CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218213Orig1s000

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	New Drug Application
Application Number(s)	218213
Priority or Standard	Standard
Submit Date(s)	03/27/2023
Received Date(s)	03/27/2023
PDUFA Goal Date	11/27/2023
Division/Office	DO2/OND
Review Completion Date	See electronic stamp date
Established Name	Repotrectinib
(Proposed) Trade Name	Augtyro
Pharmacologic Class	kinase inhibitor
Code name	Repotrectinib (BMS-986472, TPX-0005)
Applicant	Bristol Myers Squibb Company
Formulation(s)	Repotrectinib Hard gelatin capsules: 40 mg
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)	The treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)
Recommendation on Regulatory Action	Traditional approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)

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OPQ=Office of Pharmaceutical Quality
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
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AGP	human alpha-1-acid glycoprotein
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
BCRP	breast cancer resistance protein
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
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
ClinRO	Clinician reported outcome
CMC	chemistry, manufacturing and controls
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
CR	complete response
CrCl	creatinine clearance
CREST	immunofluorescent antikinetochore
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
DMF	drug master files
DOR	duration of response
DRISK	Division of Risk Management
ECG	electrocardiogram
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
ESMO	European Society for Medical Oncology
EXP	expansion cohort
FaSSIF	fasted state simulating intestinal fluid;
FDA	Food and Drug Administration
FeSSIF	fed state simulating intestinal fluid;
FISH	fluorescence in situ hybridization
GCP	good clinical practice
GHS	global health status
GI	gastrointestinal
GLP	good laboratory practice
GMR	geometric mean ratio

HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
hPXR	human pregnane X receptor
HSA	human serum albumin
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICH S9	ICH Nonclinical Evaluation for Anticancer Pharmaceuticals
ICI	immune checkpoint inhibitor
IO	immune-oncology
IC-ORR	intracranial objective response rate
IC-PFS	intracranial progression-free survival
CT	computed tomography
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
IRR	independent radiology review
ITT	intent to treat
IV	intravenous
KRAS	Kirsten rat sarcoma virus
2L	second line *(setting)*
LCK	lymphocyte kinase
LC-MS/MS	liquid chromatography with tandem mass spectrometry
mDOR	mean duration of response
mOS	mean overall survival
mPSF	mean progression-free survival
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
MET	MET proto-oncogene, receptor tyrosine kinase
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NA	not applicable
NCI	National Cancer Institute
NDA	New Drug Application
NE	not estimable
NGS	next-generation sequencing

NDA	new drug application
NME	new molecular entity
NR	not reached
NSCLC	non-small cell lung cancer
NTRK	neurotrophin receptor kinase
OAT	organic anion transporter
ObsRO	observer reported outcome
OCT	organic cation transporter
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
P-gp	P-glycoprotein
PK	pharmacokinetic
PMA	premarket approval
PMC	postmarketing commitment
PND	postnatal
PMR	postmarketing requirement
PPK	population pharmacokinetics
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
PXR	pregnane X receptor
Q	quadrant
QD	once daily
QOL	quality of life
qPCR	quantitative polymerase chain reaction
QTcF	QT interval corrected for heart rate using Fridericia formula
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
RT-PCR	reverse-transcription polymerase chain reaction

SAE	serious adverse event
SAP	statistical analysis plan
SCID	severe combined immunodeficiency
SD	stable disease
SDC4	syndecan 4 gene
SFM	solvent front mutations
SLD	sum of longest diameter
SOC	system organ class
$t_{1/2}$	elimination half-life
TDD	time to definitive deterioration
TEAE	treatment emergent adverse event
TGI	tumor growth inhibition
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
UGT	UDP-glucuronosyltransferase
Vd_{ss}	volume of distribution
UK	United Kingdom
ULN	upper limit normal
US	United States
UVR	ultraviolet radiation
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 is an inhibitor of wild-type proto-oncogene tyrosine-protein kinase *ROS1 (ROS1)*. There are currently no FDA approved indications for repotrectinib.

The Applicant's proposed indication is for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). The recommended dosage regimen is repotrectinib 160 mg orally once daily for 14 days, then increased to 160 mg twice daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted by the Applicant provides substantial evidence of effectiveness to support the traditional approval of repotrectinib for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC.

The recommendation for traditional approval is based on the results from TRIDENT-1, an international, single-arm, first-in-human, dose escalation and expansion study of repotrectinib in patients with advanced solid tumors with ALK, ROS1, or NTRK1-2 rearrangements. The statutory requirement for demonstration of substantial evidence of effectiveness is met based on the efficacy results from a single adequate and well-controlled trial (TRIDENT-1) with confirmatory evidence consisting of evidence of effectiveness of other drugs (i.e., entrectinib and crizotinib) in the same pharmacologic class for the same indication. An indication that includes patients who are ROS1 TKI naïve and who have received one prior ROS1 TKI is warranted based on the evidence of effectiveness demonstrated in both populations. Additionally, responses were observed in subsets of patients with CNS metastasis and in patients with ROS1 resistance mutations.

The primary evidence of effectiveness for this application is derived from pooled data from patients enrolled in two cohorts ("EXP-1" and "EXP-4") in the TRIDENT-1 study. Patients with ROS1-positive NSCLC from the Phase 1 and Phase 2 portions of TRIDENT-1 who received a prior ROS1 TKI and no prior chemotherapy or were ROS1 TKI-naïve with or without prior platinum-based chemotherapy, received at least one dose of repotrectinib on or before October 15, 2021, and were followed for at least 8 months from the time of enrollment were included in the primary efficacy populations. Patients received repotrectinib as a single agent administered daily at the recommended phase 2 dose (RP2D) or, for some patients, the dose administered in Phase 1. The primary objective was to determine the confirmed objective response rate (ORR) as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; ORR is defined as the proportion of patients with a

confirmed complete response (CR) or partial response (PR). Secondary endpoints included duration of response (DOR), time to response (TTR), and clinical benefit rate (CBR) of repotrectinib, as assessed by BICR, as well as progression-free survival (PFS), overall survival (OS) and intracranial objective response rate (IC-ORR) and Central Nervous System PFS (CNS-PFS) per the modified RECIST v1.1 assessment.

Among the 71 ROS1 TKI-naïve patients, the ORR was 79% (95% CI 68, 88). The median duration of response was 34.1 months (95% CI 26, NE); 70% of responders had a DOR ≥ 12 months. Among the 71 ROS1 inhibitor-naïve patients, 8 had measurable CNS metastases at baseline as assessed by BICR. Responses in measurable intracranial lesions were observed in 7 of 8 patients.

Among the 56 patients who had received 1 prior ROS1 TKI, the ORR was 38% (95% CI 25, 52). The median duration of response was 14.8 months (95% CI 7.6, NE); 48% of responders had a DOR ≥ 12 months. Among the 56 patients who had received 1 prior ROS1 inhibitor with no prior platinum-based chemotherapy, 12 had measurable CNS metastases at baseline as assessed by BICR. Responses in measurable intracranial lesions were observed in 5 of these 12 patients. Eight patients who had received 1 prior ROS1 TKI had resistance mutations following TKI therapy. Responses were observed in 6 of these 8 patients; responders included patients with solvent front (G2032R), gatekeeper (L2026M), and other mutations (S1986F/Y).

Confirmatory evidence necessary to support an approval based on a single adequate and well-controlled trial derives from data from other products in the same class which are approved in the same indication as well as strong mechanistic evidence of ROS1 alterations being molecular drivers of NSCLC. Both entrectinib and crizotinib were approved for the treatment of adult patients with metastatic NSCLC whose tumors are ROS1-positive based on robust and durable tumor response rates and repotrectinib has a similar mechanism of action as these approved therapies. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with repotrectinib is sufficient to establish clinical benefit in the genetically defined (ROS1-positive), rare subgroup of patients with advanced or metastatic ROS1-positive NSCLC.

