo, dizziness postural, dizziness exertional, and vertigo positional) was reported in 64.2% of patients; grade 3 dizziness was reported in 3.1% of patients with the median (range) time to onset being 7 days (1 day to 526 days). Dose reduction was required in 10.6% of patients and 8.9% required dose interruption of repotrectinib due to reported dizziness. No patients discontinued repotrectinib due to reported dizziness.

Ataxia (including ataxia, gait disturbances, balance disorder, cerebellar ataxia, and coordination abnormal) was reported in 26.4% of patients; grade 3 ataxia was reported in 0.2% of patients. The median time to onset was 15 days (1 day to 589 days). Dose reduction was required in 6.7% of patients, 4.6% required dose interruptions and one patient was required to discontinue repotrectinib due to ataxia.

Cognitive disorders were reported in 22.4% of patients. Cognitive disorders included memory impairment (12.5%), disturbance in attention (9.6%), cognitive disorder (5.8%), confusional state (2.1%), delirium (1.0%), amnesia, attention deficit hyperactivity disorder (0.8% each), aphasia (0.6%), altered state of consciousness, depressed level of consciousness (0.4% each), bradyphrenia, delusion, dysgraphia, hallucination, intellectual disability, mental disorder, mental status changes, and neurological decompensation (0.2% each). Grade 3 cognitive adverse reactions were reported in 0.8% of patients. The median time to onset of cognitive disorders was 37 days (1 day to 519 days). Dose reduction was required in 1.7% of patients, 1.3% required dose interruption and 0.8% of patients discontinued repotrectinib due to cognitive adverse reactions.

The incidences of CNS adverse reactions reported were similar in patients with and without CNS metastases. In the Overall population (N = 519), 182 patients were diagnosed with brain metastasis per Investigator assessment at baseline. Of these, 176 (96.7%) were reported with at least one AESI. There are no important differences in the incidence of Medical Concept terms when compared to those without brain metastasis at baseline (brain metastasis at baseline: N = 182 [Yes] vs N = 337 [No]).

The Applicant's Position:
CNS events that were reported were consistent with those reported with TRK inhibition (Drilon 2020). The median time to first event onset for the most frequently reported AESIs (≥ 10% of patients) in the Overall population was typically within the first month of study treatment, irrespective of causality. These TRK-related targeted toxicities have been adequately characterized and were included as Warnings and Precautions in the USPI. They can typically be managed through the risk mitigation, including monitoring and management guidelines and recommendations for specific clinical measures detailed in the study protocol and product label, as well as risk communication and advice on the correct use of repotrectinib provided in the prescribing information and patient information.

The FDA's Assessment:
CNS toxicity is a well characterized adverse reaction occurring in patients treated with NTRK inhibitors. In the RP2D population, 77% of patients reported a CNS adverse reaction, of which 4.5% were Grade 3 or 4. Refer to Section 8.2.4.5 for FDA's analysis of CNS adverse reactions.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Not applicable

The FDA's Assessment:
See Section 8.1.2.14 for FDA's assessment of patient-generated data.

8.2.7. Safety Analyses by Demographic Subgroups

Data:
Intrinsic factors

Table 41: Applicant Overview of Adverse Events by Demographic Subgroups (Safety Analysis Set) (TRIDENT-1)

	Overall Population (N = 519)				
Demographic Parameter	**All Patients with TEAEs n (%)**	**Leading to Discontinuation of Study Drug n (%)**	**SAEs n (%)**	**Grade ≥ 3 TEAEs n (%)**	**Fatal TEAEs n (%)**
Age					
≥ 18 to < 65 Yrs (N = 392)	390 (99.5)	24 (6.1)	131 (33.4)	191 (48.7)	14 (3.6)
≥ 65 to < 75 Yrs (N = 97)	95 (97.9)	14 (14.4)	40 (41.2)	59 (60.8)	10 (10.3)
≥ 75 Yrs (N = 30)	30 (100.0)	7 (23.3)	19 (63.3)	19 (63.3)	2 (6.7)
Sex					
Male (N = 219)	217 (99.1)	24 (11.0)	91 (41.6)	126 (57.5)	13 (5.9)
Female (N = 300)	298 (99.3)	21 (7.0)	99 (33.0)	143 (47.7)	13 (4.3)
Race					
White (N = 231)	230 (99.6)	22 (9.5)	97 (42.0)	132 (57.1)	15 (6.5)
Asian (N = 237)	235 (99.2)	19 (8.0)	70 (29.5)	110 (46.4)	9 (3.8)
Brain Metastasis					
Yes (N = 182)	180 (98.9)	13 (7.1)	57 (31.3)	88 (48.4)	11 (6.0)
No (N = 337)	335 (99.4)	32 (9.5)	133 (39.5)	181 (53.7)	15 (4.5)

Abbreviations: SAE = Serious Adverse Event; TEAE = Treatment-Emergent Adverse Event.
Sources: ISS Table 14.3.1.1.2, Table 14.3.1.1.3, Table 14.3.1.1.4, Table 14.3.1.1.7

Extrinsic factors

Table 42: Applicant Overall Summary of Treatment Emergent Adverse Events by Region (Safety Analysis Set) (TRIDENT-1)

	Overall Population (N = 519)		
TEAEs by Event Category	**US (N = 164)**	**Asia (N = 195)**	**Other (N = 160)**
Patients with TEAEs, n (%)			
All patients with TEAEs	163 (99.4)	193 (99.0)	159 (99.4)
Leading to discontinuation of study drug	20 (12.2)	13 (6.7)	12 (7.5)
Leading to dose modifications	80 (48.8)	110 (56.4)	84 (52.5)
Leading to dose reduction	48 (29.3)	79 (40.5)	53 (33.1)
Leading to drug interruption	73 (44.5)	95 (48.7)	75 (46.9)

TEAEs by Event Category	Overall Population (N = 519)		
	US (N = 164)	Asia (N = 195)	Other (N = 160)
SAEs	81 (49.4)	54 (27.7)	55 (34.4)
Grade ≥ 3 TEAEs	95 (57.9)	88 (45.1)	86 (53.8)
Fatal TEAEs	13 (7.9)	9 (4.6)	4 (2.5)
Patients with TRAEs, n (%)			
All patients with TRAEs	151 (92.1)	188 (96.4)	152 (95.0)
Leading to discontinuation of study drug	8 (4.9)	3 (1.5)	6 (3.8)
Leading to dose modifications	52 (31.7)	91 (46.7)	61 (38.1)
Leading to dose reduction	44 (26.8)	77 (39.5)	44 (27.5)
Leading to drug interruption	41 (25.0)	74 (37.9)	50 (31.3)
Treatment-related SAEs	14 (8.5)	16 (8.2)	11 (6.9)
Grade ≥ 3 TRAEs	30 (18.3)	62 (31.8)	42 (26.3)
Fatal TRAEs	0	0	0
Patients with TEAEs by maximum CTCAE grade (n [%])			
Grade 1	14 (8.5)	17 (8.7)	22 (13.8)
Grade 2	54 (32.9)	88 (45.1)	51 (31.9)
Grade 3	68 (41.5)	68 (34.9)	69 (43.1)
Grade 4	14 (8.5)	11 (5.6)	13 (8.1)
Grade 5	13 (7.9)	9 (4.6)	4 (2.5)
Patients with TRAEs by maximum CTCAE grade (n [%])			
Grade 1	57 (34.8)	40 (20.5)	37 (23.1)
Grade 2	64 (39.0)	86 (44.1)	73 (45.6)
Grade 3	29 (17.7)	57 (29.2)	40 (25.0)
Grade 4	1 (0.6)	5 (2.6)	2 (1.3)
Grade 5	0	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; TRAE = treatment-related adverse event; SAE = serious adverse event; US = United States.

Notes: Countries grouped to 'Other' include Australia, Belgium, Canada, Germany, Denmark, Spain, France, United Kingdom, Hungary, Italy, Netherlands, Poland. Percentages are based on the number of patients in the Safety Analysis Set. Adverse events were coded using the MedDRA dictionary, Version 25.0. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. A patient is counted once for each type of event reported. For maximum grade, a patient is counted once based on the maximum grade identified for the specified event type. Leading to Dose Modification includes adverse events that led to dose reduction or drug interruption.

Source: ISS Table 14.3.1.1.8

The Applicant's Position:

Intrinsic

There were no marked differences in TEAEs reported for the highest incidences (≥ 20% of patients) in the Overall population in age groups ≥ 18 to < 65 and ≥ 65 to < 75 years. Differences were noted in the ≥ 75 age group (e.g., for dizziness, dyspnea, ALT increased and fatigue), however, these should be treated with caution due to the small number of patients in the cohort (N = 30) and age associated co-morbidities.

Differences were noted for reported TEAEs leading to discontinuation of study drug in the ≥ 65 to < 75 year age group (14.4% of patients) and in the ≥ 75 year age group (23.3%) versus the ≥ 18 to < 65 year age group (6.1%).

The incidence of SAEs was highest in the ≥ 75 age group (63.3% of patients) versus the ≥ 18 to < 65 and ≥ 65 to < 75 years age groups (33.4% and 41.2%, respectively). There was no apparent difference between the ≥ 65 to < 75 years and ≥ 75 age groups for grade ≥ 3 TEAEs (60.8% and 63.3%, respectively), both of which were higher compared to the ≥ 18 to < 65 age group (48.7% of patients). These findings should be treated with caution due to the smaller number of patients in the older age cohorts.

The frequency of Grade ≥ 3 TEAEs was higher in males versus females with 57.5% vs. 47.7% of patients, respectively. For other event categories, there were no marked differences by sex.

There were no marked differences for reported TEAE event categories by the racial subgroups White and Asian. Meaningful comparisons for the subgroups were not practicable due to the size of the cohort.

In the Overall population (N = 519), 182 patients were diagnosed with brain metastasis per Investigator assessment at baseline. There was no marked difference in the incidence of TEAEs in patients with brain metastasis per Investigator assessment (YES vs. NO).

Extrinsic

In the Overall population, there was a ≥ 10% difference for the incidence of patients who required a dose reduction in Asia (40.5%) versus Other regions (33.1%) (which included EU countries) and the US population (29.3%). Fewer patients reported SAEs from the Asian (27.7%) and Other regions (34.4%) versus the US (49.4%). For grade ≥ 3 TEAEs, more events were reported for patients from the US (57.9%) versus Other (53.8%) and Asian regions (45.1%).

The FDA's Assessment:

FDA did not perform an analysis of demographics in the overall population. FDA analysis of the RP2D population; however, was similar to that of the Applicant's position by subgroups and region in the overall population as shown in **Error! Not a valid bookmark self-reference.Error! Reference source not found.**.

Table 43: FDA RP2D Safety Population Demographics, TRIDENT-1

	RP2D NTRK+ Population N=104 n (%)	Other N=2 n (%)	ROS1 NSCLC N=320 n (%)	RP2D Population N=426 n (%)
Gender				
M	53 (51)	0 (0)	122 (38)	175 (41)
F	51 (49)	2 (100)	198 (62)	251 (59)
Age				
Median (Min - Max)	59 (18 - 84)	50 (50 - 67)	56 (27 - 93)	57 (18 - 93)
>= 18 to < 65	66 (63)	1 (50)	252 (79)	319 (75)
>= 65	38 (37)	1 (50)	68 (21)	107 (25)
ECOG				
1	65 (63)	1 (50)	207 (65)	273 (64)
0	39 (38)	1 (50)	112 (35)	152 (36)
Race				
WHITE	46 (44)	0 (0)	137 (43)	183 (43)
ASIAN	41 (39)	1 (50)	157 (49)	199 (47)
NOT REPORTED	14 (13)	0 (0)	11 (3.4)	25 (6)
BLACK OR AFRICAN AMERICAN	3 (2.9)	0 (0)	9 (2.8)	12 (2.8)
OTHER	0 (0)	1 (50)	0 (0)	1 (0.2)
UNKNOWN	0 (0)	0 (0)	3 (0.9)	3 (0.7)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0 (0)	0 (0)	2 (0.6)	2 (0.5)
AMERICAN INDIAN OR ALASKA NATIVE	0 (0)	0 (0)	1 (0.3)	1 (0.2)
Ethnicity				
NOT HISPANIC OR LATINO	95 (91)	2 (100)	303 (95)	400 (94)
HISPANIC OR LATINO	2 (1.9)	0 (0)	11 (3.4)	13 (3.1)

Source: adsl.xpt

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

8.2.9.1. Human Carcinogenicity or Tumor Development

The Applicant's Position:
Not applicable. No human carcinogenicity study was performed with repotrectinib.

The FDA's Assessment:
FDA agrees.

8.2.9.2. Human Reproduction and Pregnancy

The Applicant's Position:
There are no available data on repotrectinib use in pregnant women. Females of reproductive potential should be instructed to use highly effective contraception during treatment with repotrectinib and for at least 2 months following the final dose of repotrectinib. Males with female partners of reproductive potential should be instructed to use effective contraception during treatment with repotrectinib and for 4 months following the final dose of repotrectinib.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.9.3. Pediatrics and Assessment of Effects on Growth

Data:

Table 44: Applicant Key Demographics and Baseline Disease Characteristics (CARE)

	All			< 12 years old			≥ 12 years old		
	NTRK **(N = 16)**	**Other (N = 10)**	**Total (N = 26)**	***NTRK*** **(N = 9)**	**Other (N = 7)**	**Total (N = 16)**	***NTRK*** **(N = 7)**	**Other (N = 3)**	**Total (N = 10)**
Age (years)[a]									
Mean	8.8	7.4	8.3	4.4	4.6	4.5	14.4	14.0	14.3
Standard Deviation	5.34	5.72	5.42	2.01	4.24	3.06	0.79	0.00	0.67
Median	7.0	7.5	7.0	4.0	5.0	4.5	15.0	14.0	14.0
Min, Max	1, 15	0, 14	0, 15	1, 7	0, 10	0, 10	13, 15	14, 14	13, 15
Age Group, n (%)									
Infant and Toddler: >28 days to < 2 years	1 (6.3)	2 (20.0)	3 (11.5)	1 (11.1)	2 (28.6)	3 (18.8)	0	0	0
Child: 2 years to < 12 years	8 (50.0)	5 (50.0)	13 (50.0)	8 (88.9)	5 (71.4)	13 (81.3)	0	0	0
Adolescent: 12 to ≤ 18 years	7 (43.8)	3 (30.0)	10 (38.5)	0	0	0	7 (100)	3 (100)	10 (100)
Sex, n (%)									
Female	9 (56.3)	5 (50.0)	14 (53.8)	5 (55.6)	5 (71.4)	10 (62.5)	4 (57.1)	0	4 (40.0)
Male	7 (43.8)	5 (50.0)	12 (46.2)	4 (44.4)	2 (28.6)	6 (37.5)	3 (42.9)	3 (100)	6 (60.0)
Race, n (%)									
Asian	3 (18.8)	2 (20.0)	5 (19.2)	1 (11.1)	1 (14.3)	2 (12.5)	2 (28.6)	1 (33.3)	3 (30.0)
Black or African American	1 (6.3)	1 (10.0)	2 (7.7)	1 (11.1)	1 (14.3)	2 (12.5)	0	0	0

	All			< 12 years old			≥ 12 years old		
	NTRK **(N = 16)**	**Other (N = 10)**	**Total (N = 26)**	***NTRK*** **(N = 9)**	**Other (N = 7)**	**Total (N = 16)**	***NTRK*** **(N = 7)**	**Other (N = 3)**	**Total (N = 10)**
White	12 (75.0)	5 (50.0)	17 (65.4)	7 (77.8)	4 (57.1)	11 (68.8)	5 (71.4)	1 (33.3)	6 (60.0)
Missing	0	2 (20.0)	2 (7.7)	0	1 (14.3)	1 (6.3)	0	1 (33.3)	1 (10.0)
Ethnicity, n (%)									
Hispanic or Latino	5 (31.3)	1 (10.0)	6 (23.1)	4 (44.4)	1 (14.3)	5 (31.3)	1 (14.3)	0	1 (10.0)
Not Hispanic or Latino	11 (68.8)	8 (80.0)	19 (73.1)	5 (55.6)	6 (85.7)	11 (68.8)	6 (85.7)	2 (66.7)	8 (80.0)
Missing	0	1 (10.0)	1 (3.8)	0	0	0	0	1 (33.3)	1 (10.0)
Baseline Weight (kg)									
Mean	38.11	33.14	36.20	21.70	20.04	20.98	59.21	63.70	60.56
Standard Deviation	21.494	24.181	22.221	9.071	13.335	10.758	11.031	9.832	10.359
Median	36.45	29.15	34.85	20.30	19.40	19.85	63.40	68.40	63.60
Min, Max	12.7, 73.4	5.9, 70.3	5.9, 73.4	12.7, 40.1	5.9, 38.4	5.9, 40.1	42.0, 73.4	52.4, 70.3	42.0, 73.4
Type of Cancer, n (%)									
CNS Tumor	8 (50.0)	5 (50.0)	13 (50.0)	5 (55.6)	5 (71.4)	10 (62.5)	3 (42.9)	0	3 (30.0)
Sarcoma, Soft Tissue	7 (43.8)	3 (30.0)	10 (38.5)	3 (33.3)	2 (28.6)	5 (31.3)	4 (57.1)	1 (33.3)	5 (50.0)
Kidney Cancer	1 (6.3)	0	1 (3.8)	1 (11.1)	0	1 (6.3)	0	0	0
Neuroblastoma	0	1 (10.0)	1 (3.8)	0	0	0	0	1 (33.3)	1 (10.0)
NSCLC	0	1 (10.0)	1 (3.8)	0	0	0	0	1 (33.3)	1 (10.0)
Brain Metastasis, n (%)									
Yes	2 (12.5)	2 (20.0)	4 (15.4)	1 (11.1)	2 (28.6)	3 (18.8)	1 (14.3)	0	1 (10.0)
No	14 (87.5)	8 (80.0)	22 (84.6)	8 (88.9)	5 (71.4)	13 (81.3)	6 (85.7)	3 (100)	9 (90.0)

	All			< 12 years old			≥ 12 years old		
	NTRK **(N = 16)**	**Other (N = 10)**	**Total (N = 26)**	***NTRK*** **(N = 9)**	**Other (N = 7)**	**Total (N = 16)**	***NTRK*** **(N = 7)**	**Other (N = 3)**	**Total (N = 10)**
Molecular Alteration Type, n (%)									
NTRK	16 (100)	0	16 (61.5)	9 (100)	0	9 (56.3)	7 (100)	0	7 (70.0)
ALK	0	6 (60.0)	6 (23.1)	0	4 (57.1)	4 (25.0)	0	2 (66.7)	2 (20.0)
ROS1	0	4 (40.0)	4 (15.4)	0	3 (42.9)	3 (18.8)	0	1 (33.3)	1 (10.0)
Number of Lines Prior Systemic Therapy, n (%)									
Median (Min, Max)	2.0 (0, 10)	1.0 (0, 9)	1.5 (0, 10)	2.0 (1, 4)	1.0 (0, 3)	1.0 (0, 4)	2.0 (0, 10)	1.0 (1, 9)	2.0 (0, 10)
0	1 (6.3)	3 (30.0)	4 (15.4)	0	3 (42.9)	3 (18.8)	1 (14.3)	0	1 (10.0)
1	5 (31.3)	4 (40.0)	9 (34.6)	4 (44.4)	2 (28.6)	6 (37.5)	1 (14.3)	2 (66.7)	3 (30.0)
2	6 (37.5)	1 (10.0)	7 (26.9)	3 (33.3)	1 (14.3)	4 (25.0)	3 (42.9)	0	3 (30.0)
≥ 3	4 (25.0)	2 (20.0)	6 (23.1)	2 (22.2)	1 (14.3)	3 (18.8)	2 (28.6)	1 (33.3)	3 (30.0)
Number of Lines Prior TKI Therapy, n (%)									
Median (Min, Max)	1.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)	1.0 (0, 2)	0.0 (0, 1)	0.5 (0, 2)	0.0 (0, 2)	0.0 (0, 2)	0.0 (0, 2)
0	6 (37.5)	8 (80.0)	14 (53.8)	2 (22.2)	6 (85.7)	8 (50.0)	4 (57.1)	2 (66.7)	6 (60.0)
1	8 (50.0)	1 (10.0)	9 (34.6)	6 (66.7)	1 (14.3)	7 (43.8)	2 (28.6)	0	2 (20.0)
2	2 (12.5)	1 (10.0)	3 (11.5)	1 (11.1)	0	1 (6.3)	1 (14.3)	1 (33.3)	2 (20.0)
≥ 3	0	0	0	0	0	0	0	0	0
Patients with Prior Surgery, n (%)	14 (87.5)	7 (70.0)	21 (80.8)	9 (100)	5 (71.4)	14 (87.5)	5 (71.4)	2 (66.7)	7 (70.0)
Patients with Prior Radiotherapy, n (%)	8 (50.0)	2 (20.0)	10 (38.5)	4 (44.4)	1 (14.3)	5 (31.3)	4 (57.1)	1 (33.3)	5 (50.0)

Abbreviations: ALK = anaplastic lymphoma kinase; CNS = central nervous system; Max = maximum; Min = minimum; NSCLC = non-small cell lung cancer; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene.