The submitted evidence meets the statutory evidentiary standard for traditional approval. Treatment with repotrectinib demonstrated a clinically meaningful and durable ORR among adult patients with locally advanced or metastatic ROS1-positive NSCLC who were ROS1 TKI-naïve and ROS1 TKI-pretreated. Subgroup analyses also indicated activity in CNS metastases and in patients with resistance mutations following prior ROS1 TKI therapy. Therefore, the review team recommends traditional approval of repotrectinib for the treatment of patients with locally advanced or metastatic ROS1-positive NSCLC.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

There are more than 235,000 new cases of lung cancer annually in the United States, and lung cancer is the leading cause of cancer-related death accounting for approximately 136,000 deaths per year. Nearly 85% of lung cancer cases are non-small cell lung cancer (NSCLC). ROS1 rearrangement occurs in 1 to 2% of NSCLC and ROS1 fusions have been identified as an actionable target (Rikova 2007). The clinicopathologic characteristics of patients with ROS1 positive NSCLC include median age at diagnosis of 50 years, higher incidence in patients of Asian race, and greater incidence in never-smokers compared to patients with NSCLC without ROS1 fusions. Overall survival (OS) for patients with NSCLC at 5-years has been reported as 22% (SEER Zappa 2016); patients with ROS1-positive NSCLC have similar outcomes. ROS1-targeted therapy is recommended for the treatment of ROS1-positive NSCLC; approved therapies include crizotinib and entrectinib, which were both approved based on ORR and DOR results in single-arm trials. Notably, mechanisms for resistance to TKI therapy exist in patients with ROS1 positive NSCLC. Gainor et al identified resistance mutations (G2032R [41%], D2033N [6%], and S1986F [6%]) in 53% of repeat biopsies from patients with ROS1-positive NSCLC who progressed on crizotinib (Gainor 2017). Data provided to support the approvals of crizotinib and entrectinib did not include patients previously treated with a ROS1-targeted therapy.

Repotrectinib is an inhibitor of wild-type proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and mutants $ROS1^{G2032R}$ and TPM3-ROS1. There are currently no FDA approved indications for repotrectinib.

Support for this application is based on safety and efficacy data from the TRIDENT-1 study, an open-label, multi-center, first-in-human study of repotrectinib in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements. The primary evidence of effectiveness comes from pooled cohorts EXP-1 and EXP-4 in the TRIDENT-1 study. Patients with ROS1-positive NSCLC from the Phase 1 and Phase 2 portions of TRIDENT-1 who had either received a prior ROS1 TKI and no prior chemotherapy or were ROS1 TKI-naïve with or without prior platinum-based chemotherapy, received at least one dose of repotrectinib on or before October 15, 2021, were followed for at least 8 months after enrollment were included in the primary efficacy populations. Patients received repotrectinib at the recommended phase 2 dose (RP2D) or for some patients, the dose initially administered in Phase 1. The primary objective was to determine the confirmed objective response rate (ORR) as assessed by blinded independent central review (BICR) using RECIST version 1.1. Secondary endpoints included DOR, TTR, and CBR, as assessed by BICR, as well as PFS, OS and IC-ORR) and CNS-PFS per modified RECIST v1.1.

Among the 71 ROS1 TKI-naïve patients, the ORR was 79% (95% CI 68, 88). The median duration of response was 34.1 months (95% CI 26, NE). Among the 71 ROS1 inhibitor-naïve patients, 8 had measurable CNS metastases at baseline as assessed by BICR. Responses in intracranial lesions were observed in 7 of 8 patients. Among the 56 patients who had received 1 prior ROS1 TKI (crizotinib 82%, entrectinib 16%) with no prior platinum-based chemotherapy or immunotherapy, the ORR was 38% (95% CI 25, 52). The median duration of response was 14.8 months (95% CI 7.6, NE). Among the 56 patients who had received 1 prior ROS1 inhibitor 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. Eight patients who had received 1 prior ROS1 TKI had resistance mutations following TKI therapy. Responses were observed in 6 of these 8 patients; responders included patients with solvent front (G2032R), gatekeeper (L2026M), and other mutations (S1986F/Y).

Repotrectinib appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. The pooled safety population included 351 patients with NSCLC who received at least one dose of repotrectinib at the RP2D. The ROS1 positive NSCLC safety cohort included 264 patients who received repotrectinib at the RP2D.

The warnings and precautions in the product label for repotrectinib include central nervous system effects, interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, myalgia with creatine phosphokinase (CPK) elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity. In the pooled safety population, n=351, serious adverse reactions occurred in 31% of patients who received repotrectinib. The most common (> 20%) adverse reactions were dizziness (64%), dysgeusia (50%), peripheral neuropathy (47%), constipation (37%), dyspnea (30%), ataxia (29%), fatigue (29%), cognitive disorders (23%), and nausea (20%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased gamma glutamyl transferase (13%), decreased lymphocytes (10%), increased urate (10%), decreased neutrophils (8%), decreased hemoglobin (7%), increased creatine phosphokinase (5.8%), decreased phosphate (4.9%), decreased leukocytes (3.8%), increased ALT (3.5%), decreased sodium (3.5%), increased AST (2.9%), increased magnesium (2.9%), increased alkaline phosphatase (2.6%), and increased glucose (2%).

In the ROS1 positive NSCLC safety cohort, n=264, serious adverse reactions occurred in 31% of patients who received repotrectinib. The most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, ataxia, fatigue, cognitive disorders, and muscular weakness. The most common (≥2%) Grade 3 or 4 laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, decreased leukocytes, increased alanine aminotransferase, decreased neutrophils, increased gamma glutamyl transferase, increased alkaline phosphatase, increased urate, increased magnesium, and decreased phosphate.

There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Repotrectinib will be prescribed by oncologists who are familiar with monitoring,

identifying, and managing the toxicities described in the USPI. Five post-marketing requirements (PMRs) and four commitments (PMCs) were included in the approval letter. PMRs were issued to address the requirements of the Pediatric Research Equity Act (PREA), to address the risk of ocular toxicity, to address the potential for drug-drug interactions (DDIs), and to evaluate the safety of the drug in patients with moderate or severe hepatic impairment. PMCs were issued to provide a companion diagnostic device for patient selection, updated DOR results from patients in the efficacy populations included in the product label, the results of a physiologically based pharmacokinetic (PBPK) modeling study, and the results of a clinical pharmacokinetic trial.

The clinical review team determined that it is in the best interest of U.S. patients to approve repotrectinib before a companion diagnostic assay is available. Since an application for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, the approved labeling will state that there is no FDA-approved test for selecting patients for treatment with repotrectinib. A post-marketing commitment (PMC) will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect ROS1 fusions for identifying patients who may benefit from repotrectinib.

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for traditional approval. The magnitude and duration of response rate results coupled with the rarity of ROS1-positive NSCLC renders the conduct of a randomized trial challenging and the response rate and duration itself is considered supportive of a meaningful benefit. Treatment with repotrectinib resulted in a clinically meaningful and durable ORR among adult patients with locally advanced or metastatic ROS1-positive NSCLC who were ROS1 TKI-naïve and ROS1 TKI-pretreated. Subgroup analyses also indicated activity in patients with CNS metastasis and in patients with resistance mutations following prior ROS1 TKI therapy. The review team considers these results to be sufficient to establish clinical benefit in this genetically defined, rare subgroup of patients with ROS1-positive metastatic NSCLC. Based on these results, the potential for clinical benefit outweighs the risks of repotrectinib identified during review of this NDA. The review team's regulatory recommendation is to grant repotrectinib traditional approval for the following indication: "For the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)".

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer exceeds 235,000 new cases annually in the United States, and nearly 85% of lung cancer cases are non-small cell lung cancer (NSCLC). • ROS1 rearrangement occurs in 2% of NSCLC and ROS1 fusions have been identified as an actionable target (Rikova 2007). • The clinicopathologic characteristics of patients with ROS1 positive NSCLC include median age at diagnosis 50 years, Asian race, and never-smokers. • Overall survival (OS) for patients with NSCLC at 5-years has been reported as 22% (SEER Zappa 2016); patients with ROS1-positive NSCLC have similar outcomes. Patients also experience disease and treatment sequelae such as respiratory, central nervous system (CNS), and hepatic complications. • In addition to poor long-term survival, there are resistance mechanisms to TKIs for ROS1 positive NSCLC; ROS1 resistance mutations include G2032R (41%), D2033N (6%), and S1986F (6%) (Gainer 2017).	Locally advanced ROS1 positive NSCLC is a life-threatening condition with poor survival.
Current Treatment Options	• ROS1 TKI therapy is the current standard of care for the treatment of advanced or metastatic ROS1+ NSCLC (Marinelli D 2022). • Entrectinib and crizotinib are approved for adult patients with metastatic ROS1 positive NSCLC. • The response rate included in the product labels for patients with advanced or metastatic ROS1 positive NSCLC is 66% (95% CI 51, 79) for crizotinib and is 74% (95 CI 64, 83) for entrectinib; entrectinib (but not crizotinib) has shown activity against brain metastases in ROS1 NSCLC. These therapies are associated with pulmonary, hepatic, and CNS toxicity. • Currently, there are no approved targeted therapies in patients previously treated with ROS1 TKI.	There is an unmet medical need for adult patients with ROS1 positive NSCLC. There are approved therapies for ROS1 positive NSCLC, but resistance mutations have been identified.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The primary efficacy data supporting this NDA is derived from the TRIDENT-1 Study, an open-label, multi-center, first-in-human study of repotrectinib in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements. • Among the 71 ROS1 TKI-naïve patients, the overall response rate (ORR) was reported at 79% (95% CI 68, 88). The median duration of response was 34.1 months (95% CI 26, NE). In addition, eight patients had measurable CNS metastases at baseline and responses in intracranial lesions were observed in 7. • Among the 56 patients who had received 1 prior ROS1 TKI (crizotinib 82%, entrectinib 16%, and other 2%) with no prior platinum-based chemotherapy or immunotherapy, the ORR was reported at 38% (95% CI 25, 52). The median duration of response was 14.8 months (95% CI 7.6, NE). Twelve patients had measurable CNS metastases at baseline and responses in intracranial lesions were observed in 5. • Eight of fifty-six patients who had received 1 prior ROS1 TKI had resistance mutations following TKI therapy. Responses were observed in 6 of these 8 patients; responders included patients with solvent front (G2032R), gatekeeper (L2026M), and other mutations (S1986F/Y).	The submitted evidence meets the statutory evidentiary standard for traditional approval. The durable ORR provides evidence of a clinically meaningful benefit of repotrectinib in patients with ROS1 positive NSCLC. A post-marketing requirement (PMR) will be issued to obtain a more precise estimation of the BICR-assessed ORR and DOR in the 71 ROS1 TKI-naive patients with ROS1-positive NSCLC and 56 ROS1 TKI-pretreated patients and measurable disease enrolled on TRIDENT-1.
Risk and Risk Management	• The pooled safety population for this NDA includes 351 adult patients advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements who received at least one dose of repotrectinib at the recommended phase 2 dose (RP2D). • Warnings and precautions in the product labeling for repotrectinib include central nervous system effects, interstitial lung disease/pneumonitis, hepatotoxicity, myalgia with creatine phosphokinase elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity.	Although repotrectinib can cause serious adverse reactions, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. There were no significant safety concerns identified during NDA review requiring risk

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In the pooled safety population, serious adverse reactions occurred in 33% of adult patients who received the RP2D of repotrectinib. • The most common (> 20%) adverse reactions were dizziness (64%), dysgeusia (50%), peripheral neuropathy (47%), constipation (37%), dyspnea (30%), ataxia (29%), fatigue (29%), cognitive disorders (23%), and nausea (20%). • The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased gamma glutamyl transferase (13%), decreased lymphocytes (10%), increased urate (10%), decreased neutrophils (8%), decreased hemoglobin (7%), increased creatine phosphokinase (5.8%), decreased phosphate (4.9%), decreased leukocytes (3.8%), increased ALT (3.5%), decreased sodium (3.5%), increased AST (2.9%), increased magnesium (2.9%), increased alkaline phosphatase (2.6%), and increased glucose (2%).	management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). PMRs to address issues related to safety will include a study to assess the risk of ocular toxicity, to address the impact of moderate or severe hepatic impairment, and to assess the risk of DDIs. The clinical review team determined that it is in the best interest of U.S. patients to approve repotrectinib before a companion diagnostic assay is available. Since an application for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, the approved labeling will state that there is no FDA-approved test for selecting patients for treatment with repotrectinib. The Applicant has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect ROS1 fusions for identifying patients who may benefit from repotrectinib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

1.4. Patient Experience Data

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

					Section where discussed, if applicable
X	The patient experience data that was submitted as part of the application, include:				
	x	Clinical outcome assessment (COA) data, such as			Section 8.1.2.14
			x	Patient reported outcome (PRO)	
			□	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)			
	□	Other: (Please specify)			

□	Patient experience data that was not submitted in the application, but was considered in this review.

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Lung cancer remains the global leading cause of cancer-related death, with an estimated 1.8 million deaths in 2020 (GLOBOCAN 2020a). In the US, an estimated 22.6% of all cancer deaths were attributed to lung cancer and 227,875 new cases of lung cancer (116,335 in men and 111,540 in women) were projected for diagnosis in 2020 (GLOBOCAN 2020b).

NSCLC is the most common subtype of lung cancer, representing approximately 84% of lung cancer cases, and is associated with a poor prognosis in the advanced or metastatic setting where the 5-year survival rate is estimated to be 6% to 8% (Howlader 2019; ACS 2022). It is now recognized that a significant proportion of these NSCLC patients present alterations in certain genes that drive oncogenesis, including *KRAS*, *EGFR*, *BRAF*, *MET*, *HER2*, *ALK*, *ROS1*, and *NTRK*, among others (Chevallier 2021). The *ROS1* rearrangement in NSCLC was first discovered in 2007 (Rikova 2007) as a distinct receptor tyrosine kinase, being evolutionarily close to the ALK family and sharing a high homology in the kinase domain (Ou 2012). Approximately 1% to 2% of NSCLC patients are estimated to harbor a *ROS1* chromosomal rearrangement (Jordan 2017; Ou 2019).

Clinically, *ROS1*-positive rearrangement in NSCLC is indicative of more aggressive disease and predictive of poor prognosis, particularly in the advanced or metastatic setting (Bergethon 2012). As with other common driver mutations, patients harboring a *ROS1* rearrangement tend to be younger, more frequently non-smokers, and Asian (Chevallier 2021). Similar to what has been observed in the treatment of patients with *ALK*-positive NSCLC, resistance mutations such as SFMs (eg, G2032R, D2033N) represent common mechanisms of treatment failure to current ROS1 TKIs in advanced *ROS1*-positive NSCLC.

Incidence of CNS metastasis at the time of first diagnosis and the development of CNS metastases during the natural course of disease are important considerations for the treatment of advanced *ROS1*-positive NSCLC. Estimates from clinical trials and retrospective studies approximate that the incidence of CNS metastases at time of diagnosis ranges from 20% to mid-30%, with approximately 30% to 55% of patients expected to develop CNS metastasis during treatment with approved therapy (crizotinib) (Ou 2019).

Commonly used methods for ROS1 fusion detection have included FISH, IHC, RT-PCR, and NGS (NCCN 2022; Planchard 2020). According to ESMO guidelines, IHC may be used as a screening approach, although it is currently not recommended as the primary treatment-determining test. FISH has been the standard approach to detecting *ROS1* rearrangements. NGS is a preferred technology and is rapidly being adopted as the standard approach to screening adenocarcinomas for oncogenic targets.

The FDA's Assessment:

FDA agrees with the Applicant's analysis of *ROS1*-positive non-small cell lung cancer (NSCLC). In addition, ROS1 rearrangement occurs in approximately 1 to 2% of NSCLC and ROS1 has been identified as an actionable target (Rikova 2007). The clinicopathologic characteristics of patients with ROS1 positive NSCLC include median age at diagnosis of 50 years, Asian race, and never-smokers. Overall survival (OS) for patients with NSCLC at 5-years has been reported as 22% (SEER Zappa 2016); patients with ROS1-positive NSCLC have similar outcomes.