Notes: NTRK summary pools patients with an NTRK1-NTRK3 genetic alteration. Other summary pools patients with an ALK or ROS1 genetic alteration. A baseline value is the last non-missing assessment prior to initial administration of study treatment. Percentages are based on the number of patients in the Full Analysis Set.

[a] *Age is calculated as the number of complete years between date of birth and date of informed consent.*

Sources: Table 5.3.1-1, Table 5.3.1-2, Table 5.3.2-1, Table 5.3.2-2, Table 5.3.3.1-1, and Table 5.3.3.1-2 of the CARE Ad Hoc Report, Module 5.3.5.2.

Table 45: Applicant Overall Summary of TEAEs (Full Analysis Set) (CARE)

	NTRK (N=16)	Other (N=10)	Overall Total (N=26)
Patients with Treatment-Emergent Adverse Events (TEAE), n (%)			
All Patients with TEAE	16 (100)	10 (100)	26 (100)
All Patients with Dose Limiting Toxicity (for Phase 1)	0	0	0
Leading to Discontinuation of Study Drug	0	1 (10.0)	1 (3.8)
Leading to Dose Modification	5 (31.3)	3 (30.0)	8 (30.8)
Leading to Dose Reduction	0	0	0
Leading to Drug Interruption	5 (31.3)	3 (30.0)	8 (30.8)
Serious Adverse Events	7 (43.8)	4 (40.0)	11 (42.3)
Grade ≥ 3 TEAE	9 (56.3)	9 (90.0)	18 (69.2)
Fatal AE	3 (18.8)	0	3 (11.5)
Patients with Treatment-Related Adverse Events, n (%)			
All Patients with Treatment Related Adverse Event	11 (68.8)	9 (90.0)	20 (76.9)
Leading to Discontinuation of Study Drug	0	1 (10.0)	1 (3.8)
Leading to Dose Modification	1 (6.3)	1 (10.0)	2 (7.7)
Leading to Dose Reduction	0	0	0
Leading to Drug Interruption	1 (6.3)	1 (10.0)	2 (7.7)
Related Serious Adverse Events	2 (12.5)	0	2 (7.7)
Grade ≥ 3 Treatment Related Adverse Event	2 (12.5)	3 (30.0)	5 (19.2)
Related Fatal Adverse Event	0	0	0

Abbreviations: ALK = anaplastic lymphoma kinase; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TEAE = treatment-emergent adverse event.
Note: NTRK summary pools patients with an NTRK1-NTRK3 genetic alteration. Other summary pools patients with an ALK or ROS1 genetic alteration. Percentages are based on the number of patients in the Full Analysis Set. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. A patient is counted once for each type of event reported. For maximum grade, a patient is counted once based on the maximum grade identified for the specified event type.
Leading to Dose Modification includes adverse events that led to dose reduction or dose interruption.
Source: CARE Table 14.3.1.1.1.c

Table 46: Applicant Most Common (≥ 10%) TEAEs by Preferred Term (Full Analysis Set) (CARE)

Preferred Term	NTRK (N=16)	Other (N=10)	Overall Total (N=26)
Patients with at Least One TEAE	16 (100)	10 (100)	26 (100)
Constipation	5 (31.3)	6 (60.0)	11 (42.3)

Preferred Term	NTRK (N=16)	Other (N=10)	Overall Total (N=26)
Anaemia	5 (31.3)	5 (50.0)	10 (38.5)
Fatigue	6 (37.5)	2 (20.0)	8 (30.8)
Dysgeusia	4 (25.0)	3 (30.0)	7 (26.9)
Headache	4 (25.0)	3 (30.0)	7 (26.9)
Nausea	4 (25.0)	3 (30.0)	7 (26.9)
Dizziness	3 (18.8)	3 (30.0)	6 (23.1)
Lymphocyte count decreased	3 (18.8)	3 (30.0)	6 (23.1)
Pyrexia	0	6 (60.0)	6 (23.1)
White blood cell count decreased	3 (18.8)	3 (30.0)	6 (23.1)
Blood alkaline phosphatase increased	2 (12.5)	3 (30.0)	5 (19.2)
Paraesthesia	4 (25.0)	1 (10.0)	5 (19.2)
Urinary tract infection	2 (12.5)	3 (30.0)	5 (19.2)
Vomiting	1 (6.3)	4 (40.0)	5 (19.2)
Weight increased	3 (18.8)	2 (20.0)	5 (19.2)
Aspartate aminotransferase increased	1 (6.3)	3 (30.0)	4 (15.4)
Blood creatine phosphokinase increased	2 (12.5)	2 (20.0)	4 (15.4)
Cough	1 (6.3)	3 (30.0)	4 (15.4)
Diarrhoea	2 (12.5)	2 (20.0)	4 (15.4)
Dyspnoea	1 (6.3)	3 (30.0)	4 (15.4)
Electrocardiogram QT prolonged	2 (12.5)	2 (20.0)	4 (15.4)
Hypertension	2 (12.5)	2 (20.0)	4 (15.4)
Hypotension	0	4 (40.0)	4 (15.4)
Neutrophil count decreased	2 (12.5)	2 (20.0)	4 (15.4)
Sinus tachycardia	0	4 (40.0)	4 (15.4)
Abdominal pain	2 (12.5)	1 (10.0)	3 (11.5)
Blood lactate dehydrogenase increased	1 (6.3)	2 (20.0)	3 (11.5)
COVID-19	1 (6.3)	2 (20.0)	3 (11.5)
Dermatitis acneiform	1 (6.3)	2 (20.0)	3 (11.5)
Gait disturbance	2 (12.5)	1 (10.0)	3 (11.5)
Hyperkalaemia	0	3 (30.0)	3 (11.5)
Hypermagnesaemia	1 (6.3)	2 (20.0)	3 (11.5)
Increased appetite	1 (6.3)	2 (20.0)	3 (11.5)
Muscular weakness	3 (18.8)	0	3 (11.5)
Nasal congestion	0	3 (30.0)	3 (11.5)
Paraesthesia oral	2 (12.5)	1 (10.0)	3 (11.5)
Proteinuria	1 (6.3)	2 (20.0)	3 (11.5)
Somnolence	3 (18.8)	0	3 (11.5)
Upper respiratory tract infection	0	3 (30.0)	3 (11.5)

Abbreviations: ALK = anaplastic lymphoma kinase; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TEAE = treatment-emergent adverse event.
Note: NTRK summary pools patients with an NTRK1-NTRK3 genetic alteration. Other summary pools patients with an ALK or ROS1 genetic alteration. Percentages are based on the number of patients in the Full Analysis Set. Adverse events were coded using the MedDRA dictionary version 25.0. Adverse events occurring on or after the first dose date through 28 days after last dose of study drug are considered treatment emergent. A patient is counted once for each type of event reported.
Source: Table 14.3.1.2.4.c

The Applicant's Position:

The safety and effectiveness of repotrectinib in pediatric patients with *NTRK*-positive solid tumors has not been established. In compliance with PREA and per the agreed repotrectinib PSP, an ongoing Phase 1/2 clinical trial (TPX-0005-07 [CARE]; NCT04094610) is being conducted to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of repotrectinib in pediatric and young adult patients with advanced or metastatic malignancies harboring *ALK*, *ROS1*, or *NTRK1*-3 alterations.

Preliminary safety data in 26 pediatric patients as of the data cutoff date of 19-Dec-2022 demonstrated that adverse reactions reported in pediatric patients (Table 45) were comparable in frequency and intensity with those reported in adults (Table 29). No differences in the spectrum of adverse reaction reported in adults and the pediatric population were evident with no new or unexpected adverse reactions reported.

- No DLTs have been reported.
- The most frequently reported adverse reactions (≥ 30%) in pediatric patients were anemia, constipation, fatigue (Table 46).
- The most frequently reported AESIs included dysgeusia (30.8%), dizziness (23.1%), paresthesia and sleep disorders (19.2% each), ataxia, hepatic enzyme elevation, mood disorders, and QT prolongation (15.4% each; all reported events of QT prolonged were nonserious, low grade, and did not require dose modifications), and muscle weakness and vision disorders (11.5% each).
    - Skeletal Fractures: reported in 2 (7.7%) patients (ankle fracture [grade 2]/foot fracture [grade 1]; stress fracture [grade 3]), considered related to repotrectinib by the Investigator.
- The most frequently reported (≥ 5%) Grade ≥ 3 TEAE in pediatric patients was weight increased.
- The safety profile was generally consistent between the < 12-year-old and ≥ 12-year-old patients.

The FDA's Assessment:

FDA notes that the Applicant's assessment is incorrectly placed in Section 8.2.9.3 and FDA's assessment of pediatric data from the CARE study is in Section 10.

As seen with other TKI therapies, in TRIDENT-1 a broad spectrum of CNS adverse events occurred in 77% of patients including dizziness, ataxia and cognitive disorders. Robust long-term data is not available to adequately assess the risk of long-term effects of repotrectinib on growth in pediatric patients. Preclinical data demonstrated that daily oral administration of repotrectinib to juvenile rats for 8 weeks starting on postnatal day 12 (approximately equal to a human pediatric age of a newborn) showed decreased body weight gain at doses ≥1 mg/kg (approximately ≥0.04 times the human exposure based on AUC at the recommended clinical dose of 160 mg BID) and decreased femur lengths at 3 mg/kg (approximately 0.1 times the human exposure based on AUC at the recommended clinical dose of 160 mg BID).

A PMR addressing the serious risk of long-term effects of repotrectinib on growth, neurological outcomes and development in pediatric patients will be issued for the proposed indication. See Section 13.

8.2.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:
There was no specific measure to determine overdose in the TRIDENT-1 study. Reporting of overdose was based on the Investigator's assessment. There were no reports of overdose during the conduct of the study.

No relevant studies regarding the investigation of the dependence potential of repotrectinib have been conducted.

The nonclinical and clinical data do not suggest a risk of physical dependence and subsequent withdrawal symptoms with abrupt cessation of repotrectinib. There were no TEAEs of "drug tolerance" or "drug withdrawal syndrome" reported with repotrectinib use in the TRIDENT 1 study.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

8.2.10.1. Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:
AUGTYRO™ (repotrectinib) was approved in the United States on 15 Nov 2023 for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC. No

additional safety concerns have been reported or identified. Repotrectinib has not been approved or marketed in any other region.

The FDA's Assessment:
FDA has not identified new safety signals upon review of updated safety data from the initial approval in November 2023 for the ROS1+ NSCLC indication.

8.2.10.2. Expectations on Safety in the Postmarket Setting

The Applicant's Position:
The safety of repotrectinib has been adequately demonstrated in the pivotal TRIDENT-1 study, including a differentiated safety profile when compared to other TKIs. The TKI class effects and TRK-related targeted toxicities of CNS toxicities, ILD/pneumonitis, Hepatotoxicity, Hyperuricemia, Myalgia with CPK Elevation, and Skeletal Fractures have been adequately characterized and were included as Warnings and Precautions in the USPI. They can typically be managed through the risk mitigation, including monitoring and management guidelines and recommendations for specific clinical measures detailed in the study protocol and product label, as well as risk communication and advice on the correct use of repotrectinib provided in the prescribing information and patient information.

Because the effects of repotrectinib in pregnant and breastfeeding women are not yet known, regular pregnancy testing is required per protocol and recommendation to verify the pregnancy status of females of reproductive potential prior to initiating repotrectinib is included in the product label.

Repotrectinib will be prescribed by oncologists experienced in monitoring and managing serious adverse reactions, and counselling patients on potential side effects. Based on the safety profile understood to date, routine risk minimization measures have demonstrated effectiveness in optimizing the safe use of repotrectinib. Routine pharmacovigilance will also be conducted to further characterize the safety profile of repotrectinib (i.e., adverse reaction reporting) and monitor for unexpected adverse events (i.e., signal detection). Additionally, the review of the safety profile of repotrectinib will be reflected in data and post-authorization risk-benefit assessment submitted with Periodic Benefit-Risk Evaluation Reports. Ongoing TRIDENT-1 and CARE clinical trials will support the collection of long-term safety data in adults and pediatrics, to characterize potential serious risks of long-term repotrectinib exposure.

The FDA's Assessment:
FDA agrees with the Applicant's position. Additional information will be obtained in the postmarket setting to better characterize the risk of fractures and potential risk on the effects on pediatric growth from both the TRIDENT-1 and CARE studies. Refer to Section 13 for additional information.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The overall safety profile of repotrectinib assessed in the pivotal TRIDENT-1 study in the Overall population (N = 519), the subpopulation receiving at least 1 dose of repotrectinib at the RP2D (N = 426), and the subpopulations of *ROS1*-positive NSCLC patients (N = 264) and NTRK-positive solid tumor patients (N =104) receiving at least 1 dose of repotrectinib at the RP2D demonstrated that the safety profile of repotrectinib was manageable and generally well tolerated. The TEAEs that were reported with repotrectinib were monitorable, manageable, and resolved with standard symptomatic measures, and/or dose modifications or discontinuation depending on severity, when indicated. Long-term treatment with repotrectinib (> 12 months) showed no evidence of increased/cumulative toxicity. There were no clinically meaningful differences in the safety profile of patients with or without baseline brain metastases. In addition, there were no clinically meaningful differences in the safety profile in the RP2D populations when compared to the Overall population.

The majority of TEAEs were of grade 1 or 2 severity and did not require a dose modification. The most frequently reported adverse reactions (≥ 20%) included dizziness (61.8%), dysgeusia (52.0%), anemia (36.4%), constipation (37.6%), paraesthesia (32.6%), dyspnea (28.9%), fatigue (23.7%), ALT increased (20.6%), and nausea (20.4%). TEAEs leading to discontinuation of study drug were reported for < 10% of patients in the Overall population; TEAEs were typically reported at very low incidences (≤ 2 patients). The most frequently reported TEAEs leading to discontinuation of study drug (> 2 patients) were dyspnea (4 [0.8%] patients), pneumonitis (4 [0.8%]), and muscular weakness (3 [0.6%]). The most frequently reported TEAEs leading to dose interruption (> 2% patients) were dizziness (8.5%), dyspnea (6.0%), muscular weakness (5.0%), ataxia (3.3%), pneumonia (3.3%), blood creatine phosphokinase increased (2.9%), and anemia (2.7%). The most frequently reported TEAEs leading to dose reduction (> 2% patients) were dizziness (10.2%), ataxia (5.0%), muscular weakness (3.9%), and blood creatine phosphokinase increased (2.3%).

The most frequently reported SAEs (≥ 2% of patients) in the Overall population were pneumonia (5.4%), dyspnea (3.5%), pleural effusion (2.9%), and hypoxia (2.5%). The most frequently reported TEAEs with a fatal outcome at the SOC level were in Cardiac disorders, General disorders and administration site conditions, Infections and infestations, and Respiratory, thoracic, and mediastinal disorders, each with 6 (1.2%) patients. There were no reported TEAEs with a fatal outcome assessed as treatment related by the Investigator. All other deaths were attributed to progressive disease by the Investigator. Overall, the pattern and frequency of SAEs and TEAEs with fatal outcome reported in the overall population were consistent with the seriousness, complications and/or progression of the underlying malignancy, and life-threatening nature of the disease under investigation.

Analysis of laboratory parameters, vital signs and ECGs did not suggest any safety concerns with dosing of repotrectinib.

No clinically meaningful differences were noted in the safety profile of repotrectinib by subgroup based on intrinsic or extrinsic factors.

A limited number of patients in the repotrectinib clinical development program have been treated for more than 12 months (i.e., 143 of the 519 patients). Treatment with repotrectinib has appeared safe and well tolerated for periods beyond 12 months, and no safety data has emerged to suggest a different safety profile associated with long-term use. Additional long-term safety data is planned to be provided in the Day 90 safety update.

The TKI class effects and TRK-related targeted toxicities of CNS toxicities, ILD/pneumonitis, Hepatotoxicity, Hyperuricemia, Myalgia with CPK Elevation, and Skeletal Fractures have been adequately characterized and were included as Warnings and Precautions in the USPI. No cases of TLS or DILI were reported. No meaningful cardiac toxicity or cardiac dysrhythmias were reported including no evidence of QT prolongation. No cases were reported of serious or sight threatening vision disorders, and the majority of events were of low-grade severity. Based on the safety profile understood to date, routine risk minimization measures have demonstrated effectiveness in optimizing safe use.

In the preliminary safety data reported in 26 patients treated in the pediatric CARE study, repotrectinib was well tolerated (majority of TEAEs were grade 1-2) with no DLTs reported. There were no new safety signals as compared to the adult population in TRIDENT-1.

Preliminary PRO data from validated instruments (EORTC-QLQ-C30 and EORTC QLQ-LC13) showed that most patients, both TKI-naïve and TKI-pretreated, demonstrated stable or improved GHS/QOL.

Overall, the evaluation of safety across the clinical program demonstrated a favorable safety profile for repotrectinib in adult and pediatric patients 12 years and older with locally advanced or metastatic *NTRK*-positive solid tumors.

The FDA's Assessment:

The RP2D safety population included 426 patients treated with repotrectinib at the RP2D in the TRIDENT-1 study. Overall, an analysis of the adverse reactions observed in TRIDENT-1 indicated findings consistent with other drug products in the same class, Larotrectinib and entrectinib.

The primary risks related to repotrectinib are CNS adverse reactions, ILD/pneumonitis, hepatotoxicity, myalgia with CPK elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity. These serious risks, which are described in detail in sections above, are addressed in

the Warnings and Precautions and Dose Modifications sections of the repotrectinib product labeling.

In the TRIDENT-1, among patients in the RP2D population (n=426), the most common (≥ 20%) adverse reactions were dizziness (65%), dysgeusia (54%), peripheral neuropathy (49%), constipation (38%), dyspnea (30%), fatigue (30%), ataxia (28%), cognitive impairment (25%), muscular weakness (20%) and nausea (20%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased gamma glutamyl transferase (13%), increased urate (12%), decreased lymphocytes (10%), decreased neutrophils (9%), decreased hemoglobin (8.4%), increased creatine phosphokinase (7%), decreased phosphate (6%), decreased sodium (3.8%), increased ALT (3.3%), increased AST (2.9%), increased magnesium (2.6%), increased glucose (2.4%), and increased alkaline phosphatase (2.1%).

In the RP2D NTRK+ population (n=104), the most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, ataxia, fatigue, cognitive impairment, cough, and vomiting. The most common (≥2%) Grade 3 or 4 laboratory shifts worsening from baseline were increased gamma glutamyl transferase, decreased hemoglobin, decreased lymphocytes, decreased neutrophils, increased urate, increased creatine kinase, decreased phosphate, increased AST, decreased sodium, increased ALT, increased glucose, increased alkaline phosphatase, and increased magnesium. See Sections 8.2.4.6 and 8.2.4.7 for discussions of adverse reactions and abnormal lab values.

The CARE study is ongoing and data is still being collected; however, data analyzed from the 26 patients enrolled at the time of the DCO appears similar to the safety profile of repotrectinib from the TRIDENT-1 study. A PMR for additional pediatric and young adult safety data was issued during review of the ROS1+ indication and will apply to patients with other genetic alterations including NTRK+ solid tumors.

The review team considered the safety profile of repotrectinib to be acceptable when assessed in the context of life-threatening malignancies. Although repotrectinib can cause serious and severe toxicities, the safety concerns are described in product labeling and repotrectinib will be prescribed by oncologists who are trained to monitor and treat serious treatment-related toxicities. There were no new significant safety concerns identified during the NDA review requiring additional risk management tools such as a Risk Evaluation and Mitigation Strategy (REMS).