2.2. Analysis of Current Treatment Options

Data: ***TKI-naïve ROS1-Positive NSCLC:*** Chemotherapy remained a standard treatment for *ROS1*-positive NSCLC until approval of targeted therapies. Platinum-doublet chemotherapy may typically offer an ORR of approximately 25% to 30%, median PFS of 4 to 6 months, and median OS of approximately 12 months in a previously untreated and unselected NSCLC population (Fossella 2003; Kelly 2001; Scagliotti 2002; Schiller 2002; Alimta USPI 2004). In *ROS1*-positive NSCLC, specific activity of chemotherapy is limited, and nearly all patients will ultimately experience disease progression despite treatment with chemotherapy. The patients on platinum-based chemotherapy are also challenged with higher frequency and severity of toxicities (Oun 2018).

Overall, immunotherapy given with or without chemotherapy is not recommended as initial therapy for patients with *ROS1*-positive NSCLC (NCCN 2022; Planchard 2020). One retrospective study included 7 patients with *ROS1*-rearranged NSCLC. With the exception of one patient, who showed an objective response, best response was progressive disease (Moliner 2021). In another retrospective study (Choudhury 2021), 16 patients had *ROS1*-positive NSCLC and received an ICI. Two patients achieved an objective response for an ORR of 13% (N = 2 of 16; 95% CI: 2, 38). Eleven *ROS1*-positive NSCLC patients were treated with a chemo-ICI combination, 5 of 11 patients achieved an objective response. Hence, unlike other oncogenic-driven NSCLC, there is no clear evidence to support the use of combination immunotherapy and chemotherapy in *ROS1*-rearranged tumors (Moliner 2021).

The treatment of patients with *ROS1*-positive NSCLC has been revolutionized by the discovery of targeted therapies against these mutations (D'Angelo 2020). Crizotinib (Xalkori® USPI 2021) and entrectinib (Rozlytrek® USPI 2021) are currently the only approved targeted therapies for the treatment of advanced *ROS1*-positive NSCLC and are preferred over front-line chemotherapy regimens (NCCN 2022; Planchard 2020). The clear limitations of these two approved agents lie within the limited DOR and PFS, resulting in part due to SFMs which constitute the most common mechanism of emerging resistance, lack of CNS activity with crizotinib, and tolerability profiles (eg, cardiac toxicity). Additionally, neither agent has shown clinical activity in the TKI-pretreated setting, especially against acquired resistant mutations that occur within *ROS1*-positive NSCLC. Therefore, a next generation ROS1 TKI with an improved efficacy and/or tolerability profile resulting in a more favorable benefit-risk profile is urgently needed for this serious disease.

Crizotinib initially demonstrated efficacy in 50 patients with advanced *ROS1*-positive NSCLC with a confirmed ORR by IRR of 66% (N = 50, 95% CI: 51, 79) and median DOR of 18.3 months (95% CI: 12.7, NR) (Xalkori® USPI 2021. At a subsequent data cutoff, the median PFS was reported as 19.3 months (95% CI: 15.2, 39.1) (Shaw 2019a). Patients with advanced *ROS1*-positive NSCLC can develop resistance to crizotinib through on-target resistance mechanisms (Sehgal 2018). SFMs, including G2032R (Awad 2013) and D2033N (Drilon 2016), have been reported in 40% to 50% of crizotinib-resistant tumors observed in patients with advanced *ROS1*-positive NSCLC (Gainor 2017). CNS metastases are also common outcomes of treatment failure, with the incidence of CNS metastasis ranging from mid-30% to 55% among patients who had progressed on crizotinib (Costa 2015; Ou 2019; Patil 2018). The safety profile of crizotinib, based on evaluation of 1,719 patients across clinical trials (*ROS1*- and *ALK*-positive NSCLC patients), includes warnings and precautions for hepatotoxicity, ILD/pneumonitis, QT interval prolongation, bradycardia, severe visual loss, and embryo-fetal toxicity (Xalkori® USPI 2021). Common adverse reactions (≥ 25%) include vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, upper respiratory infection, dizziness, and neuropathy.

Entrectinib was approved in 2019 (Rozlytrek® USPI 2019). Recently updated data demonstrated efficacy in 92 patients with advanced *ROS1*-positive NSCLC, with a confirmed ORR by BICR of 74% (95% CI: 64, 83), and the percent of patients with an observed DOR ≥ 9 months, ≥ 12 months, and ≥ 18 months was 75%, 57%, and 38%, respectively. In addition, for 10 subjects with measurable CNS disease who had not received radiation therapy to the brain within 2 months prior to study entry, responses in intracranial lesions were observed in 7 subjects (Rozlytrek® USPI 2021). The registrational data sets for entrectinib have recently been updated with all patients (new patients included; N = 161) with median duration of follow-up of 15.8 months (Dziadziuszko 2021). In 161 patients, the confirmed ORR was 67% (95% CI: 59, 74) with a median DOR of 15.7 months (95% CI: 13.9, 28.6). Landmark DOR analyses (Kaplan-Meier) showed the probability of patients remaining in response at ≥ 6 months, ≥ 9 months, and ≥ 12 months was 83%, 75%, and 63%, respectively. The median PFS was 15.7 months (95% CI: 11.0, 21.1). Landmark PFS analyses (Kaplan-Meier) showed that the probability of patients without a PFS event at ≥ 6 months, ≥ 9 months, and ≥ 12 months was 77%, 66%, and 55%, respectively. In the 24 patients with measurable CNS metastases at baseline, the IC-ORR was 79.2% (N = 19, 95% CI: 57.9, 92.9). The safety profile of entrectinib is based on evaluation of 355 patients across multiple clinical trials and includes warnings and precautions for congestive heart failure, CNS adverse effects including dizziness, skeletal fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, vision disorders, and embryo-fetal toxicity (Rozlytrek® USPI 2021).

TKI-pretreated ROS1-Positive NSCLC: There are currently no approved targeted therapies indicated for advanced *ROS1*-positive NSCLC patients previously treated with first line ROS1 TKI treatment (ie, crizotinib or entrectinib). Therapies that are recommended and used in this setting include platinum-based chemotherapy and lorlatinib; however, neither treatment option is approved in this setting (NCCN 2022; Planchard 2020; Mazieres 2019).

Efficacy data for platinum-based chemotherapy in the second line (2L) setting following first-line ROS1 TKIs are limited. In one retrospective study of 21 patients with *ROS1*-positive tumors who received 2L+ pemetrexed-based chemotherapy, the ORR was reported as 24% (5 of 21 patients) (Zhang 2016). There is no evidence to support immunotherapy or addition of ICI to a chemotherapy regimen in *ROS1*-positive NSCLC (Moliner 2021). Entrectinib is a recommended option for patients with CNS-only progression after crizotinib (NCCN 2022); however, recent literature shows that efficacy is limited in this setting (Drilon 2022). Lorlatinib is also recommended (NCCN 2022) but showed limited clinical activity after crizotinib, particularly in patients with *ROS1*-resistant mutation G2032R and an unfavorable safety profile (Shaw 2019b).