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
There was no major statistical issue related to the primary efficacy results. The data submitted for Study TRIDENT-1 demonstrated an ORR of 58% (95% CI: 41, 73) as assessed by BICR in patients who were TKI-naive (Pooled EXP-5 Cohort) and an ORR of 50% (95% CI: 35, 65) as assessed by BICR in patients who were TKI-pretreated (Pooled EXP-6 Cohort). The median DOR based on the original DCO was not reached (range: 3.7+ to 25.2+ months) in the TKI-naïve patients and 9.8 months (95% CI: 7.4 to 12.9 months; range: 1.8 to 17.5 months) in the TKI-pretreated patients. Based on an updated DCO of October 15, 2023, which was included in product labeling submitted as part of the 90-day safety update, the median DOR was not reached (range: 3.7+ to 43.9+ months) in the TKI-naïve patients and 9.9 months (95% CI: 7.4 to 13.0 months; range: 1.8 to 26.5+ months) in the TKI-pretreated patients. However, there are several limitations in this pivotal study. As there was no comparator arm in this single-arm trial, the results of time-to-event endpoints were not interpretable. Due to the small sample size, efficacy results in subpopulations such as tumor type and mutation subgroups should be interpreted with caution.

8.4. Conclusions and Recommendations

The FDA's Assessment:
FDA recommends Accelerated Approval of repotrectinib for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have an NTRK gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy. This recommendation is based on a clinically significant ORR and durability of response in patients with TKI-naïve or TKI-pretreated NTRK+ solid tumors from the TRIDENT-1 study.

Current standard of care for patients with NTRK+ solid tumors includes treatment with an approved TKI inhibitor (larotrectinib and entrectinib). Although both drugs are standard of care for the first-line TKI treatment, neither has received regular approval. Reported response rates in patients who received these therapies in clinical trials ranged from 59% (entrectinib) to 75% (larotrectinib). Neither of these approved product labels includes data describing the treatment effect on patients with TKI-pretreated NTRK+ solid tumors.

The primary evidence of effectiveness for this application is derived from pooled cohorts EXP-5 and EXP-6 from TRIDENT-1. Patients with NTRK+ solid tumors from the Phase 1 and Phase 2 portions of TRIDENT-1 who had either received no more than 2 prior TKIs or were TKI-naïve and received at least one dose of repotrectinib on or before December 19, 2022, were included in the primary efficacy populations. A 90-day safety update was submitted by the Applicant on

March 15, 2024, which also included additional DOR data with a DCO of October 15, 2023. This updated data is included in patient labeling. Patients received repotrectinib administered daily at the recommended phase 2 dose (RP2D). Patients enrolled on TRIDENT-1 were required to have an NTRK fusion detected by a CLIA lab or equivalent and at least 1 measurable target lesion per RECIST v1.1.

Among the 40 TKI-naïve patients, the ORR was 58% (95% CI: 41, 73) per RECIST v1.1 by BICR. The estimated mDOR was not estimable but ranged from 3.7+ to 43.9+ months. In addition, 3 patients had measurable CNS metastases at baseline as assessed by BICR. Responses in intracranial lesions were observed in 3 of 3 patients.

Among the 48 patients who had received 1 or 2 prior TKIs the ORR was 50% (95% CI: 35, 65) per RECIST v1.1 by BICR. The mDOR was 9.9 months (95% CI: 7.4, 13.0). In addition, 2 patients had measurable CNS metastases at baseline as assessed by BICR. Responses in intracranial lesions were observed in 2 of 2 patients. Twenty-six of the TKI-pretreated patients had resistance mutations at baseline including 24 solvent front mutations (SFMs), one SFM and gatekeeper mutation and one other mutation. In the 25 patients with SFMs at baseline, the ORR was 60% (95% CI: 39, 79).

Given the availability of local tests to identify NTRK fusions, and the magnitude and durability of the responses observed, the review team considers that repotrectinib should be approved in the absence of a companion diagnostic, with the Applicant's commitment to support the submission of an application for an in vitro companion diagnostic device as a PMC.

The submitted data for this NDA meets the statutory standard for demonstration of substantial evidence of effectiveness for accelerated approval. The durable responses observed in the TRIDENT-1 study, in the setting of a genetically-based biologic rationale, provide evidence of clinically meaningful benefit of repotrectinib in the rare, genetically defined subgroup of patients with locally advanced or metastatic NTRK+ solid tumors. Subgroup analyses support repotrectinib's antitumor activity in patients with CNS metastases and in patients with resistance mutations following prior TKI therapy; however, no inferences can be made given the small sample sizes. Overall, this evidence suggest repotrectinib may address an unmet clinical need as second-line therapy for patients with NTRK+ solid tumors who may or may not have received treatment with a prior TKI. FDA considers the substantial evidence standard to be met based on the evidence of effectiveness provided by the single, adequate and well-controlled trial, TRIDENT-1 (with general replication of results in two different cohorts). Based on the favorable risk:benefit assessment for this population with a serious, life-threatening disease, accelerated approval is recommended for the following indication.

Repotrectinib is indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

- have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion *and*
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, *and*
- have progressed following treatment or have no satisfactory alternative therapy

The recommended dosage is 160 mg orally once daily for 14 days, then increase to 160 mg twice daily, with or without food.

X	X
Primary Statistical Reviewer Yiming Zhang	Statistical Team Leader Chi (Chuck) Song
X	X
Primary Clinical Reviewer Caitlin Tydings	Clinical Team Leader Leslie Doros

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee as no significant efficacy or safety issue were identified during the review that required external input for the proposed indication.

10. Pediatrics

The Applicant's Position:
The Applicant reached an agreement with the FDA on the initial Pediatric Study Plan (iPSP) on 15 December 2021. The agreed iPSP consisted of a request for a deferral for the report for the molecularly targeted pediatric investigation, which is also included in the sNDA as the CARE study (TPX-0005-07; NCT04094610) in pediatric patients is currently ongoing.

The FDA's Assessment:
The CARE study is an ongoing, open-label, multicenter, single-arm study of repotrectinib monotherapy in pediatric and young adult patients with advanced or metastatic malignancies harboring ALK, ROS1 or NTRK alterations. The dose escalation part of the study enrolled patients <12 years of age and the dose expansion part enrolled patients 12-25 years of age in 3 cohorts: 1) NTRK fusions, TKI naïve, 2) NTRK fusions, TKI pretreated and 3) Other NTRK/ALK/ROS1 alterations NOS. Twenty-six patients have been enrolled, of which 16 have NTRK-positive solid tumors. Sixteen patients were <12 years old and 10 were ≥ 12 years old. Safety data from CARE is meant to be supportive and is limited due a small patient population at the time of NDA submission.

CNS tumors (n=13) followed by sarcomas (n=10) were the most common tumor types and the majority (85%) of patients did not have brain metastases. Fifteen percent of patients did not receive prior systemic therapy and 23% received ≥3 prior lines of systemic therapy.

The most common TEAE (≥20%) included constipation (42%), nausea (27%), fatigue (31%), pyrexia (23%), anemia (38%), rash (27%), arrhythmia (27%), decreased lymphocytes (23%), musculoskeletal pain (23%), dizziness (23%), headache (27%), dysgeusia (27%), and neuropathy peripheral (27%). Grade 3 or 4 TEAEs occurring in ≥2% included abdominal pain (3.8%), constipation (3.8%), fatigue (3.8%), pneumonia (3.8%), upper respiratory tract infection (3.8%), viral infection (3.8%), anemia (15%), hypoxia (8%), and weight increased (12%). Three patients died with a reported AE including glioma, brain compression and disease progression. FDA review of narratives determined these deaths to be not related to an AE and due to disease progression. Repotrectinib was discontinued in 42% of patients, none of which due to an AE.

Skeletal fracture is an AESI, found to be more common in pediatric patients treated with TKIs as seen with entrectinib. Two of 26 patients experienced a skeletal fracture, one 10-year-old and one 12-year-old. Both patients had soft tissue sarcomas, but neither patient had a pathologic fracture or prior radiation to the fracture site.

The safety and effectiveness of repotrectinib for the treatment of locally advanced or metastatic NTRK+ solid tumors have been established in adolescent patients 12 to 17 years of age. Use of repotrectinib in this age group is supported by evidence from the TRIDENT-1 study in adult patients with additional PK and safety data in pediatric patients 12 years of age and

older that demonstrate the exposure of repotrectinib in this age group is expected to result in similar safety and efficacy to that of adults. Preliminary safety data from the CARE study appears consistent with the known safety profile in adults. The Applicant will provide updated results upon completion of the CARE study as part of a PMR issued during the original NDA submission. Given the known risk of skeletal fractures and CNS effects of TKI therapies (and potential effects on growth in animal studies), PMRs will be issued to obtain long-term data to better describe and characterize the risk of skeletal fractures and the effect on pediatric growth and development.

The Applicant submitted an iPSP requesting a deferral for submitting the final study results of TPX-0005-07, entitled "A Phase 1/2, Open-label, Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity Study of Repotrectinib in Pediatric and Young Adult Subjects with Advanced or Metastatic Malignancies Harboring ALK, ROS1, or NTRK1-3 Alterations (CARE) in pediatric patients 0 to 12 years of age. Because the NRTK+ solid tumor indication was granted orphan drug designation, the drug product for this indication is exempt from the requirements under the Pediatric Research Equity Act (PREA). The approval letter for the ROS1+ NSCLC indication (November 15, 2023) has a postmarketing requirement (PMR) 4547-1 to submit the final study report for the CARE.

11. Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
INDICATIONS AND USAGE (1)	Addition of indication for AUGTYRO for adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity	Added "have progressed following treatment or have no satisfactory alternative therapy" to indication
DOSAGE AND ADMINISTRATION (2.1)	Addition of selecting patients based on the presence of *NTRK* gene fusion	Added "In patients with secretory breast cancer or mammary analogue secretory cancer, consider treatment without confirmation of NTRK rearrangements in tumor specimens.
WARNINGS AND PRECAUTIONS (5.6)	Added information on skeletal fractures in pediatric patients from CARE study	FDA generally agrees. Minor edits to align with current labeling practice
DOSAGE AND ADMINISTRATION (2.4)	Addition of dose recommendation (same as adults) for pediatric patients 12 years of age and older	FDA generally agrees. Minor edits to align with current labeling practice
ADVERSE REACTIONS (6.1)	Update of clinical safety data by adding patients from TRIDENT-1 with solid tumors that have a *NTRK* gene fusion, to a total of 426 patients	FDA generally agrees. Minor edits to align with current labeling practice
PEDIATRIC USE (8.4)	(b) (4)	FDA removed language on (b) (4) in accordance with pediatric

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
		labeling guidance
PHARMACOKINETICS (12.3)	(b) (4)	FDA rejected for redundancy with current language on (b) (4)
CLINICAL STUDIES (14.2)	Addition of clinical efficacy data from the TRIDENT-1 study for patients with solid tumors that have a *NTRK* gene fusion, including: a brief description of the study design and treatment groups; inclusion/exclusion criteria of the study; patient demographics; primary and key secondary efficacy endpoints	FDA generally agrees. Minor edits to align with current labeling practice; also added prior lines of therapy received by patients.

The Applicant's Position:
The clinical data provided in this supplemental NDA submission demonstrate the clinical benefit and safety of the use of repotrectinib for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic *NTRK*-positive solid tumors. Based on these data, the table above provides a high-level summary of the proposed changes to the labeling for repotrectinib.

The FDA's Assessment:
The FDA generally agrees with the proposed USPI and has edited as described in the above table.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of repotrectinib are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of repotrectinib can be adequately implemented in the post-marketing setting through product labeling. No additional risk management strategies are recommended.

13. Postmarketing Requirements and Commitment

The FDA's Assessment:
BMS has agreed to the following postmarketing requirements (PMR) and commitments (PMC):

Clinical

1. PMR 4649-1

Conduct an analysis of patients from ongoing or planned trials to verify and describe the clinical benefit of repotrectinib through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and pediatric patients 12 years of age and older with solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion who have locally advanced or metastatic disease or would require surgical resection that would result in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment.

A sufficient number of patients will be evaluated to more precisely characterize response and durability of response for a spectrum of patients with different TKI-naïve and TKI-pretreated tumor types. All responding patients will be followed for at least 12 months from the onset of response or until disease progression whichever comes first.

Trial Completion:	11/2029
Final Report Submission:	05/2030

Submit the datasets with the final report submission.

2. PMR 4649-2

Complete the analysis of the 23 responding patients in the efficacy evaluable population of 40 TKI-naïve patients and the 24 responding patients in the efficacy evaluable population of 48 TKI-pretreated patients in the TRIDENT-1 trial intended to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to repotrectinib. All responding patients will be followed for at least 2 years from the onset of response or until disease progression, whichever comes first. Duration of response will be assessed by independent central review.

Trial Completion:	09/2024
Final Report Submission:	03/2025

Submit the datasets with the final report submission.

3. PMR 4649-3

Conduct integrated safety analyses from an adequate number of patients enrolled in clinical trial(s) designed to characterize the known serious risk of fractures and sequelae of fractures in patients exposed to repotrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to identify mitigating measures for the risk of skeletal fractures. Include sufficient bone monitoring to achieve these objectives including but not limited to initial and serial assessment of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans, and markers of bone formation, bone resorption, and calcium metabolism.

Trial Completion:	05/2029
Final Report Submission:	11/2029

4. PMR 4649-4

Conduct a clinical trial or analysis of clinical trials of repotrectinib in a sufficient number of pediatric patients 12 years of age and older with NTRK-fusion positive solid tumors to evaluate the potential serious risk of adverse long-term effects of repotrectinib on growth and development and neurological outcomes, with reasonable precision. Patients will be monitored for growth and developmental milestones using age-appropriate screening tools and undergo neurological examination at appropriate intervals. Evaluations will include neurological exams with neurocognitive assessment, Karnofsky/Lansky score, growth as measured by height, weight, height velocity, and height standard deviation scores (SDS), age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner Stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

Trial Completion:	11/2029
Final Report Submission:	05/2030

CDRH

5. PMC 4649-5

Complete an appropriate clinical validation study using clinical trial data to establish and support the availability of an in vitro diagnostic device that is essential to the safe and effective use of repotrectinib for patients with solid tumors that carry NTRK1/2/3 gene fusions.

Final Report Submission: 07/2025]

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		**Is a PMC/PMR needed?**
X	In general, the patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication. Although uncertainties exist with respect to the incidence of NTRK tumors in different US population, the ultra-rarity of the NTRK tumors would make further investigation in different groups of patients challenging.	__ Yes _X_ No
X	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g., race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

14. Division Director (OCP)

X

Stacy Shord

15. Division Director (OB)

X

Pallavi Mishra-Kalyani

16. Division Director (Clinical)

X

Steven Lemery

I agree with the recommendation to approve this application based on the reasons described by the clinical/statistical teams in this review.

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

17. Appendices

17.1. References

The Applicant's References:

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17.2. Financial Disclosure

The Applicant's Position:

A list of all Investigators in the TRIDENT-1 and CARE studies are provided and includes a financial disclosure package with details of the process followed for collecting financial disclosures, a table of Investigators with disclosable interests reported by Investigators, and if

applicable, a table with due diligence efforts for the collection of missing financial disclosures. If/when an Investigator reported disclosable financial interest, an assessment of the potential bias was included.

A summary of the financial interests or arrangements with clinical Investigators is disclosed in the table below.

Covered Clinical Study (Name and/or Number): TPX-0005-01 (TRIDENT-1)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1970		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 1 Sponsor of covered study: Bristol-Myers Squibb Company		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 39		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number): TPX-0005-07 (CARE)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 269		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: Bristol-Myers Squibb Company		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:
The Applicant submitted a Financial Interests and Arrangements of Clinical Investigators Certification for TRIDENT-1, which stated that the Applicant did/did not enter into any financial arrangements with the clinical investigators.

17.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable

17.4. OCP Appendices (Technical documents supporting OCP recommendations)

17.4.1. Summary of Bioanalytical Method Validation and Performance

The FDA's Assessment:

The Applicant provided updated results of bioanalytical validation and performance for methods used to support PK collection in TRIDENT-1 and data presented in the clinical study report. Table 47 shows the pertinent updated results of the Applicant's evaluations. Additional FDA review of the Applicant's bioanalytical method validation and performance can be found in the FDA review under the original AUGTYRO™ approval.

Table 47: FDA Summary of Bioanalytical Methods

Method Validation	Method MN16112 (b) (4)		
Method Description	Method for the Determination of TPX-0005 in Human Plasma using High-Performance Liquid Chromatography with Mass Spectrometric Detection		
Materials used for standard calibration curve and concentration	Repotrectinib in human K2EDTA plasma at 1.00, 2.00, 4.00, 8.00, 20.0, 40.0, 100, 200, 500, and 1000 ng/mL		
Validated assay range	1.00 to 1,000 ng/mL		
Material used for quality controls (QCs) and concentration	Repotrectinib in human K2EDTA plasma 3.00, 40.0, 400, 800, 2500, and 10000 ng/mL		
Regression model and weighing	Linear with $1/x^2$ weighting		
Validation parameters	Method validation summary		FDA Acceptability
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	10	Acceptable.
	Cumulative accuracy (%bias) from LLOQ to ULOQ Repotrectinib	-2.00% to 2.25%	Acceptable.
	Cumulative precision (%CV) from LLOQ to ULOQ Repotrectinib	2.45% to 7.07%	Acceptable.
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 3 QCs QCs for Repotrectinib	2.33%	A & P should be established with at least three independent A & Pruns, four QC levels per run (LLOQ, L, M, H QC), and ≥ five replicates per QC level. Applicant included 15 runs within acceptable thresholds; thus, FDA accepts based on totality.

	Inter-batch precision (%CV) in 3 QCs QCs for Repotrectinib	5.63% to 9.39%	See previous.
	Total Error (TE)	NA	
Dilution linearity & hook effect	800 ng/mL, 10x dilution; bias = -9.88% to 10.5%		Acceptable.
Incurred sample reproducibility	83 samples were reassayed; 100% were within 20% of original value.		Acceptable.

Source: Adapted from Applicant's submitted "TPX-0005-01 Phase 2 Interim Bioanalytical Report-2"

17.4.2. Population PK Analysis

17.4.2.1. PPK Executive Summary

The FDA's Assessment:

This Applicant seeks approval of repotrectinib monotherapy for the treatment of adult and pediatric patients 12 years of age and older that have locally advanced or metastatic solid tumors with an NTRK gene fusion. Repotrectinib is mainly metabolized by CY3A4 and exhibits a time-dependent autoinduction.

Previously, a population PK model of repotrectinib was developed based on data from adult healthy participants and patients with cancer and characterized by a 2-compartment model structure with first-order rate absorption with a lag time, a nonlinear elimination with autoinduction described by a time-dependent Emax function, and an allometrically scaled baseline body weight effect on CLs and volumes of distribution parameters. In the current application, the previous PopPK model structure was maintained and refined with additional data to support the recommended dosage for the treatment of ROS1-positive NSCLC in adults and NTRK1-3 positive solid tumors in adult and pediatric patients 12 years and older.

17.4.2.2. PPK Assessment Summary

The Applicant's Position:

The initial PopPK model for initial ROS1 NDA for repotrectinib was updated by adding additional data from Phase 1/2 study TPX-0005-01 (TRIDENT-1, data cutoff 19-Dec-2022) and adding pediatric study CARE [TPX-0005-07] to the dataset. The final model maintains the similar model structure as the initial adult final model with the refinements including:

- Autoinduction was driven by trough concentration instead of dose in the initial model.
- In the allometric scaling, estimated the exponent of body-weight effects on CLs and volumes of distribution (V) instead of fixed exponent value in the initial model.
- Adding age effect as a continuous variable for patients < 18 years old on CLMAX.

The repotrectinib PK in adults and pediatric patients was well described with a 2-compartment model structure with first-order absorption with a Tlag, non-linear elimination modeled

through a time-dependent Emax function using concentration, an allometrically scaled baseline body-weight effect on CLs and V, food effects on KA and F1, and age effect (up to 18 years old) on CLMAX.