Table 1. Treatment Armamentarium in ROS1-Positive Non-Small Cell Lung Cancer

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Crizotinib Xalkori®	Patients with metastatic NSCLC whose tumors are ALK or *ROS1*-positive as detected by an FDA-approved test	Initial US accelerated approval: 2011 US approval in (ROS1+): 2016	Metastatic NSCLC: 250 mg orally twice daily	PROFILE 1001 Multicenter, single-arm, open label ORR by BICR (95%, CI): 66% (51, 79) mDOR median, months by BICR (95%, CI): 18.3 (12.7, NR) IC-ORR by BICR (95%, CI): NA	Hepatoxicity, ILD/pneumonitis, QT prolongation, bradycardia, severe visual loss, gastrointestinal toxicity, embryo-fetal toxicity	No evidence of efficacy in patients pretreated with ROS1 TKI or those with brain metastasis at baseline. Development of on-target resistance mutations, including SFMs in 40% to 50% of crizotinib-resistant tumors (ROS1+ NSCLC)
Entrectinib Rozlytrek®	Adult patients with *ROS1*-positive metastatic NSCLC as detected by an FDA-approved test	Initial US approval: 2019	Recommended Dosage for *ROS1*-Positive NSCLC: 600 mg orally once daily	ALKA, STARTRK-1, STARTTRK-2 Multicenter, single-arm, open label cORR by BICR (95%, CI): 74% (64, 83) Observed DOR, by BICR (%): ≥ 9 months, 75% ≥ 12 months, 57%	Congestive heart failure, CNS effects, skeletal fractures, hepatoxicity, hyperuricemia, QT prolongation, visual disorders, embryo-fetal toxicity	Entrectinib is not approved in patients pretreated with a ROS1 TKI. Limited efficacy in patients with CNS-only progression following crizotinib (Drilon 2022)

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
				≥ 18 months, 38% IC-ORR (%, n/N): 70 (7/10)		
Other Treatments						
Platinum-doublet Chemotherapy	No relevant indications for *ROS1* positive NSCLC	NA	No labeled dosing guidelines in this setting	Treatment naïve NSCLC: ORR ~ 25%-30%, mPFS ~ 4-6 months mOS: ~ 12 months	Bone marrow suppression, hypersensitivity reactions, ototoxicity, ocular toxicity, secondary leukemia, embryo-fetal toxicity	Evidence of limited efficacy in *ROS1*-positive NSCLC. Efficacy data in the 2L setting following first-line ROS1 TKIs are limited; ORR of 24% (5/21 patients) in a retrospective 2L+ study.
Ceritinib Zykadia®	No relevant indications for *ROS1*-positive NSCLC	NA	750 mg orally once daily (Lim 2017)	Crizotinib-naïve (Lim 2017): ORR (n/N) (95%, CI): 67% (20/30) (48, 81) mDOR months (95%, CI): 21.0 (17, 25) mPFS months (95%, CI): 19.3 (1, 37)	Gastrointestinal toxicity, hepatoxicity, ILD/pneumonitis, QT prolongation, hyperglycemia, bradycardia, pancreatitis, embryo-fetal toxicity	No evidence of clinical activity in patients pretreated with crizotinib (Shaw 2019b) No evidence of efficacy in subjects with resistance mutations (Lin 2017)

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Lorlatinib Lorbrena®	No relevant indications for *ROS1* positive NSCLC	NA	100 mg orally once daily (Shaw 2019b).	TKI-naïve ORR (95%, CI): 62% (38, 82) Crizotinib-treated: ORR (95%, CI): 35% (21, 52)	Hepatoxicity with strong CYP3A inducers, CNS effects, hyperlipidemia, atrioventricular block, ILD/pneumonitis, embryo-fetal toxicity.	Safety data are based on ALK patient population No evidence of clinical activity in subjects with the common G2032R solvent front mutation (Shaw 2019b).

Abbreviations: BICR = Blinded Independent Central Review; CI = confidence interval; CNS = central nervous system; cORR = confirmed overall response rate; DOR = duration of response; FDA = Food and Drug Administration; IC-ORR = intracranial overall response rate; ILD = interstitial lung disease; 2L = second line; n = number of subjects in the category; mDOR = mean duration of response; mOS = mean overall survival; mPSF= mean progression-free survival; N = number of subjects; NA = not applicable; NR = not reached; NSCL = non-small cell lung cancer ORR = objective response rate; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; SFM = solvent front mutations; TKI = tyrosine kinase inhibitor; US = United States.

The Applicant's Position:

Patients with *ROS1*-positive NSCLC who are ROS1 TKI-naïve represent a population for which existing targeted therapies have demonstrated high response rates, including activity in patients with CNS disease (entrectinib). However, there remains an unmet medical need for a targeted therapy that not only yields robust response rates but also overcomes common mechanisms of treatment failure to provide high and sustained durability of response, intracranial activity, and that remains well tolerated. In addition, for the TKI-pretreated population for which there is no approved targeted therapy, and no approved agent with clinical activity in patients who have developed an acquired resistant mutation, there remains a high unmet medical need.

Repotrectinib is an oral ATP-competitive small molecule inhibitor of ROS1. To gain high binding affinity, most kinase inhibitors, including crizotinib and entrectinib, 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 such as crizotinib and entrectinib, 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 including a variety of clinically reported resistance mutations, especially SFMs (Section 5.3). 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 an improved benefit-risk profile in the context of historical benchmarks of currently available therapies in the TKI-naïve setting and in the TKI-pretreated setting where there are currently no approved targeted therapies (Section 8).

The FDA's Assessment:

The FDA agrees with the Applicant's discussion of current treatment options for patients with ROS1 positive NSCLC. Although ceritinib and lorlatinib are described above, they are not approved in the U.S. for ROS1 positive NSCLC.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Repotrectinib (TPX-0005) is currently not marketed (or approved) in the US or any other country. The clinical development program is being conducted under IND 130465 within the Division of Oncology 2.

The FDA's Assessment:

FDA agrees with the Applicant's position. Repotrectinib is not currently approved in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicants Position:

Key Agency interactions for the repotrectinib development program are summarized in Table 2.

Table 2. Overview of Key Regulatory Interactions US Timelines

Date	Content
30 Sep 2016	**Submission of IND and protocol TPX-0005-01 (TRIDENT-1)** – A Phase 1/2, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics and Anti-Tumor Activity of TPX-0005 in Patients with Advanced Solid Tumors Harboring *ALK, ROS1*, or *NTRK1-3* Rearrangements
22 Jun 2017	**Granted: Orphan Drug Designation # 17-5735 (NSCLC with adenocarcinoma histology)**
07 Dec 2018	**Type B EOP1 Meeting (Clinical)** Outcome: Discussed and obtained feedback on the TRIDENT-1 study design, target ORR for approvability, clinical pharmacology plan, companion diagnostic, and nonclinical program
22 Jul 2019	**Type C Meeting (Clinical Pharmacology)** Preliminary Comments only[a]: Agreement with FDA on RP2D
27 Nov 2019	**Type B EOP1 Meeting (CMC)** Preliminary Comments only[a]: Agreement with FDA on CMC-related strategy and specifications
19 Aug 2020	**Type C Meeting, Written Responses Only (Clinical)** Written Responses: Agreement with FDA that efficacy data from the Phase 1 and Phase 2 portions of the TRIDENT-1 study can be pooled for the primary analysis of efficacy to support registration in the targeted patient populations with *ROS1*+ advanced NSCLC (both TKI-naïve and TKI-pretreated)
07 Dec 2020	**Granted: Breakthrough Therapy Designation (*ROS1*+ NSCLC TKI-Naïve, EXP-1)**
12 Apr 2021	**Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting (*ROS1*+ NSCLC TKI-Naïve, EXP-1)**

Date	Content
	Outcome: Feedback on the nonclinical safety data package, proposed efficacy population, TRIDENT-1 statistical analysis plan, proposed integrated safety data plan, QT assessment plan, (b) (4) mg strength capsule formulation, clinical pharmacology plan, stability data, companion diagnostic and pre-NDA meeting
15 Dec 2021	**Agreement reached with FDA on initial Pediatric Study Plan (iPSP)** (b) (4) , the Applicant plans to submit a deferral request for the report for the molecularly targeted pediatric investigation (Study TPX-0005-07 [CARE])
09 May 2022	**Granted: Breakthrough Therapy Designation (*ROS1*+ NSCLC Previously Treated with One ROS1 TKI and No Prior Chemotherapy, EXP-4)**
27 Jun 2022	**Type B pre-NDA Meeting (Clinical)** Outcome: Discussion and agreements regarding the clinical efficacy, safety and pharmacology plans for an NDA submission
28 Jun2022	**Type B pre-NDA Meeting (CMC)** Preliminary Comments only[a]: Feedback regarding formulation, dosage strengths, and registration plans for the formulations
(b) (4)	
16 Feb 2023	**Type B Meeting (CMC and CDx)** Preliminary Comments only[a]: Agreement reached with FDA on the formulation to be submitted in the planned NDA, that it may be acceptable for a supplemental PMA filing for a CDx to be a post marketing commitment and that MAPP 5015.13 "Quality Assessment for Products in Expedited Programs" may apply to the repotrectinib NDA review

Abbreviations: CMC = chemistry, manufacturing and controls; iPSP = initial Pediatric Study Plan; NDA = New Drug Application; NSCLC = non-small cell lung cancer; ORR = objective response rate; PMA = premarket approval; RP2D = recommended Phase 2 dose; TKI = tyrosine kinase inhibitor.