General Information		
Objectives of PPK Analysis		• To characterize the PK of repotrectinib following oral administration in adult and adolescent (≥ 12 to <18 years) patients with advanced solid tumors harboring *ALK*, *ROS1*, or *NTRK1-3* rearrangements. • To identify potential covariates that may be important predictors of variability in repotrectinib absorption, distribution, and elimination. • To confirm the exposures in adolescents (≥ 12 to < 18 years) are comparable to those in adults and support repotrectinib dose recommendation in adolescents with advanced or metastatic malignancies harboring NTRK1-3 fusions using model-based simulation.
Study Included		TPX-0005-01 (TRIDENT-1), TPX-0005-07, TPX-0005-08, TPX-0005-09, TPX-0005-10, TPX-0005-11, TPX-0005-12, and TPX-0005-14.
Dose(s) Included		40 mg to 240 mg
Population Included		Healthy adult subjects (N = 118), pediatric (N = 24) and adult patients (N = 502) with advanced solid tumors
Population Characteristics	General	Median (range) age: 51.5 (0.8, 93) years. Median (range) baseline body weight: 70.6 (5.9, 169) kg Sex, n (%): 344 (53.4) males, 300 (46.6) females Race, n (%): White: 319 (49.5), Black/African American: 43 (6.7), Asian: 245 (38.0), Others: 8 (1.2), Unknown: 29 (4.5)
	Organ Impairment	Hepatic (NCI), n (%): normal: 582 (90.4), mild: 59 (9.2), moderate: 1 (0.2), severe: 0 (0), and missing: 2 (0.3) Renal (eGFR by CKD-EPI), n (%): normal: 448 (69.6), mild: 157 (24.4), moderate: 33 (5.1), severe: 0 (0), and missing: 6 (0.9)
	Pediatrics (if any)	Median (range) age: 6.8 (0.8, 16) years. Median (range) baseline body weight: 27.1 (5.9, 73.4) kg Sex, n (%): 11 (45.8) males, 13 (54.2) females Race, n (%): White: 15 (62.5), Black/African American: 2 (8.3), Asian: 5 (20.8), Unknown: 2 (8.3)
No. of Patients, PK Samples, and BLQ		644 patients, 9222 PK samples, Post first dose BLQ 112 samples.
Sampling Schedule	Rich Sampling	Predose and up to 168 hours postdose
	In ITT Population	Cycle 1 Day 1: Predose, and up to 72 hours postdose after single dose. Cycle 1 Day 15: Predose, and up to 24 hours postdose following multiple QD or BID doses. Sparse samples: Cycle 1 Day 1 and Day 15, as well as Cycles 2-4, Day 1 at predose and 4 hours postdose.
Covariates Evaluated	Static	See more covariates evaluated in the initial PopPK report for initial ROS1 NDA. Covariates evaluated in the updated model include: Age, race, ethnicity, body weight, body surface area, hepatic (NCI) and renal functions (eGFR by CKD-EPI), subject classifications (healthy versus patient), formulations, food status, TKI-pretreatment status, and genetic mutations (*ALK*, *ROS1*, or *NTRK1-3*)
	Time-varying	NA

Final Model	**Summary** The model diagnostic plots and model evaluations show adequate model performance. Final model parameters were reasonably well estimated (<20% RSE on most fixed effects and <25% RSE on all random effects). Predicted exposures based on the developed final repotrectinib model were used to evaluate covariate effects on exposure and to support dose recommendation in adolescents.	Yes, FDA generally agrees with the final model selection and the parameter estimates. Upon analysis, FDA was able to reproduce the final model estimates and the goodness-of-fit plots (Please refer the appended FDA's analysis GOF plot figures below, Figure 10).
Software and Version	NONMEM (Version 7.4.3); Statistical Analysis System (SAS®; Version 9.4); R (Version 3.6.1 or later); Xpose® and PsN (Department of Pharmacy, Uppsala University, Uppsala, Sweden); Pirana (Version 2.9.1); R (Version 3.6.3 or above; R Foundation for Statistical Computing, Vienna, Austria); RStudio (Version 1.2.5033; RStudio, Boston, MA, USA)	Yes, FDA agrees that the software and their versions used to conduct the analyses are acceptable. Standard software were used for conducting the PopPK analysis.
Model Structure	A 2-compartment model structure with first-order absorption with a Tlag, non-linear elimination modeled through a time-dependent Emax function using concentration, an allometrically scaled baseline body-weight effect on CLs and V, food effects on KA and F1, and age effect (up to 18 years old) on CLMAX.	Yes, FDA agrees that the utilized model structure adequately described the data. The previous structural model was optimized and used in the current application.
Model Parameter Estimates	Table 48: Applicant	Yes, FDA's repeated analysis showed comparable model parameter estimates as shown in the Applicant – Table 48.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All model parameters were reasonably well estimated, with the % RSE of all fixed effects well below 20% except TC50 (time to achieve half of CLMAX) which was <25%, and the % RSE of all random effects were below 25%.	Yes, FDA agrees that uncertainty and variability measures of most estimated model parameters were within acceptable range (<20%) except TC50 that showed 22.5%. The shrinkage values are also generally acceptable to FDA

	Shrinkage values: CL for healthy volunteers = 17.3%, CL for patients = 14.6%; Vc = 32.6%; Q = 31.8%; KA = 36.2%; F1 = 40.2%. Bootstrap was not repeated for the updated model. In the initial PopPK model for initial ROS1 NDA, the results of Bootstrap indicate the model had good precision for parameter estimates.	specially for critical model parameters. Also, FDA accepts the applicant's position on the bootstrap.
BLQ for Parameter Accuracy	Exclusion of BLQ is not expected to impact PopPK parameter estimates as only approximately 1% (112 of 9222) of total PK concentrations had BLQ.	Yes, FDA agrees that censoring of the BLQ (1.2%) was not expected to impact PopPK model parameter estimates given the analyzed samples as indicated in the PopPK report Table 3.3.1.2-1
GOF, VPC	Figure 7: Applicant and Figure 8: Applicant	Yes, FDA generally agrees that the GOF and VPC plots indicated that the final model adequately described the observed data. The GOF plots lines of identify and unity of the observed vs predicted concentrations generally align and divide the data nearly in equal parts. The VPC plots show that the model adequately predicted the central tendency and variability of the plasma concentrations. Applicant – Figure 7 and Applicant Figure 8.
Significant Covariates and Clinical Relevance	Figure 9: Applicant Baseline body weight (BW) was allometrically scaled on CLs and volumes of distributions. Food effects on KA and F1 were significant, while age up to 18 years old was a significant covariate on CLMAX.	Yes, repeated analysis by FDA confirmed that allometrically scaled baseline body weight on CLs and Vds, food effects on KA and F1 and age on CLMAX were identified as significant covariates.
Analysis Based on Simulation (optional)	Table 49: Applicant Stochastic simulations were conducted for adult patients and adolescents for the following dosing regimens: 160, 120, and 80 mg QD/BID.	Yes, stochastic simulations were done for adult patients and pediatrics for 160, 120 and 80 mg QD/BID dosing regimens. After the first dose, the simulated concentrations are comparable between adult and pediatric patients (Table 49).
Labeling Language	Description	Yes, FDA's PopPK simulation

	(b) (4) analyses corroborate with the stated labeling language. (b) (4) (b) (4)	
12.3 PK	See details in USPI for ROS1-positive NSCLC. Updates to USPI: In Elimination, update single-dose and steady terminal half-life to '60.7 h' and '40.3 h', respectively. In Specific Populations, update 'age (18 to 84 years)' to 'age (12 to 93 years)'. Also update 'race/ethnicity (Caucasian 54%, Asian 38%, black 7%)' to race/ethnicity (Caucasian 50%, Asian 38%, black 7%)'.	

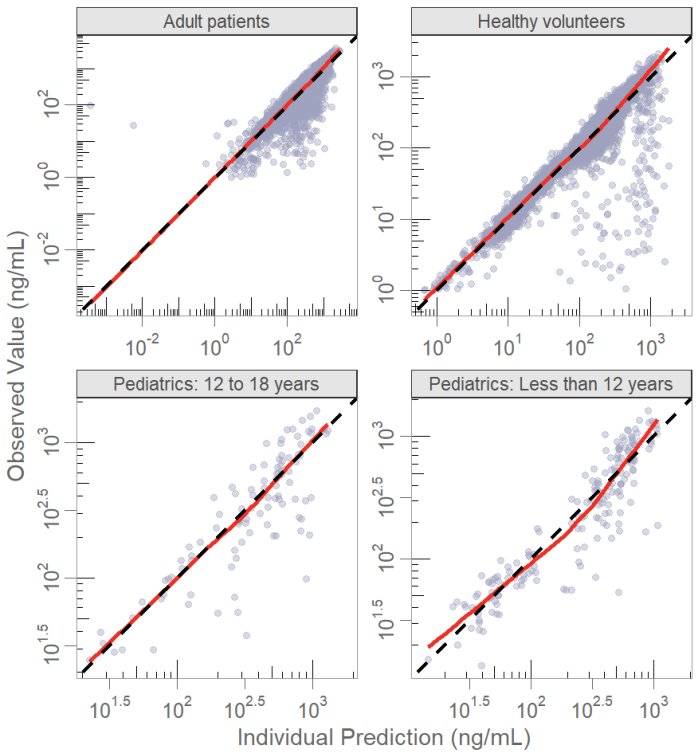
Table 48: Applicant Parameter Estimates and SE from Final Population PK Model

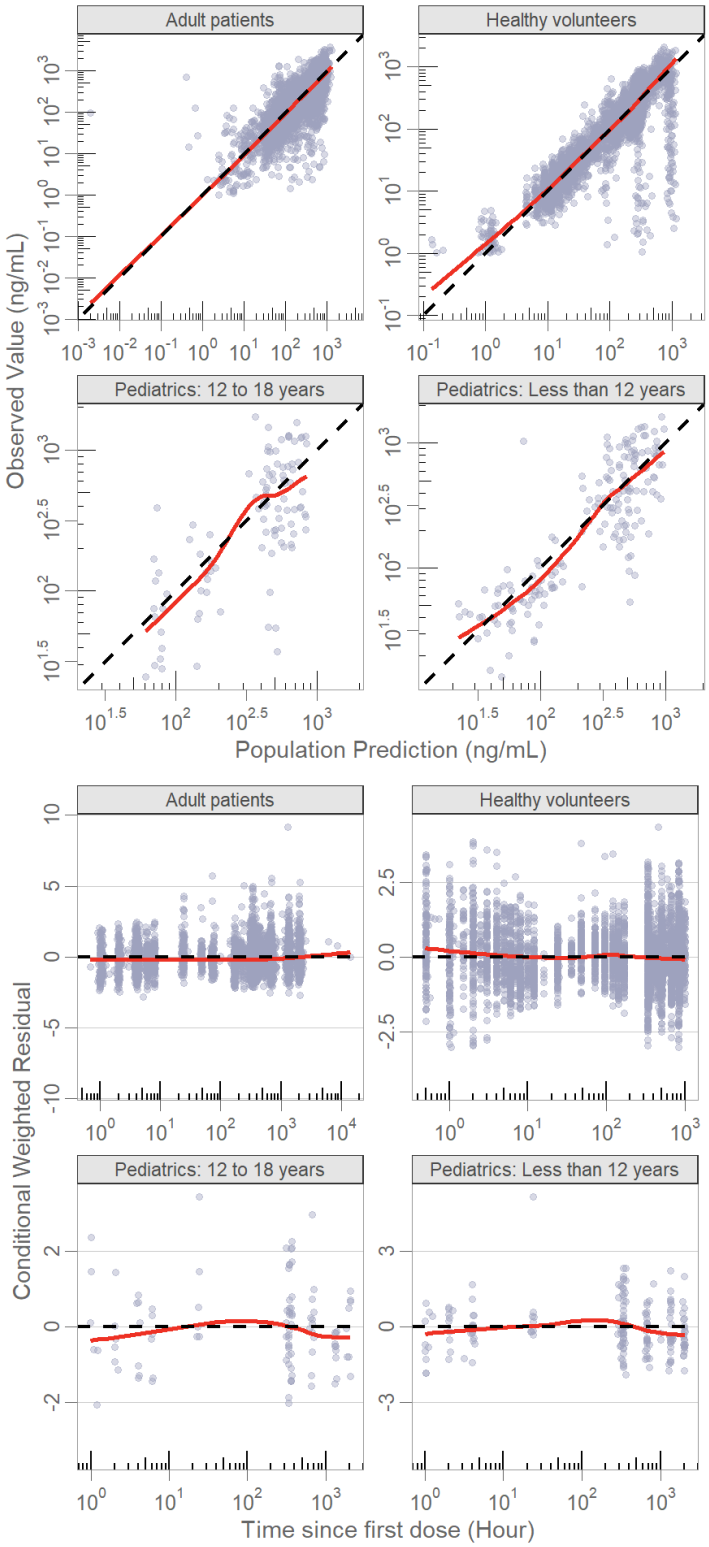
Symbol	Parameter (Units)	Parameter Estimate	Standard Error	Standard Error (RSE%)	95% CI
θ1	CL: central clearance (L/hour)	7.11	0.337	4.7	[6.449, 7.771]
θ2	Vc: central volume (L)	19.9	1.98	10	[16.02, 23.78]
θ3	Vp; peripheral volume (L)	222	9.25	4.2	[203.9, 240.1]
θ4	Q: intercompartmental clearance (L)	4.98	0.323	6.5	[4.347, 5.613]
θ5	KA fasted: first-order absorption rate constant under fasted (/hour)	0.0541	0.00205	3.8	[0.05008, 0.05812]
θ6	KA fed: first-order absorption rate constant under fed (/hour)	0.124	0.00469	3.8	[0.1148, 0.1332]
θ7	KA modified fasted: first-order absorption rate constant under modified fasted (/hour)	0.141	0.00807	5.7	[0.1252, 0.1568]
θ8	KA unknown: first-order absorption rate constant under unknown food status (/hour)	0.193	0.00693	3.6	[0.1794, 0.2066]
θ9	F1 fasted: bioavailability under fasted status	0.52	0.0284	5.5	[0.4643, 0.5757]

Symbol	Parameter (Units)	Parameter Estimate	Standard Error	Standard Error (RSE%)	95% CI
θ10	F1 fed: bioavailability under fed status	0.761	0.0388	5.1	[0.685, 0.837]
θ11	F1 modified fasted: bioavailability under modified fasted status	0.639	0.0404	6.3	[0.5598, 0.7182]
θ12	F1 unknown: bioavailability under unknown food status	0.533	0.0314	5.9	[0.4715, 0.5945]
θ13	ALAG1: lag time (hours)	0.421	0.00691	1.6	[0.4075, 0.4345]
θ18	$ALLOM_1$: allometric scaling for body weight on clearances	0.477	0.0682	14.3	[0.3433, 0.6107]
θ19	$ALLOM_2$: allometric scaling for body weight on volumes of distribution	0.962	0.0516	5.4	[0.8609, 1.063]
θ20	V2HV: healthy volunteers effect on Vc	-0.854	0.0207	2.4	[-0.8946, -0.8134]
θ21	CLMX: maximum induced clearance	1.59	0.0641	4	[1.464, 1.716]
θ22	EC50: concentration to achieve half of CLMAX (ng/mL)	77	7.16	9.3	[62.97, 91.03]
θ23	GAMMA: Hill coefficient	1 FIX	-	-	
θ24	TC50: time to achieve half of CLMAX (hours)	47.1	10.6	22.5	[26.32, 67.88]
θ25	Age on CLMAX (for subjects < 18 years)	-0.291	0.0271	9.3	[-0.3441, -0.2379]
ω.1.1.	IIV on CL for healthy volunteers	0.0392	0.00805	20.6	[0.02342, 0.05498]
ω.2.2.	IIV on Vc	0.768	0.0739	9.6	[0.6232, 0.9128]
ω.4.4.	IIV on Q	0.458	0.0528	11.5	[0.3545, 0.5615]
ω.5.5.	IIV on KA	0.0961	0.0127	13.2	[0.07121, 0.121]
ω.6.6.	IIV on F1	0.356	0.0591	16.6	[0.2402, 0.4718]
ω.7.7.	IIV on CL for patients	0.289	0.0253	8.8	[0.2394, 0.3386]
θ14	Proportional error in healthy volunteers	0.335	0.00452	1.3	[0.3261, 0.3439]
θ15	Additive error in healthy volunteers	0.00001 FIX	-	-	NA
θ16	Proportional error in patients	0.424	0.00556	1.3	[0.4131, 0.4349]
θ17	Additive error in patients	10.6	0.563	5.3	[9.497, 11.7]

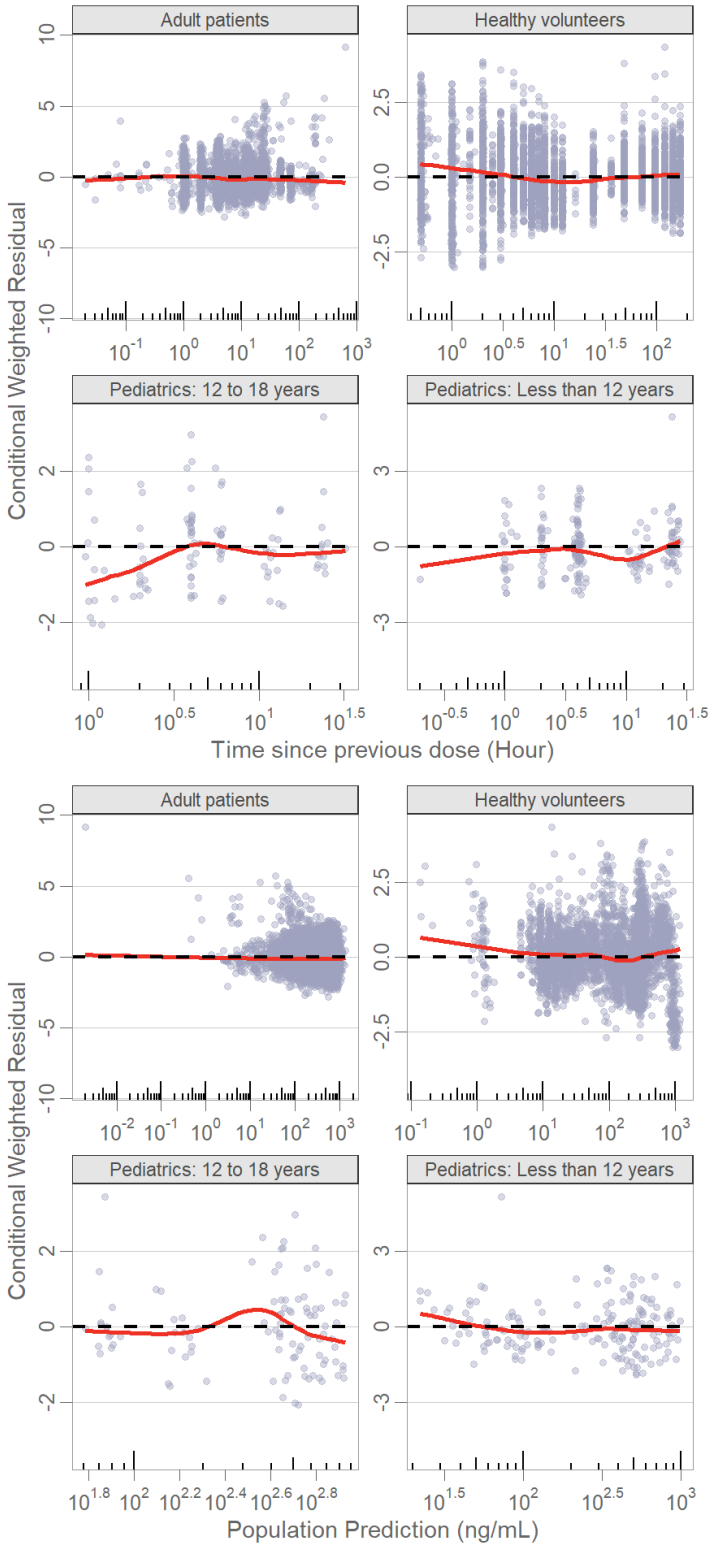
Note: Shrinkages: CL for healthy volunteers = 17.3%, Vc = 32.6%; Q = 31.8%; KA = 36.2%; F1 = 40.2%; CL for patients = 14.6%
The minimum value of the BIC = 88,508.8. Condition number = 95.08.
CI was calculated using parameter estimate and the corresponding standard error (parameter estimate ± standard error).
Source: Repotrectinib Updated PopPK Report Table 5.1.1.2-2

Figure 7: Applicant Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)



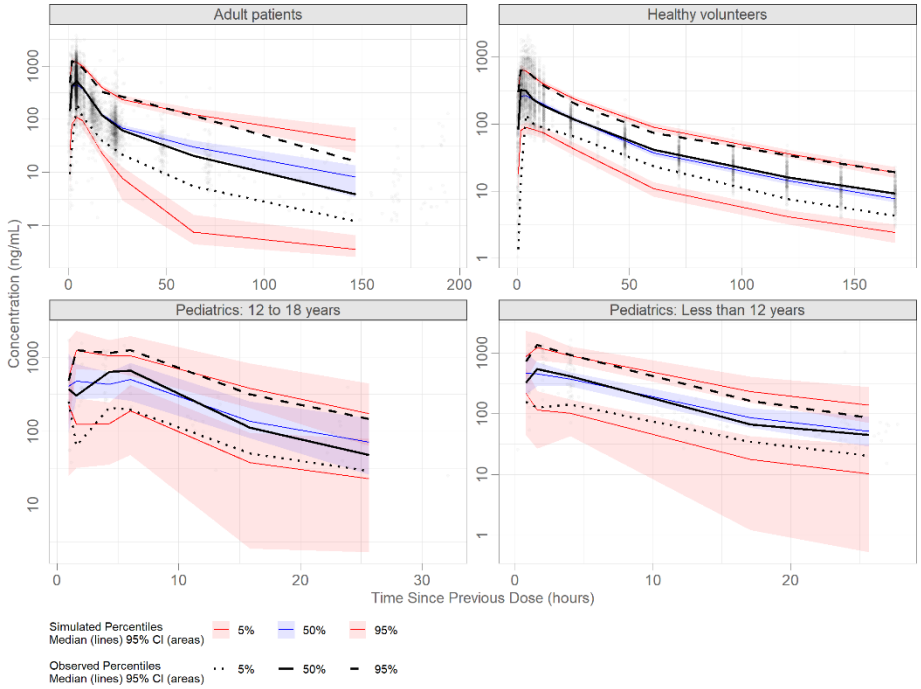


Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.



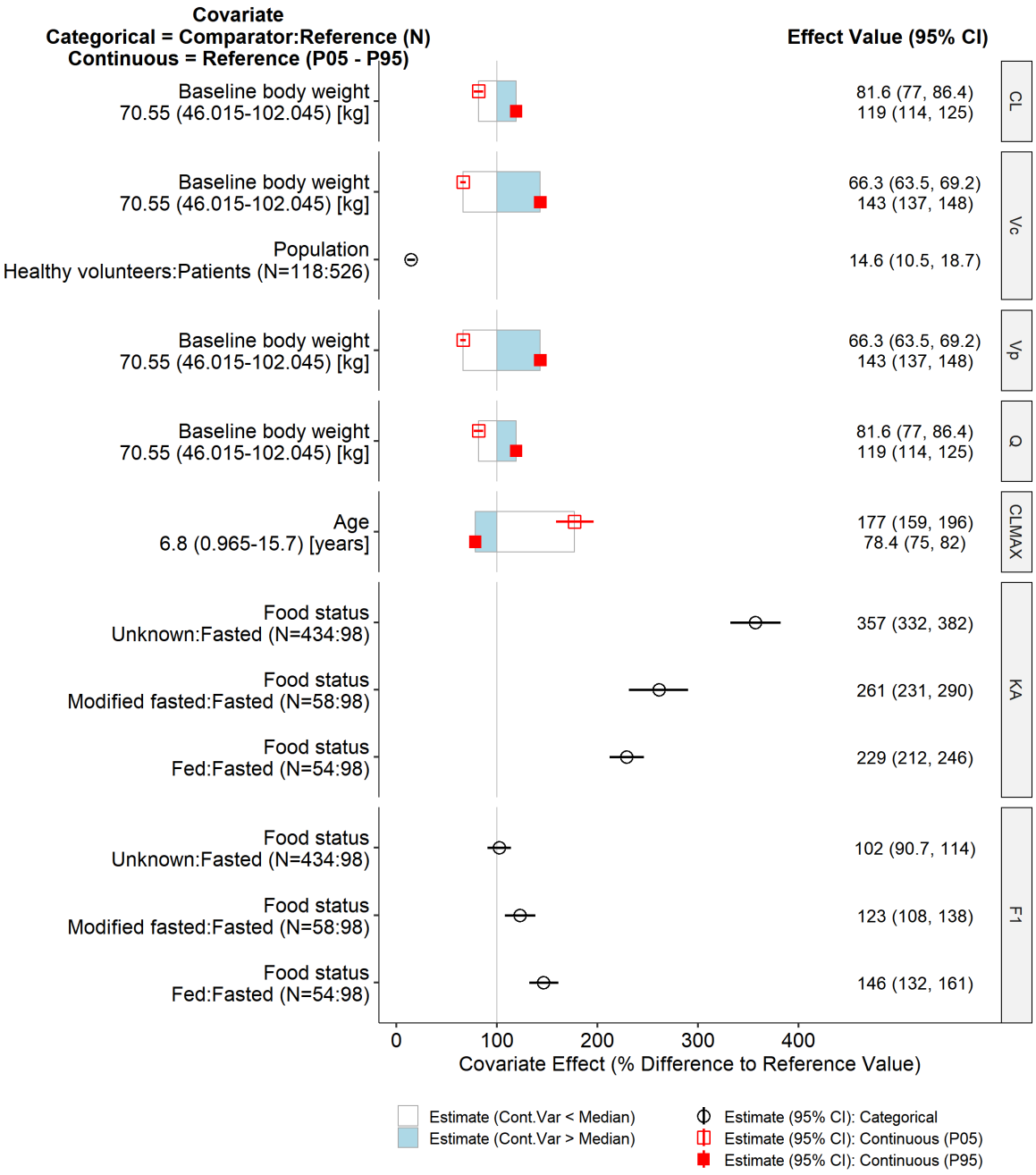
Note: The red line is the LOESS smooth curve.
Source: Repotrectinib Updated PopPK Report Figure 5.1.1.2-2

Figure 8: Applicant pcVPC of Final Population PK Model



Source: Repotrectinib Updated PopPK Report Figure 5.1.2.1-2
Note: The pcVPC plots show the median (solid black line) and spread (5th to 95th percentiles; dashed black lines) of the DV in all subjects. The blue area is the 95% CI of the simulated median (solid blue line), and the pink area is the 95% CI of the simulated 5th and 95th percentiles (solid red lines).

Figure 9: Applicant Covariate-Parameter Relationship: Final Repotrectinib Population Pharmacokinetic Model



Notes: Categorical covariate effects (95% CI) are represented by black open circles (horizontal black lines). Continuous covariate effects (95% CI) at the 5th/95th percentile of the covariate are represented by the end of horizontal boxes (horizontal red lines).

Open/blue area of boxes represents the range of covariate effects from the median to the 5th/95th percentile of the covariate. For the subject with multiple food status during treatment, the first food status of this subject was used for analysis.
Source: Repotrectinib Updated PopPK Report Figure 5.1.1.2-3

Table 49: Applicant Adolescents Versus Adult Patients Exposure Comparison: 160 mg Once Daily for 14 Days and then 160 mg Twice Daily to Steady State

Exposure	Body Weight (kg)	Pediatrics (N)	Pediatrics GM (CV%)	Adult Range[a]	Adults (N)	Adults GM (CV%)	Adult GM Range
Cavgss	30-40 kg	100	408 (49.8)	Yes	100	485 (39.8)	266-485
	40-50 kg	100	388 (47.1)	Yes	100	371 (38.2)	
	50-60 kg	100	336 (44.2)	Yes	100	384 (48.2)	
	60-70 kg	100	324 (52.4)	Yes	100	359 (49)	
	70-80 kg	100	297 (51.7)	Yes	100	323 (45.9)	
	80-90 kg	100	311 (44.3)	Yes	100	312 (51)	
	90-100 kg	100	278 (46.8)	Yes	100	300 (40.4)	
	100-110 kg	100	268 (40)	Yes	100	321 (46.5)	
	≥ 110 kg	100	267 (42.1)	Yes	100	266 (43.5)	
Cminss	30-40 kg	100	163 (69.8)	Yes	100	196 (61.7)	125-196
	40-50 kg	100	161 (60.5)	Yes	100	162 (60.2)	
	50-60 kg	100	137 (55.6)	Yes	100	170 (68.9)	
	60-70 kg	100	141 (68.4)	Yes	100	161 (64.5)	
	70-80 kg	100	131 (70.7)	Yes	100	149 (62)	
	80-90 kg	100	139 (61.3)	Yes	100	144 (65.2)	
	90-100 kg	100	125 (58.1)	Yes	100	132 (54.3)	
	100-110 kg	100	122 (58.8)	No (-2.4%)	100	152 (70.3)	
	≥ 110 kg	100	126 (61.9)	Yes	100	125 (61.5)	
Cmaxss	30-40 kg	100	740 (52.3)	Yes	100	851 (47.1)	428-851
	40-50 kg	100	692 (48)	Yes	100	633 (41.1)	
	50-60 kg	100	603 (52.2)	Yes	100	658 (47.2)	
	60-70 kg	100	557 (53.1)	Yes	100	599 (53.6)	
	70-80 kg	100	500 (50)	Yes	100	528 (48.2)	
	80-90 kg	100	512 (48)	Yes	100	506 (51.6)	
	90-100 kg	100	463 (51.6)	Yes	100	509 (46.6)	
	100-110 kg	100	433 (39.6)	Yes	100	523 (45.3)	
	≥ 110 kg	100	419 (44.5)	No (-2.1%)	100	428 (40.9)	

[a] *Whether the exposures in adolescents are within the adult range. If no, the percentage in difference is provided.*
Source: Repotrectinib Updated PopPK Report Table 5.1.3.6-1

The FDA's Assessment:

FDA generally agrees with the final model selection and the parameter estimates. Upon

analysis, FDA was able to reproduce the final model estimates and the goodness-of-fit plots (Please refer the appended FDA's analysis GOF plot figures below, Figure 10).

The model diagnostic plots and model evaluations show adequate model performance. Final model parameters were reasonably well estimated (<20% RSE on most fixed effects and <25% RSE on all random effects). Predicted exposures based on the developed final repotrectinib model were used to evaluate covariate effects on exposure and to support dose recommendation in adolescents.

17.4.2.3. PPK Review Issues

In relation with the current application, the following key PPK review issues were identified: Assessment whether the proposed recommended dosage of 160 mg QD for 14 days followed by 160mg BID in pediatric patients 12 years and older provided exposures derived from PPK model simulation within range of those in adults administered the same dosing regimen. Additionally, the effect of intrinsic and extrinsic factors on the exposures was evaluated, including the effect of food and baseline total body weight (Figure 11).

17.4.2.4. Reviewer's Independent Analysis

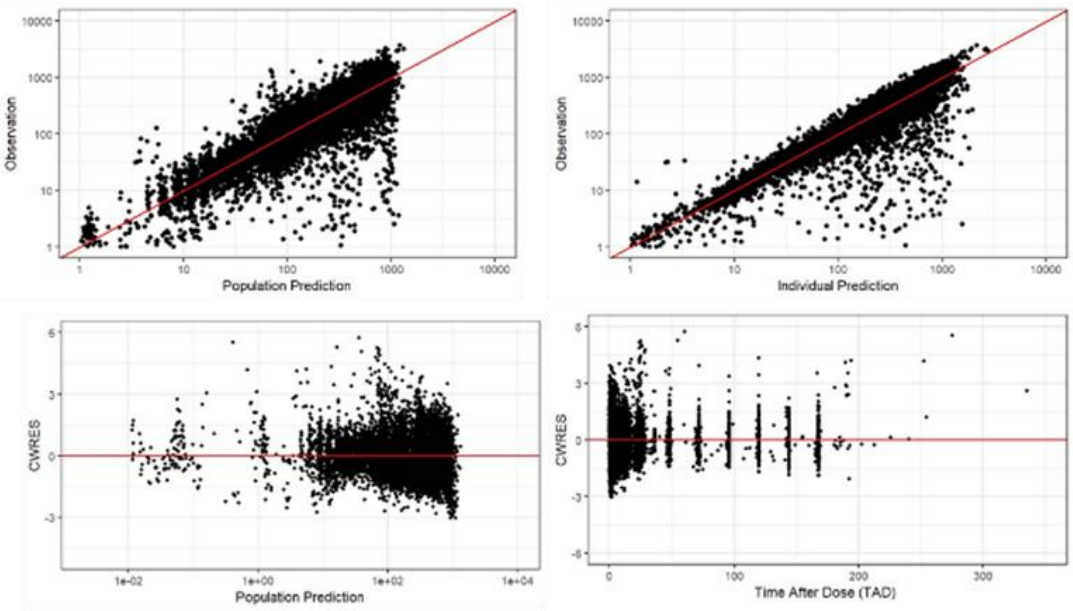
FDA conducted independent analysis to assess the key review questions stated above. Briefly, to assess the adequacy and the performance of the updated PPK model, using NOMMEM v. 7.5, Rstudio v 4.3.3 and PsN in Pirana v 2.9, the final model was replicated using the applicant's supplied model programs and dataset. The GOF plots were inspected for their adequacy to describe the observed data (Figure 10), and the model parameter estimates were checked for their consistency with the applicant's parameter estimates. Using the final model, stochastic simulations were then conducted for proposed dose to simulate exposure metrics for comparing adults and pediatric patients aged 12 and older and to evaluate the impact of food on exposure.

A total of 9,222 quantifiable concentrations of repotrectinib from 644 subjects (502 adult patients including 95 new adult patients, 24 new pediatric subjects, and 118 healthy participants) were included in the analysis. In general, the GOF plots and the pcVPC showed that the PPK model adequately described the observed data (Figure 10) and the model parameter estimates as well as the objective function values were in par with the applicant's findings. The model parameters were reasonably estimated with acceptable level of precision and random variability (< 20% RSE) for most parameters and (< 25% RSE) for random effects. The following refinements on the previous structural model improved the model fit as the BIC values dropped by greater than 800 (applicant's analysis). Auto-induction was driven by trough concentration, instead of dose, CLMAX as a multiplicative factor of CL instead of additive, IIV was one parameter on CL and CLMAX instead of two IIV parameters but estimated separately

for healthy subjects and patients, estimating the exponent of CL and V in the allometric scaling instead of fixed value of 0.75 and 1, respectively, and adding age effect as a continuous variable for subjects < 18 years old on CLMAX. The model predicted exposures were used to evaluate the covariate effect on the exposure and to support dose recommendation in adolescents.

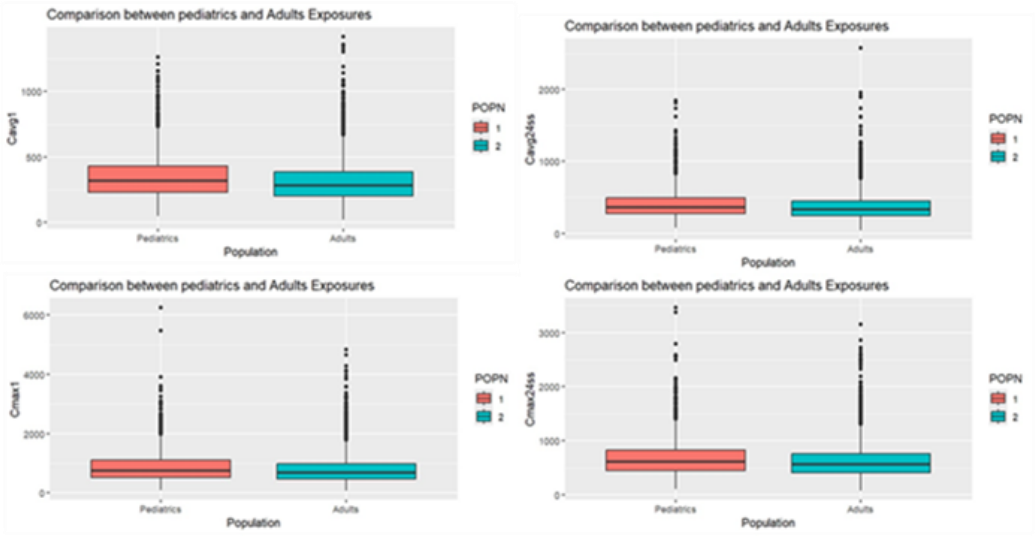
Based on the results from FDA's simulation analysis, pediatric patients 12 years and older, have comparable exposure metrics to that of adults when the recommended dosing regimen of 160 mg QD/BID were applied to the simulated population, suggesting that the proposed 160 mg QD/BID is suitable to pediatric patients of 12 years and older (Figure 11). Additionally, the PopPK model was applied to investigate the impact of food conditions on the recommended dosing regimens and no difference in the steady-state exposure measures was observed by comparing the simulated exposure measures in different food condition, suggesting that no food effect at steady state (Figure 11). However, this result needs to be interpreted with caution since a large portion of patients' food status was unknown. Moreover, simulation was conducted using the PopPK model to compare steady-state exposures in the 5th, 95th percentiles and the median body weights and no notable difference in exposure metrics was observed ().

Figure 10. Goodness of Fit Plots (Reviewer's Analysis)

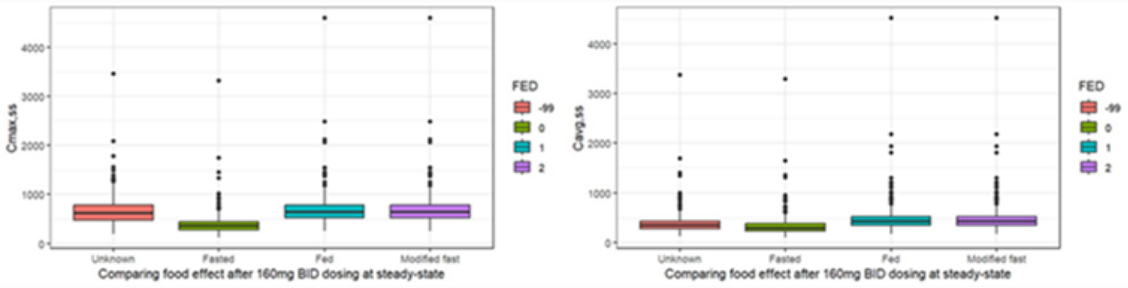


Source: FDA Analysis

Figure 11. Comparing Simulated Exposures Between Pediatrics and Adults, Different Food Conditions, and Bodyweight Percentiles After the Proposed 160 mg BID Dosing at Steady-State (Reviewer's Analysis).

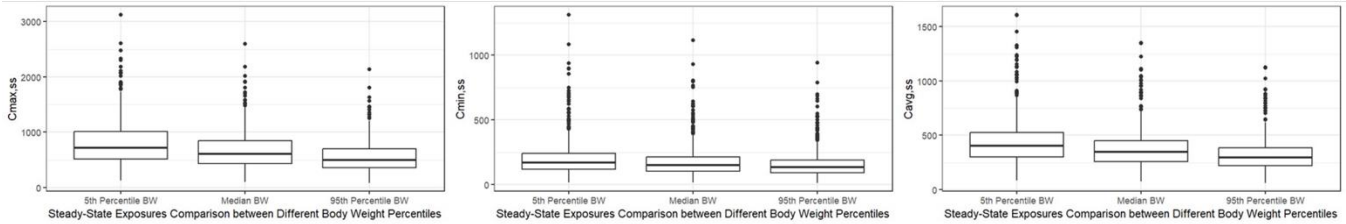


Comparing Food Status after the recommended 160 mg BID Doing at Steady State



Source: FDA Analysis

Comparisons of Simulated Steady-State Exposures Between Different Body Weight Percentiles



Source: FDA Analysis

17.4.3. Exposure-Response Analysis

17.4.3.1. ER (efficacy) Executive Summary

The FDA's Assessment:

Previously, E-R efficacy analyses of repotrectinib in patients with NSCLC harboring ROS1 rearrangements (ROS1 positive) were conducted. In this application, the E-R analysis was conducted to support the efficacy of repotrectinib via E-R models in patients with advanced or metastatic malignancies harboring ALK, ROS1, or NTRK1-3 (NTRK) fusions that are TKI naïve or TKI pretreated. This analysis intended to inform the benefit-risk assessment and support the proposed recommend dosing regimen for the treatment of patients with ROS1-positive NSCLC or NTRK-positive locally advanced or metastatic malignancies. The E-R efficacy relationships were evaluated by using exposure indices, Cavg56 and Cavgc, of repotrectinib and efficacy endpoints, mainly ORR and PFS, were characterized, respectively.

17.4.3.2. ER (efficacy) Assessment Summary

The Applicant's Position:

The results showed exposure (Cavg56 for ORR; Cavgc for PFS) was not statistically significant for probability of OR and PFS for *NTRK*-positive solid tumors. However, there was a trend of longer PFS with increasing exposure. The median probability of PFS increased with dose and the 160 mg QD/BID dosing regimen showed higher median probability of PFS than 160 mg QD. There was no meaningful increase in efficacy at doses higher than 160 mg QD/BID (i.e., 200 mg). The predicted efficacy at 120 mg QD/BID and 80 mg QD/BID support the recommended dose reductions to 120 mg or 80 mg for management of adverse events. The model-predicted probabilities of OR or PFS are similar among different food conditions.