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

The FDA's Assessment:

FDA agrees with the Applicant's timeline of events. The current NDA was submitted on March 27, 2023.

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

4.1. Office of Scientific Investigations (OSI)

Clinical data from Study TPX-0005-1 (TRIDENT-1) were submitted to the Agency in support of NDA 218213 for repotrectinib (TPX-0005) for the treatment of adults with locally advanced or

metastatic ROS1-positive NSCLC. Two clinical investigators, Drs. Misako Nagasaka (Site # 1001/2101), and Alexander Drilon (Site # 1002/2102), as well as the imaging Contract Research Organization (CRO) (b) (4) and the study sponsor, Turning Point Therapeutics Inc. (Turning Point), a wholly owned subsidiary of Bristol Meyers Squibb (BMS), were inspected.

Inspections of the clinical investigators, Drs. Nagasaka, and Drilon, the sponsor, Turning Point, and the imaging CRO, (b) (4) revealed no discrepancies or regulatory violations. Based on these inspections, Study TPX-0005-1 appears to have been conducted adequately by the study sponsor and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the applicant, BMS appear acceptable in support of the proposed indication. For the full report see OSI's September 6, 2023, site inspection submission.

4.2. Product Quality

The product quality review team has recommended approval. Please refer to the complete OPQ Review and Evaluation uploaded in DARRTS on October 11, 2023, for full details. Briefly, appropriate controls for release and stability testing have been established to ensure the quality of the drug substance batches manufactured under cGMP process. Based on available (b) (4)-month long-term stability data, the Applicant's proposed (b) (4)month retest period when stored at (b) (4), and the applicant's proposed 36-months shelf life for the drug product when stored at 20°C to 25°C (68° to 77°F) with excursions permitted between 15°-30°C (59°-86°F) have been determined to be acceptable. The bridging between the clinical batches and the proposed commercial drug product batches has been found acceptable with the Applicant's commitment to provide confirmatory dissolution profile data of three process performance qualification (PPQ) batches that possess the final commercial image of the repotrectinib 40 mg capsules. All drug substance and drug product manufacturing and controls facilities were found to be acceptable.

4.3. Clinical Microbiology

There are no clinical microbiology issues that would preclude approval.

4.4. Devices and Companion Diagnostic Issues

In TRIDENT-1, assessment of ROS1 status determined by tissue-based, local test for enrollment and central confirmation was required. ROS1 status in the tumor was assessed locally by next-generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR) testing or a

fluorescence in situ hybridization (FISH) test with prospective confirmation of fusion status by a central diagnostic laboratory test selected by the Applicant prior to enrollment.

The development of a companion diagnostic (CDx) for the detection of ROS1 positive NSCLC is currently in progress and a PMC will be included in the approval letter for the ROS1 positive NSCLC indication. Per the PMC, the CDx will be validated through an appropriate analytical and clinical validation study using clinical trial data that demonstrates the device is essential to the safe and effective use of repotrectinib for the treatment of adult patients with locally advanced ROS1 positive NSCLC.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Repotrectinib is a small molecule inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1). The established pharmacological class for repotrectinib is kinase inhibitor. ROS1 fusion proteins are oncogenic drivers in non-small cell lung cancer (NSCLC) driving tumorigenic potential through hyperactivation of downstream signaling pathways causing increased cellular proliferation.

Pharmacological assessment of repotrectinib showed inhibitory activity against wild type ROS1 and ROS1 mutants in enzymatic assays and antiproliferative activity against ROS-1 mutant containing cells in cellular assays (IC_{50}s = 0.07 to 0.5 nM). Repotrectinib also inhibited autophosphorylation of ROS1 wild type and ROS1 mutant fusion proteins. Evaluation of antitumor activity was conducted in subcutaneous xenograft models and did not include NSCLC cell lines or patient derived NSCLC cell lines. Cell lines such as NIH/3T3 cells, a murine fibroblast cell line, or Ba/F3 cells, a murine pro-B cell line, were engineered to express ROS1 mutants/fusion proteins for xenograft studies. Oral twice daily administration of repotrectinib (15 to 75 mg/kg/day) to mice bearing ROS1 mutant subcutaneous tumors led to significant tumor growth inhibition ranging from 64 to 200% inhibition.

Additional targets of repotrectinib included ALK and ALK mutants along with wild type TRKA/B/C with IC_{50} values in the nanomolar range (0.05 – 0.8 nM). Secondary pharmacological targets included 21 additional kinases with IC_{50} values (1 -50 nM) less than the Cmax of unbound repotrectinib (92 nM).

Repotrectinib had no toxicologically significant effects on cardiovascular function in vivo in monkeys or in vitro on hERG, hNaV1.5, or hCaV1.2 channels. Repotrectinib had no effect on respiratory function rats and monkeys. Central nervous system (CNS) toxicity was observed in the 28-day and 91-day repeat-dose toxicology studies in rats and included ataxia and tremors, consistent with clinical observations of ataxia in treated patients. A functional observational battery (FOB) was not conducted for repotrectinib; however, cognitive impairment occurred in the clinic and is included in the label under Warnings and Precautions along with ataxia.

The distribution of repotrectinib was widespread by 1 hour post-dose with the highest exposures in pigmented skin, uveal tract, liver, renal cortex, and kidneys with low distribution into non-circumventricular CNS tissue (protected by blood-brain barrier). The major route of excretion of repotrectinib was fecal with minor excretion via the urinary route in monkeys and rats. All metabolites formed in humans were also formed in rat and/or monkey, and no individual metabolite represented greater than 10% exposure to the parent compound in any

species or in humans. In consultation with the FDA clinical pharmacology team, animal to human exposure multiples were calculated using the steady-state geometric mean AUC of 7210 h*ng/mL.

The Applicant evaluated the safety of repotrectinib administered orally once daily in 28-day and 91-day GLP-compliant general toxicology studies using rats and cynomolgus monkeys. The oral route of administration is consistent with the intended clinical route of administration. Repotrectinib caused mortalities in both rats and monkeys in the 28- and 91-day studies. The cause of death in the rat studies was not determined; however, clinical signs included significant CNS toxicity (ataxia, tremors), decreased body weight/thin appearance, decreased appetite, weakness, and skin abrasions. The cause of death in the monkey studies was due to drug-related severe GI toxicity. Drug-related findings/target organs in both species included bone marrow (hypocellularity, granulocytic hyperplasia [monkey only]), lymphoid tissues (hypocellularity), and thymus (hypocellularity). Additional toxicities observed in rats included skin (scabs/ulcers) and CNS (ataxia/tremors) toxicities. The Applicant attributed tremors, ataxia, and some skin toxicities to rumbunctious play among animals; however, reports of other inhibitors of ALK, ROS, and TRKs include incidences of neural and skin toxicity, and clinical findings in patients treated with repotrectinib suggest that these effects are drug related. Additional toxicities observed in monkey included GI toxicity (watery feces, emesis, inflammation, mucosal gland hyperplasia). Skin toxicity in rats and GI toxicity in monkeys trended towards recovery 28-days after cessation of dosing. Repotrectinib had no adverse effects on male and female reproductive organs in the repeat-dose studies in rats and monkeys. Exposure range in the rats was up to 3-fold higher compared to exposure in patients observed at the recommended dose of 160 mg BID (AUC = 20500 vs. 7210 ng*h/mL, respectively). Exposure in the monkey was approximately 2-fold lower compared to patients at the recommended dose (AUC = 3910 vs. 7210 ng*h/mL, respectively).

Repotrectinib was negative for genotoxicity in the in vitro AMES assay and positive for genotoxicity in the in vitro micronucleus assay. In vivo, repotrectinib was positive for genotoxicity in male rats for micronucleated polychromatic erythrocytes (PCEs) in bone marrow at doses ≥500 mg/kg. Therefore, repotrectinib labeling is based on a determination of potentially genotoxic.