General Information		
Goal of ER analysis		1. To characterize the relationship between repotrectinib exposure and OR or PFS in patients with *NTRK*-positive solid tumors
Study Included		2 pooled patient populations in the TRIDENT-1 study: • TKI-naïve *NTRK*-positive solid tumors (Pooled EXP-5, N = 40, 35 of 40 from Phase 2 at RP2D) • TKI-pretreated *NTRK*-positive solid tumors (Pooled EXP-6, N = 48, 44 of 48 from Phase 2 at RP2D)
Endpoint		Primary: ORR Secondary: PFS
No. of Patients (total, and with individual PK)		40 TKI-naïve patients and 48 TKI-pretreated patients
Population Characteristics	General	Age median (range): 60 (20, 84) years Weight median (range): 70.1 (42.0, 116) kg Sex, n (%): 41 (46.6) males, 47 (53.4) females Race, n (%): White: 41 (46.6), Black/African American: 3 (3.4), Asian: 33 (37.5), Other: 1 (1.1), Missing/Unknown: 10 (11.4)
	Pediatrics (if any)	No.
Dose(s) Included		40 mg to 240 mg

Exposure Metrics Explored (range)	Cavg56 (average concentration over the first 56 days) for OR Cavgc (time varying cumulative half-daily Cavg from Day 1 to the event or sensor) for PFS	
Covariates Evaluated	Age, baseline body weight, sex, race, baseline performance status (ECOG), baseline tumor size, TKI-pretreatment (TKI-pretreated vs TKI-naïve), genetic mutation (*NTRK3* vs *NTRK1* or *NTRK2*), tumor type (Others vs NSCLC)	
Final Model Parameters	**Summary**	**Acceptability** Yes, in general FDA agrees that the selected E-R model parameters are acceptable. Although, there was a trend of longer PFS with increasing exposure, FDA agrees that no significant relationship between exposure and response in terms of efficacy was established.
Model Structure	**ORR:** The relationship between repotrectinib exposure (Cavg56) and probability of achieving OR was described by a logistic regression model and included assessments of the modulatory effect of covariates on the E-R relationship. **PFS:** The relationship between repotrectinib time varying exposure (Cavgc) and PFS was described by a semi-parametric Cox Proportional Hazard (CPH) model and included assessments of the potential modulatory effect of covariates on the E-R relationship.	Yes, FDA generally agrees with the E-R efficacy model structures used in the analysis. The relationship between exposure and success rates in objective response rate (ORR) and progress free survival (PFS) are generally described by a logistic regression model and Cox Proportional Hazard (CPH) model, respectively.
Model Parameter Estimates	**ORR:** Applicant - Table 50, **PFS:** Applicant - Table 51: Applicant	Yes, FDA reproduced the model parameter estimates and the parameter estimates generally agree with the Applicant's estimates.
Model Evaluation	Model performance was assessed by VPC. The model-predicted OR or PFS is generally consistent with the observed OR or PFS across patients with different TKI-pretreatment status and genetic mutations.	Yes, generally FDA agrees with the model evaluations through the VPC that model predictions are generally consistent with the observed OR and PFS.
Covariates and Clinical Relevance	**ORR:** The probability of OR was significantly higher in patients with *NTRK3* than those with *NTRK1-2*.	Yes, FDA agrees with the assessment that patients with NTRK3 genetic mutations had significantly higher success in

	PFS: The risk of disease progression or death was significantly lower in patients with smaller baseline tumor size, TKI-naïve patients (relative to TKI-pretreated), and *NTRK3* (relative to *NTRK1-2*).	terms of ORR. While the TKI-pretreated patients showed higher risk of disease progression.
Simulation for Specific Population	Food effect was evaluated based on simulated PK exposures under fasted, modified fasted, and fed conditions.	Yes, FDA agrees with the statement that the effect of unknown food status was evaluated on efficacy endpoints (ORR and PFS) based on simulated exposures metrics that were derived from various dosing regimens. In general, efficacy was greater with the proposed dosing regimen (Figure 15).
Visualization of E-R relationships	**ORR:** ***Error! Reference source not found.*** (Exposure-OR), **PFS:** Figure (Exposure-PFS), **Error! Reference source not found.** (Dose-PFS) Note: The E-R visualization for OR and PFS were presented in different formats as exposure measure for OR is static (Cavg56) while the exposure measure for PFS (Cavgc) is time varying.	FDA generally accepts the presented E-R relationships visualizations. Applicant - Figure 9 is a forest plot of the full model visually showing the relationship between all tested covariates (including the exposure metric, Cavg56) and ORR, with the model parameter estimates. Applicant - Figure 13 represents KM-plot of the exposure metric (Cavgc) percentiles plotted against PFS stratified by subgroups. Applicant - Figure 14 shows KM-plots of different dosing regimen strata as exposure metrics plotted against PFS stratified by subgroups of patient population.
Overall Clinical Relevance for ER	The results showed exposure (Cavg56 for ORR; Cavgc for PFS) was not significant for probability of OR and PFS for *NTRK*-positive solid tumors. However, there was a trend of longer PFS with increasing exposure. The median probability of PFS increased with dose and the 160 mg QD/BID dosing regimen showed higher median probability of PFS than 160 mg QD. The model-predicted probabilities of OR or PFS are similar among different food conditions	Yes, in general, FDA corroborates with the overall results of the E-R efficacy analysis. Exposure measures (Cavg56 and Cavgc) did not significantly predict the efficacy outcomes (ORR and PFS), respectively. However, though insignificant, a tendency towards PFS was noted with increasing exposure. Also, the probability of PFS increased with increased dosing. Neither ORR nor PFS was impacted by food status.

Labeling Language	Description	Acceptability No E-R efficacy results were included in the labeling.
12.2 Pharmacodynamics	No E-R efficacy or safety results are provided in Section 12.2 of the USPI.	Yes, FDA agrees that no E-R efficacy results were included in 12.2 Section of USPI.

Table 50: Applicant Parameter Estimates of the Exposure-Response of OR for NTRK-Positive Solid Tumors (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Odds Ratio (95% CI)[c]
Repo Log Cavg56 [ng/mL]	0.2871	0.4737	165	1.333 (0.5266, 3.372)
Age [yr]	-0.03726	0.0197	52.86	0.9634 (0.9269, 1.001)
Body Weight [kg]	0.01421	0.01964	138.2	1.014 (0.976, 1.054)
Baseline Tumor Size (cm)	-0.07697	0.04836	62.83	0.9259 (0.8422, 1.018)
Sex [Female: Male]	0.3882	0.5972	153.8	1.474 (0.4574, 4.753)
Race [Asian:Caucasian/Others]	0.7497	0.6621	88.32	2.116 (0.5781, 7.748)
Performance Status [1:0]	-0.1154	0.5662	490.6	0.891 (0.2937, 2.703)
TKI pretreatment [TKI-pretreated: TKI-naïve]	-1.054	0.6384	60.58	0.3486 (0.09976, 1.218)
Genetic Mutation (*NTRK3*: *NTRK1-2*)	2.259	0.6189	27.39	9.575 (2.847, 32.2)
Tumor Type (Others:NSCLC)	-0.3631	0.6001	165.3	0.6955 (0.2145, 2.255)

a Continuous predictors are indicated by [unit], and categorical predictors by [comparator:reference].
b RSE: Relative Standard Error = (100 SE/|Estimate|).*
c Increase in odds ratio for every unit increase in continuous predictor variables [for repotrectinib exposure, the odds ratio is for every unit increase in Log(Cavg56)]; for categorical variables, it represents the odds ratio of the comparator group to reference group.
Source: E-R Report Table 5.1.2.1-1.

Table 51: Applicant Parameter Estimates of the Exposure-Response of PFS for NTRK-Positive Solid Tumors (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio (95% CI)[c]
Repo Log Cavgc [ng/mL]	-0.4988	0.3829	76.76	0.6073 (0.2867, 1.286)
Age [yr]	0.01592	0.01126	70.72	1.016 (0.9939, 1.039)
Body Weight [kg]	-0.001836	0.01077	586.7	0.9982 (0.9773, 1.019)
Baseline Tumor Size (cm)	0.05532	0.02353	42.53	1.057 (1.009, 1.107)
Sex [Female: Male]	-0.02179	0.3367	1545	0.9784 (0.5058, 1.893)
Race [Asian: Caucasian/Others]	-0.1071	0.3953	369.2	0.8984 (0.414, 1.95)
Performance Status [1:0]	0.1702	0.309	181.5	1.186 (0.647, 2.172)

Predictor[a]	**Estimate**	**Standard Error**	**RSE%**[b]	**Hazard Ratio (95% CI)**[c]
TKI pretreatment [TKI-pretreated: TKI-naïve]	1.232	0.4189	34.01	3.427 (1.508, 7.788)
Genetic Mutation [*NTRK3*: *NTRK1-2*]	-1.167	0.3491	29.91	0.3112 (0.157, 0.6169)
Tumor Type [Others:NSCLC]	0.1612	0.3693	229.1	1.175 (0.5697, 2.423)

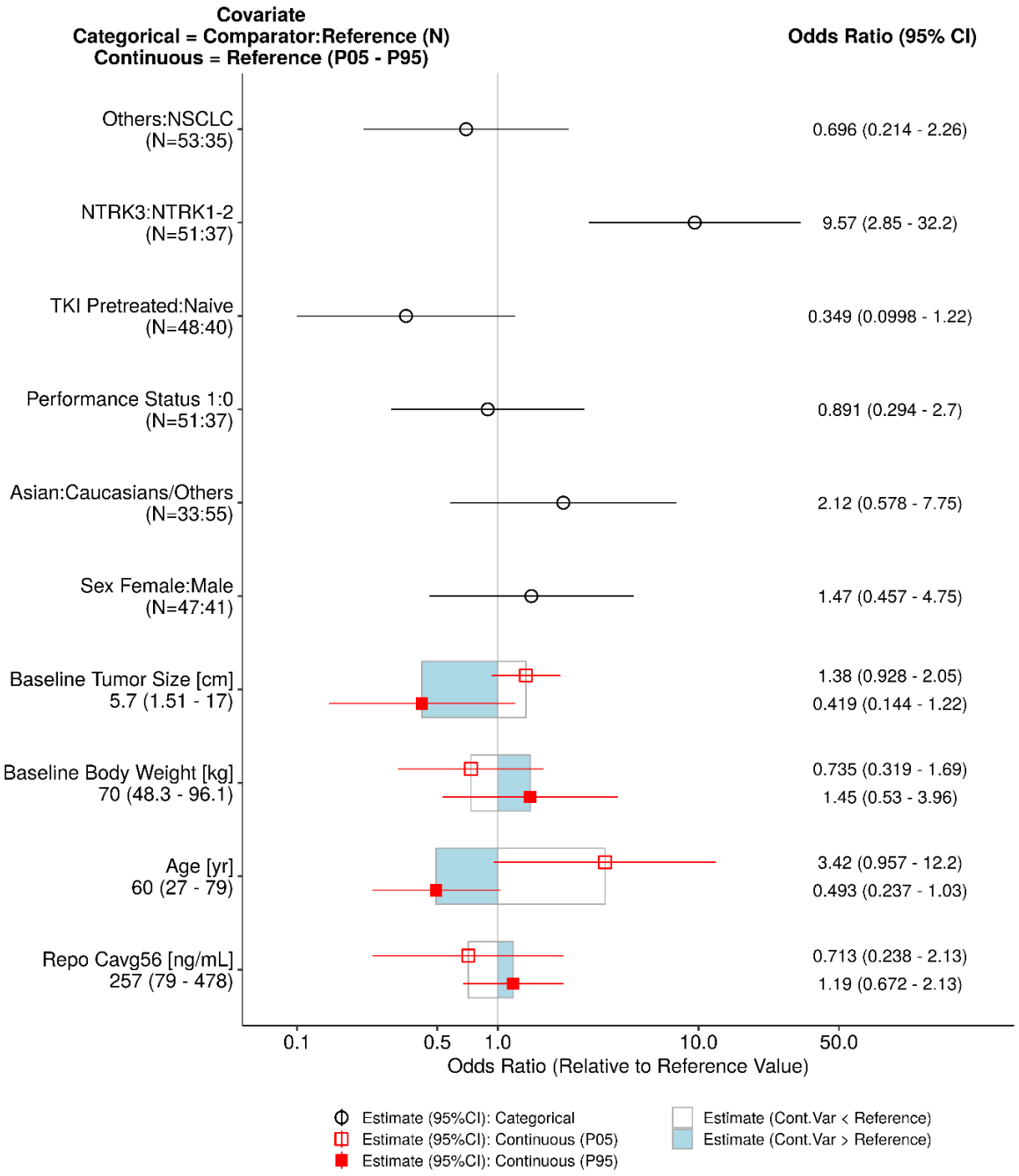
a Continuous predictors are indicated by [unit], and categorical predictors by [comparator:reference].

b RSE: Relative Standard Error = (100 SE/|Estimate|).*

c Increase in hazard ratio for every unit increase in continuous predictor variables [for repotrectinib exposure, the odds ratio is for every unit increase in Log(Cavg56)]; for categorical variables, it represents the hazard ratio of the comparator group to reference group.

Source: E-R Report Table 5.2.2.1-1.

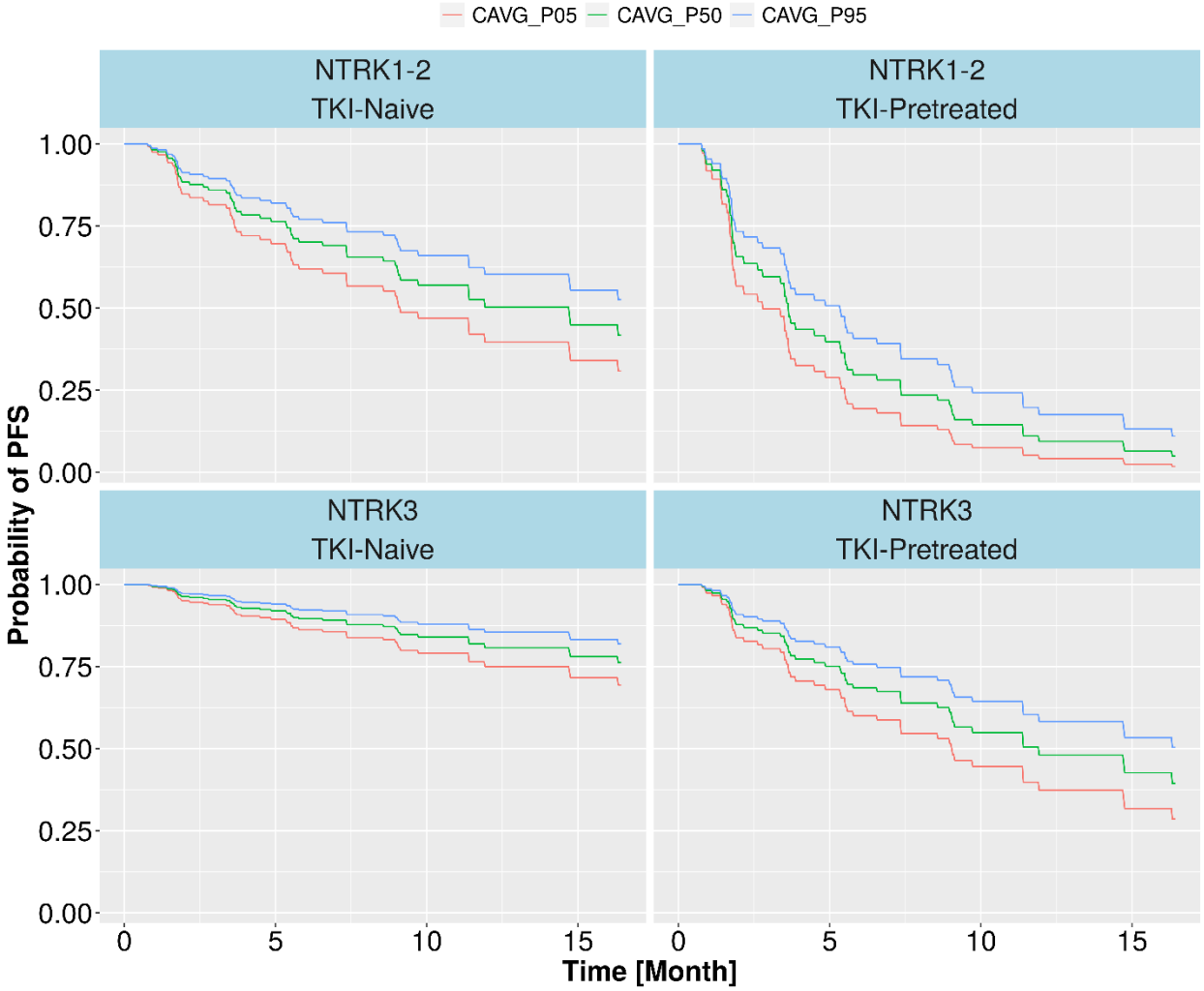
Figure 12: Applicant Estimated Covariate Effects of the Exposure-Response of OR for NTRK-Positive Solid Tumors (Full Model)



Note: Continuous covariate effects (95% CI) at the 5th/95th percentiles of the covariate are represented by horizontal width of boxes (horizontal lines). Open/shaded width of boxes represents the range of covariate effects from the reference to the 5th/95th percentile of the covariate. Reference subject: Subject with median value of Cavg56, age, body weight, baseline tumor size, male, Caucasian/others, PS = 0, TKI-naïve, NTRK1-2 and NSCLC.

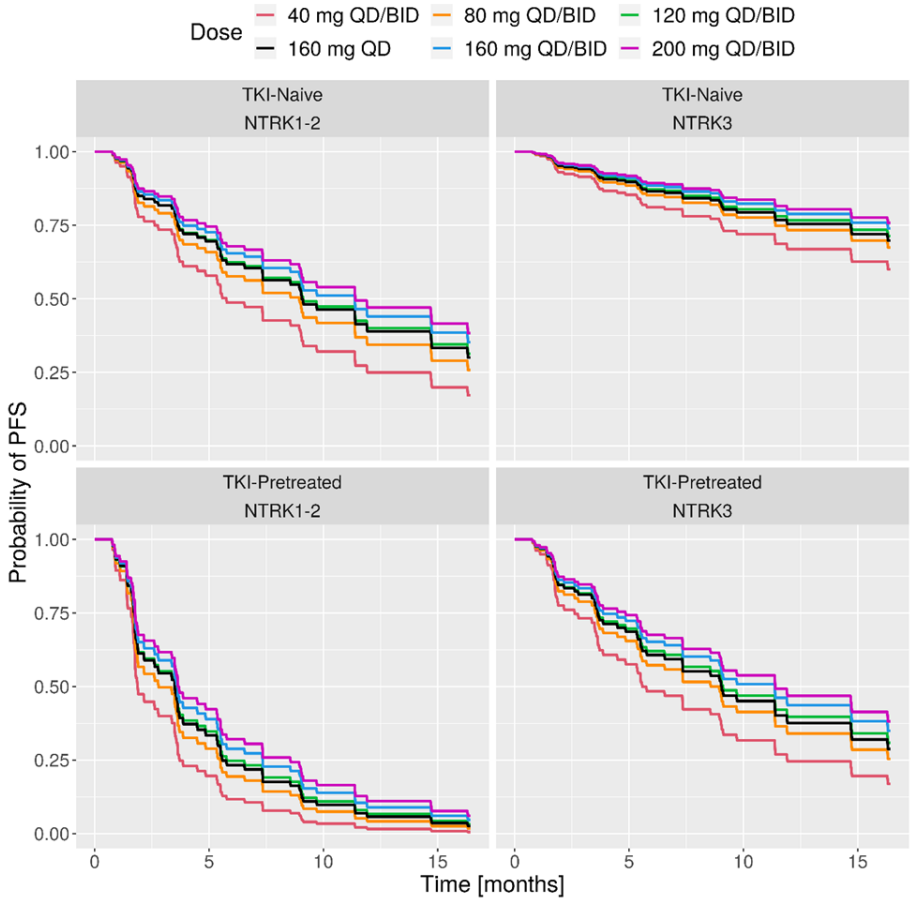
Source: E-R Report Figure 5.1.2.1-2.

Figure 13: Applicant Estimated Effect of Repotrectinib Exposure on the Predicted Probability of PFS in a Typical Subject with NTRK-Positive Solid Tumors (Full Model, 160 mg QD/BID)



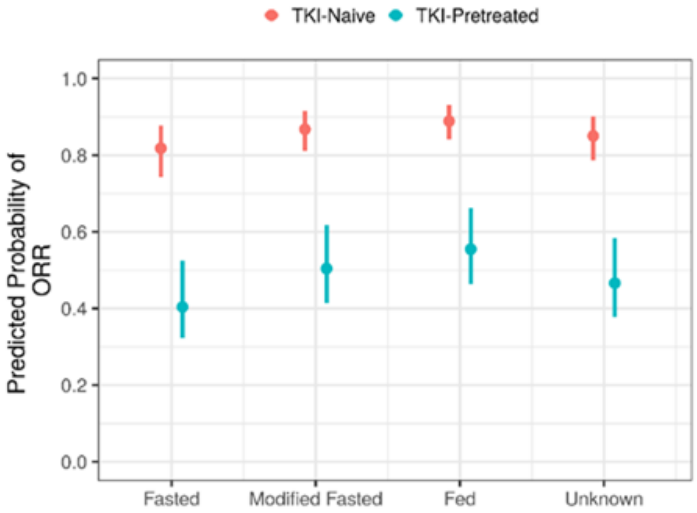
Note: Probability of PFS for a typical subject was obtained by simulating at exposure quantiles of P05, P50, and P95. Typical subject: Subject with median value of Cavgc, age, body weight, baseline tumor size, male, Caucasian/others, PS = 0, TKI-naïve, NTRK1-2, and NSCLC. The repotrectinib Cavgc were simulated based on 502 adult subjects from TRIDENT-1 using individual EBE-based PK parameters from the PPK model of repotrectinib.
Source: E-R Report Figure 5.2.2.1-3

Figure 14: Applicant Predicted Median Probability of PFS for NTRK-Positive Solid Tumors by Dosing Regimens, TKI-Pretreatment, and Genetic Mutation



Source: E-R Report Figure 5.2.2.4-1

Figure 15: Applicant Predicted Probability (90% PI) of OR for ROS1-Positive NSCLC by Food Status at 160 mg QD/BID



*Source: E-R Report Figure **5.1.1.4-2:***

17.4.3.3. ER (safety) Executive Summary

The FDA's Assessment:

Previously, E-R safety analyses of repotrectinib in patients with NSCLC harboring ROS1 rearrangements (ROS1 positive) were conducted. In this application, the E-R analysis was conducted to assess the safety of repotrectinib via E-R models in patients with advanced or metastatic malignancies harboring ALK, ROS1, or NTRK1-3 (NTRK) fusions that are TKI naive or TKI pretreated. The E-R safety relationships were evaluated by using C_{avgc} of repotrectinib as the exposure index and time to first occurrence of ≥ Grade 2 (Gr2+) dizziness, Grade ≥2 anemia, ≥ Grade 3 TEAEs, and Grade ≥2 neurological adverse event ([NEAEs] including dyspnea, dysgeusia, paresthesia, and ataxia) time to first occurrence of dose reduction or interruption due to AEs (DRDI) as safety endpoints.

17.4.3.4. ER (safety) Assessment Summary

The Applicant's Position:

E-R analyses for safety showed patients with higher repotrectinib exposure (Cavgc) had significantly higher risk of Gr2+ dizziness and dose reduction or interruption (DRDI) due to AEs. The predicted median probabilities of Gr2+ dizziness, Gr2+ neurological AEs (NEAEs, including dyspnea, dysgeusia, paresthesia, and ataxia), and DRDI were higher at higher dose levels, but 160 mg QD and 160 mg QD/BID had comparable probabilities with overlapping 90% prediction

intervals. The predicted probability of AEs at 160 mg QD/BID dosing regimen are comparable among different food status with relatively small numeric differences.

General Information			
Goal of ER analysis		2. Characterize the relationship between repotrectinib exposure and time to first occurrence of Gr2+ dizziness, Gr2+ anemia, Gr3+ treatment emergent AEs (TEAEs), Gr2+ NEAEs (including dyspnea, dysgeusia, paresthesia, and ataxia), and DRDI in subjects with advanced solid tumors harboring *ALK*, *ROS1*, or *NTRK1-3* rearrangements.	
Study Included		TRIDENT-1 study	
Population Included		All enrolled subjects with advanced solid tumors harboring *ALK*, *ROS1*, or *NTRK1-3* alterations who received at least 1 dose of repotrectinib in the TRIDENT-1 study.	
Endpoint		Gr2+ dizziness, Gr2+ anemia, Gr3+ TEAEs, Gr2+ NEAEs (including dyspnea, dysgeusia, paresthesia, and ataxia), and DRDI	
No. of Patients (total, and with individual PK)		502 patients	
Population Characteristics	General	Age median (range): 56.0 (18, 93) years Weight median (range): 69.0 (39.5, 169) Sex, n (%): 215 (42.8) males, 287 (57.2) females Race, n (%): White: 217 (43.2), Black/African American: 15 (3.0), Asian: 236 (47.0), Other: 7 (1.4), Unknown: 27 (5.4)	
	Organ impairment	Not specifically evaluated.	
	Pediatrics (if any)	*No*	
	Geriatrics (if any)	Age [56.0 (18, 93) years] evaluated as a covariate.	
Dose(s) Included		40 mg to 240 mg	
Exposure Metrics Explored (range)		Cavgc (time varying cumulative half-daily Cavg from Day 1 to the event or sensor)	
Covariates Evaluated		Age, baseline body weight, sex, race (Asian, Others vs Caucasian), baseline performance status (ECOG, 0 vs 1), TKI-pretreatment (TKI-naïve vs TKI-pretreated), genetic mutation (*ALK* vs *NTRK* vs *ROS1*), tumor type (NSCLC vs Others)	
Final Model Parameters		**Summary**	Acceptability FDA generally agrees with the applicant's conclusion. The E-R safety model was used to show that higher exposure metric (Cavgc) was predicted to marginally produce higher risk of GR2+ dizziness, Gr2+ NEAEs (including dyspnea, dysgeusia, paresthesia, and ataxia). Also, while higher DRDI were shown to occur at higher doses, the proposed 160 mg QD/BID dosing regimens predicted to show

		comparable and overlapping prediction bounds.
Model Structure	The relationship between repotrectinib time varying exposure (Cavgc) and safety endpoints was described by a semi-parametric Cox Proportional Hazard (CPH) model and included assessments of the potential modulatory effect of covariates on the E-R relationship	Yes, FDA agrees that the utilized Cox Proportional Hazard (CPH) model adequately described the relationship between a time-varying predictor variable such as Cavgc (the exposure metrics) and a time-to-event outcome variables such as all the assessed safety endpoints.
Model Parameter Estimates	Only the parameter estimate table for Gr2+ dizziness is shown in this document (Applicant - Table 52: Applicant). See all the other parameter estimates in the E-R report.	Yes, FDA agrees to the list of model parameter estimates included here in the Applicant – Table 52 and those in the appended E-R report.
Model Evaluation	VPCs of the cumulative probability of the first occurrence of safety events show that the model predicted cumulative probabilities were generally in good agreement with the model predictions.	Yes, FDA agrees with the assessment that Kaplan-Meier (KM) VPCs plots with 90% CI of safety events occurrence were generally in agreement with model predictions.
Covariates and Clinical Relevance	**Gr2+ Dizziness:** Older age was associated with higher risk of Gr2+ dizziness. **Gr2+ Anemia:** Fully active subjects (PS = 0) had 48% lower risk of Gr2+ anemia than the restricted subjects (PS = 1), lower body weight was associated with higher risk of Gr2+ anemia. **Gr3+ TEAEs:** Fully active subjects (PS = 0) had 43% lower at risk of Gr3+ TEAEs than restricted subjects (PS = 1), Asian had 33% lower risk of Gr3+ TEAEs compared to Caucasian, male subjects had 34% higher risk than female subjects. **Gr2+ NEAEs**: Older age and higher body weight were associated with increased risk of Gr2+ NEAEs. **DRDI:** Older age and higher body weight were associated with increased risk of DRDI. NTRK-positive subjects had 63% higher	Yes, FDA agrees with the assessments that older age was associated with Gr2+ Dizziness. While fully active subjects showed lower risk of Gr2+ anemia compared to restricted subjects, lower body weight on the other hand predicted higher risk of Gr2+ anemia. Again, fully active subjects had a lower risk of Gr+3 TEAEs, Asian showed lower risk of Gr3+ TEAEs compared to caucuses. Male subjects had higher risk to develop Gr2+ TEAEs compared to females. Older age and higher body weights predicted both Gr2+ NEAEs and DRDI, whereas NTRK-positive subjects had higher risk of DRDI than ROS1-positive subjects.

	risk of DRDI than ROS1-positive subjects.	
Simulation for Specific Population	Food effect was evaluated based on simulated PK exposures under fasted, modified fasted, and fed conditions.	Yes, FDA agrees with the assessment that food effect was evaluated in the full CPH E-R safety analysis. Additionally, predicted exposure quartiles of 160mg QD/BID and predicted medians for other dosing regimens were evaluated.
Visualization of E-R relationships	Figure 16: Applicant , Only the visualization for Gr2+ dizziness is shown in this document. See all the other E-R visualization in the E-R report.	Yes, FDA agrees that the presented E-R safety visualizations have been utilized. Show casing here in this document, Figure 16 is KM-plot used to visually display the application of the E-R safety relationship developed for predicting the relationship between predicted exposure quartiles after 160 mg QD/BID doing regimen in a typical subject to predict cumulative Gr2+ dizziness as a response (safety) outcome.
Overall Clinical Relevance for ER	E-R analyses for safety showed subjects with higher repotrectinib exposure (Cavgc) had significantly higher risk of Gr2+ dizziness and DRDI due to AEs. The predicted median probabilities of Gr2+ dizziness, Gr2+ NEAEs (including dyspnea, dysgeusia, paresthesia, and ataxia), and DRDI were higher at higher dose level, but 160 mg QD and 160 mg QD/BID had comparable probabilities with overlapping 90% prediction intervals. The predicted probability of AEs at 160 mg QD/BID dose regimen are comparable among different food status with relatively small numeric differences.	Yes, in general, FDA agrees with the overall assessment of the E-R safety relationships. The E-R safety model was used to show that higher exposure metric (Cavgc) was predicted to marginally produce higher risk of GR2+ dizziness, Gr2+ NEAEs (including dyspnea, dysgeusia, paresthesia, and ataxia). Also, while higher DRDI were shown to occur at higher doses, the proposed 160 mg QD/BID dosing regimens predicted to show comparable and overlapping prediction bounds. AE predictions were not different between different food conditions.
Labeling Language	**Description**	**Acceptability** No E-R safety results were included in the labeling.

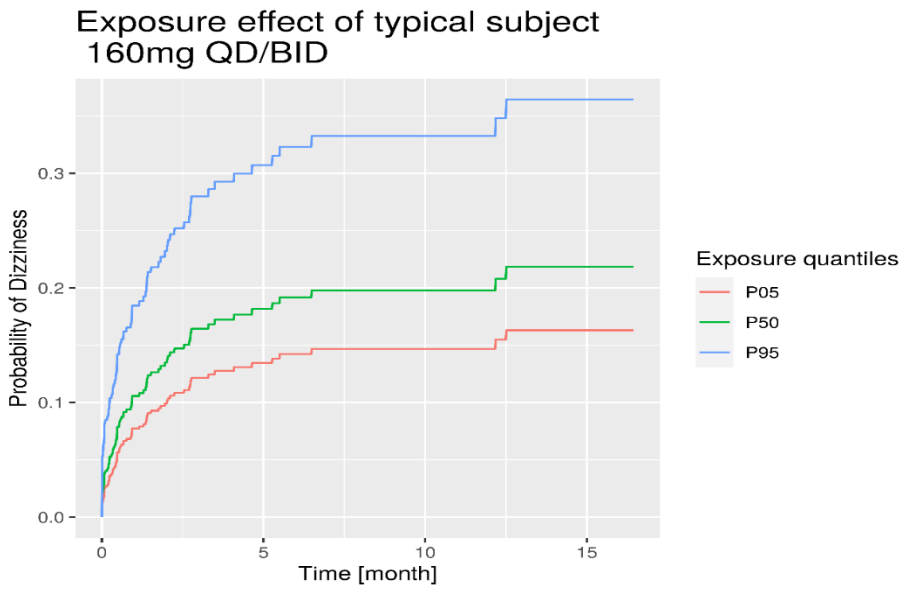
12.2 Pharmacodynamics	No E-R efficacy or safety results are provided in Section 12.2 of the USPI.	Yes, FDA agrees that no E-R safety results were included in 12.2 Section of the USPI.

Table 52: Applicant Parameter Estimates of the Exposure-Response of Gr2+ Dizziness (Full Model)

Predictor[a]	Estimate	Standard Error	RSE%[b]	Hazard Ratio Coefficient[c] (95% CI)
Repo cumulative half- daily Cavg [ng/mL]	0.002152	0.000499	23.17	1.002 (1.001, 1.003)
Age [yr]	0.05004	0.01002	20.02	1.051 (1.031, 1.072)
Body Weight [kg]	-0.00305	0.008907	292.3	0.997 (0.9797, 1.015)
Sex [Male:Female]	-0.08083	0.2505	309.9	0.9223 (0.5645, 1.507)
Race [Asian:White]	-0.3705	0.2925	78.95	0.6904 (0.3891, 1.225)
Race [Others:White]	0.09189	0.367	399.3	1.096 (0.534, 2.25)
Performance Status [0:1]	-0.4272	0.2658	62.22	0.6523 (0.3874, 1.098)
TKI-pretreatment [TKI-Naïve:TKI pretreated]	0.2136	0.2451	114.7	1.238 (0.7658, 2.002)
Genetic mutation [*NTRK:ROS1*]	0.2511	0.3635	144.7	1.285 (0.6305, 2.621)
Genetic mutation [*ALK:ROS1*]	0.3809	0.6098	160.1	1.464 (0.443, 4.836)
Tumor type [Others:NSCLC]	0.3859	0.4107	106.4	1.471 (0.6577, 3.29)

a Continuous predictors are indicated by [unit], and categorical predictors by [comparator:reference].
b RSE: Relative Standard Error = (100 SE/|Estimate|).*
c Increase in hazard for every unit increase in continuous predictor variables; for categorical variables, it represents the hazard ratio of the comparator group to reference group.
Source: E-R Report Table 5.3.1.1-1

Figure 16: Applicant Predicted Cumulative Probabilities (90% PI) of Gr2+ Dizziness for Repotrectinib at 160 mg QD/BID



Note: Probability of typical subjects was obtained by simulating three typical subjects at exposure quantiles of P05, P50, and P95, where all the covariates of the typical subject were assigned to the reference value (PS = 1, AGE = 56y, BW = 69 kg, SEX = Female, RACE = Caucasian, TKI-pretreatment = TKI-pretreated, Genetic mutation = ROS1, Tumor type = NSCLC)
Source: E-R Report Figure 5.3.1.3-1

The FDA's Assessment:

FDA generally agrees with the applicant's conclusion. The E-R safety model was used to show that higher exposure metric (Cavgc) was predicted to marginally produce higher risk of Gr2+ dizziness, Gr2+ NEAEs (including dyspnea, dysgeusia, paresthesia, and ataxia). Also, while higher dose reduction or dose interruption (DRDI) were shown to occur at higher doses, the proposed 160 mg QD/BID dosing regimen predicted to show comparable and overlapping prediction bounds.

17.4.3.5. ER Review Issues

Upon the review of E-R (Efficacy and Safety) analyses, the following two issues were identified.

Key efficacy issue:

1. According to the Applicant's analysis, the probability of ORR was higher in patients with NTRK3 than those with NTRK1 or NTRK2. The key issue identified was: did subjects with NTRK3 have greater exposure than those with NTRK1 or NTRK2? Please refer Section 17.4.3.6.

Key safety issue:

- It was identified that dosage modification strategy was implemented to accommodate AEs arising from the proposed recommended dosage. FDA requested that the Applicant summarize all the evidence to support that the proposed dose reduction strategy would not compromise efficacy in the target patient population.

17.4.3.6. Reviewer's Independent Analysis

Strategy to answer key E-R Efficacy issue:

FDA compared exposure (Cavg56), the metric used in the E-R efficacy analysis, between pooled data of patients with either NTRK1or NTRK2 and NTRK3. The analysis showed that no exposure difference was observed between the subgroups (Figure 17), even though subjects with NTRK3 had higher ORR success rates than the other two subgroups. This finding correlated with the overall notion that exposure may not seem to drive the efficacy response (

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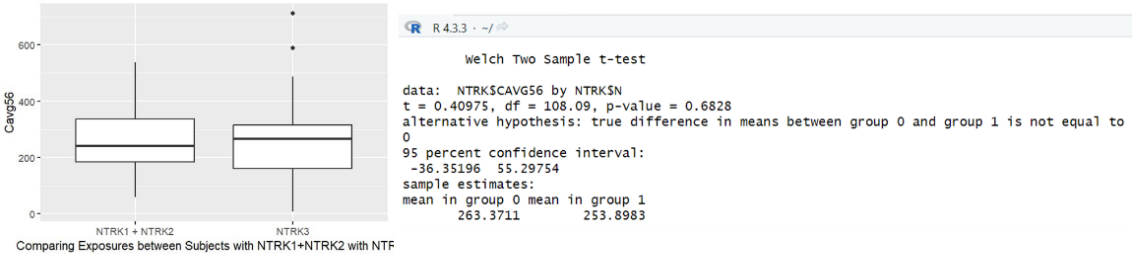
- Figure 17). However, at this time, given limited patient numbers, it cannot be assessed whether NTRK3 is more sensitive to NTRK inhibition (or whether certain NTRK1 or 2 fusions might be resistant).

Figure 17. Comparing Exposures Between Subjects with NTRK1+NTRK2 and NTRK3 (Reviewer's Analysis).



Source: FDA Analysis

For the other identified key E-R safety issue, the applicant's responded the following:

- "Based on the E-R efficacy (ORR) analysis for NTRK-positive solid tumors, clinically meaningful efficacy is still maintained at reduced dose levels of 120 mg QD/BID and 80 mg QD/BID. For TKI-naïve subjects, the predicted ORR at 80 mg QD/BID and 120 mg QD/BID was 58.8% and 60.9%, respectively. For TKI-treated subjects, the predicted ORR at 80 mg QD/BID and 120 mg QD/BID was 48.8% and 51.0%, respectively (Refer to 2.7.2 SCP Appendix 3.6.1.1-1). So, despite the predicted ORRs being numerically lower than those at the recommend 160 mg QD/BID dose, the ORRs remain clinically relevant for

this serious condition and may allow the patient to continue on treatment beyond toxicity as needed."

- FDA in general accepted the response to the request for the issue identified so no further independent analysis was required.

17.4.3.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

At the recommended dose of 160 mg QD/BID, the E-R safety and efficacy analyses demonstrated an optimized benefit-risk profile for subjects with *NTRK*-positive solid tumors and supports the proposed dose reductions of 120 mg QD/BID and 80 mg QD/BID to manage safety events with a predicted efficacy benefit. Subjects were predicted to have better efficacy (i.e., PFS) and incremental higher risk of AEs (i.e., Gr2+ dizziness, Gr2+ NEAEs, and DRDI) with increasing dose. As compared with 160 mg QD, the dose regimen of 160 mg QD/BID was predicted to show improved efficacy but with only a small increase in AEs (e.g., Gr2+ dizziness 15% vs 13%). There was no meaningful increase in efficacy at dose higher than 160 mg QD/BID (i.e., 200 mg QD/BID) while the increase in AEs was incremental.

The FDA's Assessment:

FDA generally agrees with the applicant's position. Based on the E-R safety and efficacy analyses, the recommended dosage of 160mg QD/BID is appropriate for patients with NTRK-positive solid tumors given the benefit-risk profile. Also, the proposed dose reductions strategies of 120mg QD/BID and 80 mg QD/BID to manage adverse reactions, are acceptable. Improved marginal efficacy in terms of PFS along with marginally higher degree of risk to ARs such as Gr2+ dizziness, Gr2+ NEAEs, and DRDI. While the benefit-risk assessment favors 160 mg BID compared to 160 mg QD dosing regimen, further dose increase greater than 160 mg BID is not predicted to offer better benefit-risk profile.