Carcinogenicity studies have not been conducted with repotrectinib and are not warranted for the proposed indication.

Reproductive and developmental toxicology assessment of repotrectinib included a dose range finding embryofetal development study in female rats with orally administered repotrectinib. Once daily dosing for 12 days, between gestation days 6 and 17 during the period of organogenesis, resulted in fetal external malformations and decreased fetal body weight at 12 mg/kg which is approximately 0.3 times the recommended 160 mg twice daily dose based on body surface area (BSA). In addition, the number of late resorptions was increased at the high

dose (20 mg/kg/day) compared to controls but with no effect on litter size or post implantation loss. Treated dams showed skin toxicity at doses ≥6 mg/kg/day. No toxicokinetic data was collected in the embryofetal development study to use for comparison to clinical exposure in patients. Repotrectinib labeling was based on FDA guidance, "Oncology Pharmaceutical: Reproductive Toxicity Testing and Labeling Recommendations" for embryofetal toxic and genotoxic drugs. The review team recommends an embryofetal toxicity warning. Since repotrectinib may render some hormonal contraceptives ineffective and its half-life is 35.4 hours, the label advises females of reproductive potential to use effective non-hormonal contraception during treatment with repotrectinib and for (b)(4) months after the dose. Males with female partners of reproductive potential should use effective contraception during treatment with repotrectinib and for 4 months after the last dose.

Administration of once daily oral repotrectinib in juvenile rats led to decreased body weight gain, food consumption, and femur length at a dose of 3 mg/kg/day. Additionally, platelet counts were increased by approximately 20% at the 3 mg/kg dose during the dosing phase but recovered to control values by the end of the recovery period. Repotrectinib had no effect on the age or body weight at attainment of balanopreputial separation or attainment of vaginal patency nor any effects on auditory startle responsiveness, motor activity, learning, or memory up to the highest dose of 3 mg/kg tested. Higher doses in the dose range finding study (10 and 30 mg/kg/day) led to significant CNS toxicity (ataxia, hypoactivity, labored breathing, decreased respiration rate, cool body and extremities, splayed limbs) leading to early euthanasia or death. CNS toxicity observed in animal studies with repotrectinib may be related to inhibition of TRK proteins.

There are no approvability issues from a pharmacology/toxicology perspective. The Pharmacology/Toxicology team recommends approval of repotrectinib for NSCLC with ROS-1 mutations.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Not applicable.

The FDA's Assessment:
We agree that this is not applicable because this is an original NDA.

5.3. Pharmacology

Primary Pharmacology

In vitro studies

The inhibitory activity of repotrectinib against recombinant human kinases and corresponding mutants was evaluated using the radiolabeled HotSpot™ kinase assay platform, with IC_{50} values at 10 µM ATP of 0.0706 nM and 0.456 nM, respectively. Repotrectinib showed potent kinase inhibitory activity against ROS1 and its G2032R mutant.

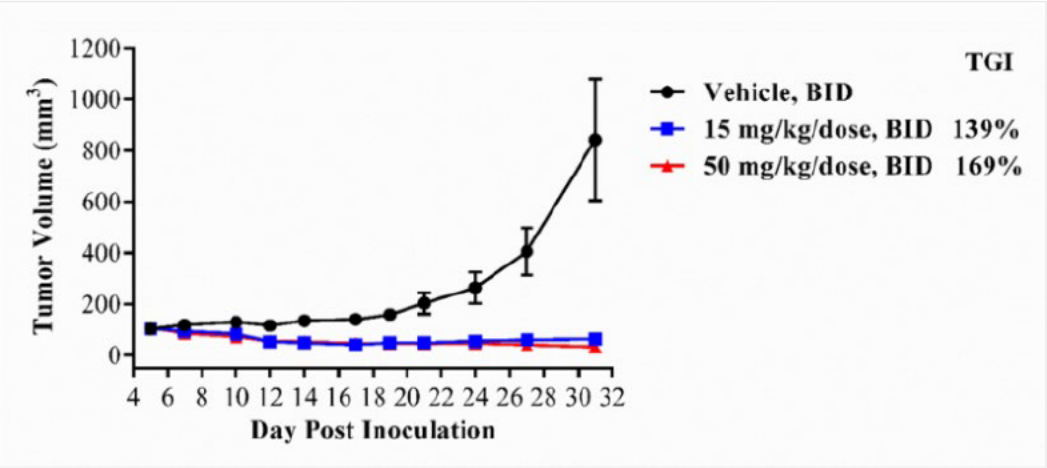
Engineered murine Ba/F3 cells expressing ROS1 fusion proteins, or their mutants, were used to evaluate the antiproliferative activities of repotrectinib. Repotrectinib demonstrated potent activity against SDC4-ROS1- or CD74-ROS1-expressing Ba/F3 cells with IC_{50} values of < 0.2 nM. The compound also exhibited potent antiproliferative activity against the solvent-front mutations SDC4-ROS1 G2032R (IC_{50} = 3 nM), CD74-ROS1 G2032R (IC_{50} = 8.4 nM), and CD74-ROS1 D2033N (IC_{50} = 0.15 nM) and the gatekeeper mutation CD74-ROS1 L2026M (IC_{50} = 10 nM).

In another experiment, engineered murine NIH3T3 cells expressing ROS1 fusion proteins were used to evaluate the inhibitory activities of repotrectinib on autophosphorylation of WT ROS1 and the ROS1 mutants. Repotrectinib inhibited autophosphorylation of ROS1 and mutant CD74-ROS1 fusion proteins G2032R, L2026M, and D2033N with IC_{50} values of < 1, 3, 10, and 1 nM, respectively.

In vivo studies

The anti-tumor activity of repotrectinib alone was evaluated in female athymic mice bearing NIH3T3 SDC4-ROS1 WT xenograft tumors. Mice (5-8 weeks old) were inoculated subcutaneously with NIH3T3 cells (5×10^6) engineered to express the SDC4-ROS1 WT protein. Dosing was initiated when the average tumor volume reached approximately 100 mm^3. Repotrectinib was administered via oral gavage at doses of 15 and 50 mg/kg/dose BID for 26 days to 8 mice/group. Tumor growth inhibition (TGI) was calculated based on the changes in tumor volume for treated over control group. A TGI > 100% indicates a regression in tumors. BID dosing with 15 or 50 mg/kg/dose of repotrectinib resulted in a potent inhibition of tumor growth with TGIs of 139% and 169%, respectively (Figure 1). The TGI was statistically significant for both the 15 and 50 mg/kg/dose groups (each with $p < 0.001$ compared to vehicle) without overt toxicity.

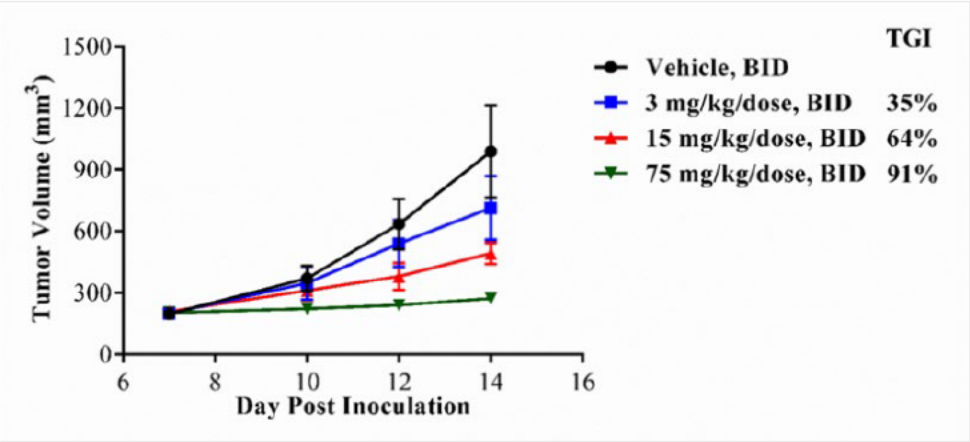
Figure 1. Anti-Tumor Activity of Repotrectinib in a NIH3T3 SDC4-ROS1 WT Xenograft Model in Female Athymic Nude Mice