17.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

None

Signatures NDA 218213 S-001

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTION(S) AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Team Leader	Matthew Thompson, PhD, MPH	OOD/DHOT	Sections: 5	**Select one:** ☒ Authored ☒ Approved
	Signature:			
Clinical Pharmacology Reviewers	Justin Collazo, Pharm.D., M.S.	OCP/DCPI	Section: 6, 19.4	**Select one:** ☒ Authored ☐ Approved
	Signature:			
	Abiy Eyakem, PhD	OCP/DPM	Section: 19.4	**Select one:** ☒ Authored ☐ Approved
	Signature:			
Clinical Pharmacology Team Leaders	Jason Moore, PharmD	OCP/DCPII	Section: 6, 19.4	**Select one:** ☒ Authored ☒ Approved
	Signature:			
	Youwei Bi, PhD	OCP/DPM	Section: 6, 19.4	**Select one:** ☐ Authored ☒ Approved
	Signature:			
Genomics Reviewer/Team Leader	Sarah Dorff, PhD	OCP/DTPM	Section: 6	**Select one:** ☒ Authored ☒ Approved
	Signature:			
Clinical Pharmacology Deputy Division Director	Stacy Shord, PharmD	OCP/DCPII	Section: 6, 19.4	**Select one:** ☐ Authored ☒ Approved
	Signature:			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTION(S) AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Caitlin Tydings, MD	OOD/DO3	Section: 2, 3 4, 7-13, 19.1, 19.2	**Select one:** ☒ Authored ☐ Approved
	Signature:			
Clinical Team Leader	Leslie Doros, MD	OOD/DO3	Section: 1, 2, 3 4, 7-13, 19.1, 19.2	**Select one:** ☐ Authored ☒ Approved
	Signature:			
Statistical Reviewer	Yiming Zhang, PhD	OB/DBV	Section: 8.1, 8.3	**Select one:** ☒ Authored ☐ Approved
	Signature:			
Statistical Team Leader	Chi (Chuck) Song, PhD	OB/DBV	Section: 8.1, 8.3	**Select one:** ☒ Authored ☒ Approved
	Signature:			
Deputy Division Director (OB)	Mishra-Kalyani Pallavi, PhD	OB/DBV	Section: 8.1, 8.3	**Select one:** ☐ Authored ☒ Approved
	Signature:			
Associate Director for Labeling (ADL)	Doris Auth, PharmD	OCE	Section: 11	**Select one:** ☒ Authored ☒ Approved
	Signature:			
Cross-Disciplinary Team Leader (CDTL)	Leslie Doros, MD	OOD/DO3	Section: All	**Select one:** ☐ Authored ☒ Approved
	Signature: Signature will be added to final Assessment Aid			
Division Director (Clinical)	Steven Lemery, MD, MHS	OOD/DO3	Section: All	**Select one:** ☐ Authored ☒ Approved
	Signature: Signature will be added to final Assessment Aid			

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/s/

LESLIE A DOROS
06/13/2024 10:34:43 AM

STEVEN J LEMERY
06/13/2024 10:38:59 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s001

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-218213-SUPPL-001
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	12/15/2023	12/15/2023	12/22/2023	06/15/2024	04/22/2024

3. **Provides For:**
   The information submitted in this supplemental NDA is intended to support the following new indication:
   Augtyro is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

4. **Review #**: 01

5. **Clinical Review Division**: DO2

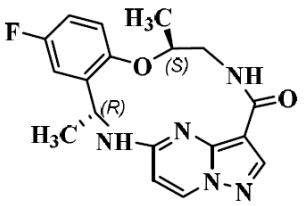
6. **Name and Address of Applicant**:
   Bristol Myers Squibb Company
   P.O. Box 4000
   Princeton, NJ, USA 08543

   Contact: Lise Alessio
   Phone: (b) (6)
   Email: lise.alessio@bms.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product	Orphan Designation
Augtyro™ (repotrectinib)	Capsules	40 mg	Oral	Rx	Yes	17-5735

8. Chemical Name and Structure of Drug Substance:

	USAN: repotrectinib Chemical name: (3R,6S)-45-Fluoro-3,6-dimethyl-5-oxa-2,8-diaza-1(5,3)-pyrazolo[1,5-a]pyrimidina-4(1,2)-benzenanonaphan-9-one Molecular formula: $C_{18}H_{18}FN_5O_2$ MW: 355.37 g/mol

9. Indication:

- Augtyro is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

10. Supporting/Relating Documents: None

11. Consults: None

12. Executive Summary:

This submission is intended to support the following new indication:
Augtyro is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

The applicant has claimed categorical exclusion from the determination of an environmental assessment under 21 CFR Part 25.31 (b). The total US annual peak sales volume of repotrectinib will be less than (b) (4), considering both the currently approved indications of therapeutic regimens and the indication in the supplement. Assuming that a daily discharge of water to sewage treatment facilities in the United States is about 1.26×10^{11} liters (US EPA 2016), a maximum expected introduction concentration of repotrectinib at the point of entry to the environment (EIC) will be less than (b) (4) µg/L. Since the EIC is below 1 part per billion (1 µg/L), a categorical exclusion is deemed appropriate by 21 CFR 25.31 (b). To the applicant's knowledge, no extraordinary circumstances exist in accordance with 21 CFR sections 25.15(a) and 21. Therefore, the request for categorical exclusion may be granted.

The supplement provides updated PI. There are no proposed CMC related changes to sections 2, 3, 11 and 16.

The changes proposed in S001 are acceptable from a CMC standpoint.

13. Conclusions & Recommendations: This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Qi Liu, Ph.D., CMC reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Rohit Kolhatkar, Ph.D., SPQA, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

Qi Charles Liu

Digitally signed by Qi Charles Liu
Date: 5/02/2024 09:55:13AM
GUID: 53b4299e000120abe375af2240eda3f5

Rohit Kolhatkar

Digitally signed by Rohit Kolhatkar
Date: 5/02/2024 11:30:20AM
GUID: 57bf531500b52a2eccd5395bec77ebc2
Comments: Concur with the recommendation to approve from CMC standpoint

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s001

OTHER REVIEW(S)

Review Memorandum

U.S. FOOD & DRUG ADMINISTRATION

Date:	June 6, 2024
To:	Caitlin Tydings, MD, CDER/OND/OOD/DOIII Autumn Zack-Taylor, RPM, CDER/OND/ORO/DROOD
From:	Erdem Coskun, Ph.D., CDRH/OHT7/DMGP/MPCB
Through:	Soma Ghosh, Ph.D., Branch Chief, CDRH/OHT7/DMGP/MPCB Donna Roscoe, Ph.D., Acting Division Director, CDRH/OIR/OHT7/DMGP Reena Philip, Ph.D., Associate Director of Biomarkers and Precision Oncology, OCE
ICC Number:	ICC2300822
ICCR Number:	ICCR# 00968571
Subject:	CDER consult request for NDA 218213
Drug:	Augtyro (repotrectinib)
Study Sponsor:	Bristol Myers Squibb Company (BMS)
Analytes Detected	NTRK gene fusion
Device	FoundationOne®CDx (F1CDx)
Device sponsor	Foundation Medicine
Related submissions	ICCR# 00943253
Protocol:	NDA filing is based on the clinical study results from the pivotal study TPX-0005-01 (TRIDENT-1), a Phase 1/2, open-label, multicenter study conducted in patients with locally advanced or metastatic solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements, supported by the preliminary results from the pediatric study TPX-0005-07 (CARE), a Phase 1/2, open-label, safety, tolerability, pharmacokinetics, and antitumor activity study of repotrectinib in pediatric and young adult subjects with advanced or metastatic malignancies harboring ALK, ROS1, or NTRK1-3 alterations (this ICCR is for NTRK1/2/3-positive in solid tumors)

Erdem Coskun -S
Digitally signed by Erdem Coskun -S
Date: 2024.06.07 13:55:18 -04'00'

I. PURPOSE

The sponsor submitted this supplemental NDA to support the following proposed indication:

Augtyro is a kinase inhibitor indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

CDER is asking for CDRH feedback for the language to be used for the PMC to fulfill the requested PMA.

II. DEVICE USE IN THE TRIAL

The information/history below is taken from BMS's (Turning Point Therapeutics, Inc.) IND 157539 application which is useful to understand the device related issues in this NDA:

The sponsor was initially in partnership with Almac Diagnostic Services (henceforth referred to as Almac) to develop a qualitative NGS based CDx. For Phase 2 of the TRIDENT-1 study, a prototype CDx was developed, validated, and used as a CTA in Almac's CLIA/CAP accredited laboratory. The repotrectinib CTA is currently being used to determine molecular eligibility prior to enrollment onto the TRIDENT-1 Phase 2 study by prospectively confirming a patient's *NTRK1-3* gene fusion status if FISH was used as the local test. In this case, patients reported positive by the repotrectinib CTA for the respective *NTRK1-3* gene fusion will be eligible for enrollment onto the TRIDENT-1 Phase 2 clinical trial provided they meet all other eligibility criteria. For patients locally tested with NGS or qPCR local test results, the repotrectinib CTA is used to retrospectively to confirm the *NTRK1-3* gene fusion status after enrollment.

(b) (4)

(b) (4). Based on the low likelihood of successful delivery, as well as commercial accessibility of the test, the sponsor determined that the Almac assay (device name: (b) (4)) was no longer the best testing option for patients.

The sponsor recognized the need for an alternative testing option as an opportunity to harmonize with the FDA approved CDx assay for NTRK which has an established global footprint to support patient access. With this aim, the sponsor has contracted with Foundation Medicine, Inc. (FMI) for the development and validation of a CDx assay for the identification of patients that are candidates for treatment with repotrectinib. The Foundation Medicine assay, FoundationOne®CDx (F1CDx) is a qualitative NGS based in vitro diagnostic test that uses DNA isolated from FFPE specimens. The test is currently intended as a CDx to identify patients who may benefit from treatment with the targeted therapies in accordance with the approved therapeutic product labeling. Most importantly to this development effort, the F1CDx assay was approved by FDA on 23 Oct 2020 (P170019/S017) and 07 Jun 2022 (P170019/S014) to identify patients with a *NTRK1-3*-positive solid tumor as a CDx for VITRAKVI®(larotrectinib) and Rozlytrek®(entrectinib), respectively. These patient populations align to the target *NTRK1-3*-positive solid tumor population in the TRIDENT-1 study.

(b) (4)

(b) (4)

With these changes to the CDx development, the delivery of the CDx is now delayed with respect to the drug. However, sponsor is pointing out the precedents where FDA permitted PMA submissions as a post-marketing commitment (PMC). Specifically, Rozlytrek®(entrectinib) received full drug approval for *ROS1*-positive NSCLC with a PMC for the F1CDx on 15 Aug 2019 and VITRAKVI®(larotrectinib) also received approval under accelerated drug approval provisions for *NTRK*-positive pan-tumor indication on 28 Nov 2018 with a PMC for the F1CDx as a CDx. In the Type B meeting preliminary comments received on 16 Feb 2023 (Reference ID: 5128022), FDA acknowledged the Sponsor's rationale for requesting an sPMA filing for a *ROS1* CDx as a PMC and stated that it may be acceptable for repotrectinib, but the final determination will be a review issue.

III. CDRH COMMENTS FOR CDER'S CONSIDERATION

As mentioned above (under Section III), BMS is currently partnering with the device sponsor, Foundation Medicine, Inc. (FMI), for a companion diagnostic (CDx) indication for identifying patients with solid tumors harboring *NTRK1*, *NTRK2* and *NTRK3* gene fusions who may benefit from treatment with AUGTYRO™ (Repotrectinib, or TPX-0005).

FMI's test, FoundationOne CDx (F1CDx), was previously approved for *NTRK1*, *NTRK2* and *NTRK3* fusions in solid tumor patients for entrectinib and larotrectinib therapies (please see the screenshot below taken from https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools).

Diagnostic Name (Manufacturer)	Indication - Sample Type	Drug Trade Name (Generic) NDA / BLA	Biomarker(s)	Biomarker(s) (Details)	PMA / 510(k) / 513(f)(2) / HDE (Approval / Clearance / Grant Date)
FoundationOne CDx (Foundation Medicine, Inc.)	Solid Tumors - Tissue	Rozlytrek (entrectinib) NDA 212725	NTRK1, NTRK2 and NTRK3	NTRK1, NTRK2 and NTRK3 fusions	P170019/S014 (06/07/2022)
FoundationOne CDx (Foundation Medicine, Inc.)	Solid Tumors - Tissue	Vitrakvi (larotrectinib) NDA 210861	*NTRK1*, *NTRK2* and *NTRK3*	*NTRK1*, *NTRK2* and *NTRK3* fusions	P170019/S017 (10/23/2020)

We previously provided CDRH feedback for IND 157539, where we acknowledged FMI's proposal (b) (4)

(b) (4)

(b) (4)

(b) (4)

Therefore, the CDx PMA will likely be filed as a post marketing commitment. Please see the proposed language for the PMC below.

The language to be used for the PMC (asking the sponsor for an sPMA)

CDRH proposes the language below for a post marketing commitment to be communicated with the drug sponsor for a CDx PMA:

Submit the final report of an appropriate clinical validation study using clinical trial data to establish and support the labeling and availability of an in vitro diagnostic device that is essential to support the safe and effective use of Augtyro (repotrectinib), for patients with solid tumors that carry NTRK1/2/3 gene fusions. The results of the validation study may inform product labeling.

This consult review is limited to the information provided in NDA 218213. If there are any questions regarding this review, please contact Erdem Coskun by phone at (301) 796-3513 or by email at Erdem.Coskun@fda.hhs.gov.

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/s/

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Consult review is being uploaded to DARRTS on behalf of Erdem Coskun, Ph.D., CDRH/OHT7/DMGP/MPCB

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:	May 15, 2024
To:	Autumn Zack-Taylor, MS Regulatory Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Helen Young, MSN, MPH, CRRN, PHN, RN 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):	AUGTYRO (repotrectinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 218213
Supplement Number:	S-001
Applicant:	Bristol Myers Squibb Company

1 INTRODUCTION

On December 15, 2023, Bristol Myers Squibb Company submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 218213 S-001 for AUGTYRO (repotrectinib) capsules. With this submission, the Applicant proposes an additional indication for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.

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 III (DO3) on December 21, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for AUGTYRO (repotrectinib) capsules.

2 MATERIAL REVIEWED

- Draft AUGTYRO (repotrectinib) capsules PPI received on December 15, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on May 7, 2024.
- Draft AUGTYRO (repotrectinib) capsules Prescribing Information (PI) received on December 15, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on May 7, 2024.
- Approved AUGTYRO (repotrectinib) capsules labeling dated November 15, 2023.
- Approved ROZLYTREK (entrectinib) capsules comparator labeling dated January 26, 2024.

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 APHont 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 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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/s/

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KELLE E CARUSO
05/15/2024 02:22:21 PM

LAURIE J BUONACCORSI
05/16/2024 07:01:45 AM

LASHAWN M GRIFFITHS
05/16/2024 08:37:35 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: May 16, 2024

To: Autumn Zack-Taylor, Regulatory Project Manager
Division of Oncology 3 (DO3)

Doris Auth, Associate Director for Labeling, DO3

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

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for AUGTYRO™ (repotrectinib) capsules, for oral use

NDA: 218213, S-001

Background:
In response to DO3's consult request dated December 21, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for supplement 001 for AUGTYRO™ (repotrectinib) capsules, for oral use. This supplement supports the indication for treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 7, 2024, 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 on May 16, 2024.

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

PI:

Section	Statement from Draft (if applicable)	OPDP Comments
HIGHLIGHTS OF PRESCRIBING INFORMATION **and** **1.2 *NTRK* Gene Fusion-Positive Solid Tumors**	(b) (4) (underlined emphasis added.)	We note that according to Section 14.2, the major efficacy outcome measures in evaluating the efficacy of Augtyro were overall response rate and duration of response. We recommend updating Section 1.2 and the Highlights to be consistent with Section 14.2.
8.4 Pediatric Use	"The safety and effectiveness of AUGTYRO in pediatric patients with ROS1-positive NSCLC have not been established. The safety and effectiveness of AUGTYRO have not been established in pediatric patients younger than 12 years of age with solid tumors who have an NTRK gene fusion."	OPDP agrees with having this information up front so as not to suggest/imply unapproved indications, which we recommended during the labeling meeting on April 29, 2024.
14.2 Locally Advanced or Metastatic NTRK Gene Fusion-Positive Solid Tumors	"The efficacy of AUGTYRO was evaluated in TRIDENT-1 (NCT03093116), a multi-center, single-arm, open-label, multi-cohort clinical trial in 88 adult patients with locally advanced or metastatic *NTRK* gene fusion-positive (*NTRK1, NTRK2, NTRK3*) solid tumors who had either received a prior TKI treatment or were TKI-naïve, (b) (4) (underlined emphasis added.)	OPDP notes that Section 14.2 of the USPI for Rozlytrek in NTRK Gene Fusion-Positive Solid Tumors includes "measurable disease per RECIST v1.1" and "at least 2 years of follow-up from first post-treatment tumor assessment" to describe the efficacy population. We also note that a similar description is included in Section 14.1 of this label. It is helpful from our perspective to have this information in the labeling, as it is often translated into promotion when describing the study design. Would DO3 consider (b) (4) ? We defer to DO3.

	"Among the 88 patients, 5 had measurable CNS metastases at baseline as assessed by BICR. Responses were seen in 2 (100%) TKI-naïve patients and 3 (100%) TKI-pretreated patients. (b) (4) [redacted]	We note that many of the NSCLC drugs include subgroup data in patients with CNS metastases, as this may be of particular clinical relevance for lung cancer patients. Does this data have the same clinical relevance in this solid tumor group and therefore is important to keep in the label? Also, was this a pre-specified exploratory analysis? If so, OPDP recommends adding "In a pre-specified exploratory analysis" to this statement to help characterize this data and, in promotional materials, help the audience more clearly understand any potential limitations of the analysis. We defer to DO3 on whether this is accurate/appropriate. We also agree with FDA's comment to provide the "number of responders who received prior radiotherapy" and "when they received radiotherapy in regards to timing of anti-tumor responses", as this information seems necessary for interpretation of these data.

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/s/

KELLE E CARUSO
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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:	May 7, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 218213/ S-001 & S-002
Product Name, Dosage Form, and Strength:	Augtyro (repotrectinib) Capsule, 40 mg, 160 mg (proposed)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Bristol Myers Squibb Company
FDA Received Date:	December 15, 2023 (Supplement 1) and February 21, 2024 (Supplement 2)
TTT ID #:	2023-7571 and 2024-8421
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 INTRODUCTION

Bristol Myers Squibb Company submitted the following supplements for Augtyro (repotrectinib) Capsules:

Supplement 1 - an Efficacy Supplement to seek approval for the use of Augtyro for the following proposed indication:

> *For the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.*

Supplement 2 - a Chemistry Manufacturing and Controls (CMC) - Prior Approval Supplement (PAS) to seek approval of a proposed 160 mg strength capsule in addition to the currently approved 40 mg strength capsule. The addition of a higher strength capsule is intended to reduce the pill burden for patients.

Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Augtyro Prescribing Information (PI), Patient Information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 218213/ S-001 & S-002.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Augtyro Prescribing Information (PI) and Patient Information and determined that they are acceptable from a medication error perspective.

However, the proposed Augtyro container labels and carton labeling for the proposed 160 mg strength may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Bristol Myers Squibb Company in Section 4.

4 RECOMMENDATIONS FOR BRISTOL MYERS SQUIBB COMPANY

Supplement 2-

A. General Comments (Container Labels & Carton Labeling)

1. The 160 mg (b) (4) is not clearly differentiated due to the dark green color (b) (4) which overlaps with the dark green font color used for the proprietary name. For products with multiple strengths, a lack of differentiation may contribute to wrong strength errors. Color differentiation is most effective when the color used has no association with a particular feature. We recommend revising the color scheme of the 160 mg such that the (b) (4) appears in its own unique color that does not overlap with the dark green color used for the proprietary name for all strengths.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Augtyro[a] received on February 21, 2024 from Bristol Myers Squibb Company.

Table 2. Relevant Product Information for Augtyro	
Initial Approval Date	November 15, 2023
Active Ingredient	repotrectinib
Indication	For the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) *(Proposed) For the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity.*
Route of Administration	Oral
Dosage Form	Capsule
Strength	40 mg, 160 mg (proposed)
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	40 mg capsules: • 60-count bottles • 120-count bottles 160 mg capsules (proposed): • 14-count bottles • 60-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	High density polyethylene (HDPE) bottles with (b) (4) closures. Both closures have an aluminum-foil induction seal (inner seal).

APPENDIX B. LABELS AND LABELING

[a] Augtyro [Prescribing Information] DailyMed. U.S. National Library of Medicine. Nov 2023. [Cited 2024 MAY 02]. Available from: https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=fb526827-40ba-4462-94cf-179ae3b0cb8a&type=pdf.

B.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 Augtyro labels and labeling submitted by Bristol Myers Squibb Company.

Supplement 1

- Prescribing Information with Patient Information received on December 15, 2023, available from \\CDSESUB1\EVSPROD\nda218213\0058\m1\us\pas-ntrk-repo-ann.docx

Supplement 2

- Prescribing Information with Patient Information received on February 21, 2024, available from \\CDSESUB1\EVSPROD\nda218213\0066\m1\us\add-160mg-repo-pro.docx

- Container label(s) received on February 21, 2024, May 1, 2024
- Carton labeling received on February 21, 2024, May 1, 2024

B.2 Container Label(s) and Carton Labeling Images

Container label(s)

40 mg; 60-count and 120-count

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On April 25, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, repotrectinib and Augtyro. Our search identified 3 previous reviews[c,d,e] and we considered our previous recommendations to see if they are applicable for this current review.

[c] Stewart, J. Label and Labeling Review for Augtyro (NDA 218213). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 NOV 13. TTT ID No.: 2023-4198-2.

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

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

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/s/

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