Abbreviations: BID = twice daily; TGI = tumor growth inhibition.
Notes: Data represent mean ± SD of 8 animals per group. The TGI was statistically significant for both the 15 and 50 mg/kg/dose groups (each with $p < 0.001$ compared to vehicle).
Source: Study 00153 Figure 1

The anti-tumor effect of repotrectinib alone against the CD74-ROS1 G2032R fusion protein was also evaluated in female athymic nude mice bearing NIH3T3 CD74-ROS1 G2032R xenograft tumors. Mice (5-8 weeks old) were subcutaneously inoculated with NIH3T3 CD74-ROS1 G2032R cells (5×10^6), and dosing was initiated when the average tumor volume reached approximately 200 mm^3. Mice (n = 6/group) were dosed for 7 days BID with vehicle or three dose levels of repotrectinib. BID dosing with 3 mg, 15 mg, or 75 mg/kg/dose of repotrectinib resulted in a dose-dependent inhibition of tumor growth with TGIs of 35%, 64%, and 91%, respectively (Figure 2). The TGI was statistically significant at the 15 mg/kg/dose and 75 mg/kg/dose groups ($p < 0.001$ and $p < 0.0001$, respectively, compared to vehicle). Treatment of tumor-implanted mice with repotrectinib was well tolerated.

Figure 2. Anti-Tumor Activity of Repotrectinib in the NIH3T3 CD74-ROS1 G2032R Xenograft Model in Female Athymic Nude Mice

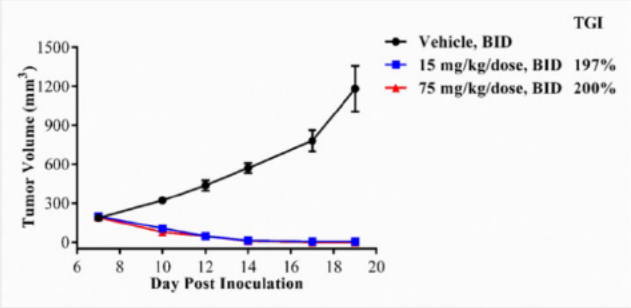


Abbreviations: BID = twice daily; SD = standard deviation; TGI = tumor growth inhibition.
Data represent mean ± SD of 6 animals per group. The TGI was statistically significant at 15 mg/kg/dose and 75 mg/kg/dose groups ($p < 0.001$ and $p < 0.0001$, respectively, compared to vehicle).
Source: Study 00183 Figure 1

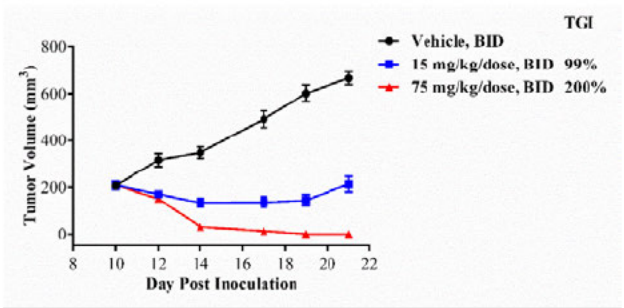
A third study evaluated the anti-tumor activity of repotrectinib in female SCID/Beige mice bearing Ba/F3 CD74-ROS1 WT or Ba/F3 CD74-ROS1 G2032R xenograft tumors. Mice (5-6 weeks old) were subcutaneously inoculated with Ba/F3 cells expressing CD74-ROS1 WT or Ba/F3 cells expressing CD74-ROS1 G2032R (5×10^6 cells/mouse) and dosing was initiated when the average tumor volume reached approximately 200 mm^3. Repotrectinib at 15 mg or 75 mg/kg/dose was administered via oral gavage BID for 12 days in mice bearing Ba/F3 CD74-ROS1 WT tumors and BID for 11 days in mice bearing Ba/F3 CD74-ROS1 G2032R tumors (8 mice/group). A vehicle group was included as a control. In mice bearing Ba/F3 CD74-ROS1 WT xenograft tumors, BID dosing with 15 mg or 75 mg/kg/dose of repotrectinib resulted in potent inhibition of tumor growth with TGIs of 197% and 200%, respectively (Figure 3A). The TGI was statistically significant for the 15 mg/kg/dose and 75 mg/kg/dose groups (each with $p < 0.0001$ compared to vehicle). Treatment with repotrectinib resulted in nearly complete tumor regression in Ba/F3 CD74-ROS1 WT xenograft tumors without overt toxicity in female SCID mice. In mice bearing Ba/F3 CD74-ROS1 G2032R xenograft tumors, BID dosing with 15 mg or 75 mg/kg/dose of repotrectinib resulted in potent inhibition of tumor growth with TGIs of 99% and 200%, respectively (Figure 3B). The tumor growth inhibition was dose-dependent and statistically significant at both dose levels (each with $p < 0.0001$ compared to vehicle) in Ba/F3 CD74-ROS1 G2032R xenograft models. Treatment with repotrectinib at 75 mg/kg/dose resulted in complete tumor regression in Ba/F3 CD74-ROS1 G2032R xenograft tumor model without overt toxicity in female SCID mice.

Figure 3. Anti-Tumor Activity of Repotrectinib in the Ba/F3 CD74-ROS1 WT and ROS1 G2032R Xenograft Models in Female SCID/Beige M

A. Ba/F3 CD74-ROS1 WT



B. Ba/F3 CD74-ROS1 WT



Abbreviations: BID = twice daily; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TGI = tumor growth inhibition; WT = wild type.
Notes: Data represent mean ± SD of 8 animals per group. The TGI was statistically significant for the 15 mg/kg/dose and 75 mg/kg/dose groups (each with $p < 0.0001$ compared to vehicle).
Source: Study 00182 Figure 1 and Figure 3

The FDA's Assessment:

The Applicant uses terminology such as "potent" to describe study results; such terms should be avoided as they are vague, subjective, and promotional.

The FDA generally agrees with the Applicant's conclusions on the pharmacology of repotrectinib, with additional pertinent details below. In vitro in enzymatic assays, repotrectinib showed kinase inhibitory activity against wild type ROS1 and ALK and their mutants along with wild type TRKA/B/C (Table 3). Repotrectinib bound to ROS1, ALK, TRKA, TRKB, and TRKC with K_d values of 0.19, 5.7, 0.019, 0.054, and 0.088 nM, respectively.

Table 3. Inhibitory Activity of Repotrectinib Against ALK, ROS1, and TRK Family Kinases and Their Mutants

Target	Repotrectinib IC_{50} (nM)	Target	Repotrectinib IC_{50} (nM)
ROS1	0.0706	ALK (L1152R)	1.23
ROS1 (G2032R)	0.456	ALK (R1275Q)	2.79
TPM3-ROS1	0.113	ALK (1151T Ins)	2.16
ALK	1.04	ALK (T1151M)	0.491
AKL (L1196M)	1.08	ALK (G1269A)	5.50
ALK (G1202R)	1.21	ALK (G1269S)	14.1
ALK (F1174L)	1.46	ALK-NPM1	1.23
ALK (F1174S)	1.02	TRKA	0.826
ALK (C1156Y)	0.932	TRKB	0.0517
ALK (S1206R)	0.525	TRKC	0.0956

Evaluation of antitumor activity was conducted in subcutaneous xenograft models and did not include NSCLC cell lines or patient derived NSCLC cell lines. In addition to the antitumor activity observed in xenograft mouse models bearing tumors with ROS1 mutations, repotrectinib

exhibited antitumor activity against mice bearing tumors with TRKA mutations and certain ALK mutations at the same doses and schedule used in the ROS1 antitumor activity evaluation. Cell lines listed in Table 4 were engineered to express various ROS1, TRK, or ALK mutations.

Table 4. In Vivo Antitumor Activity of Repotrectinib in Mice Bearing ROS1, TRK, or ALK Mutant Tumors

Cell Line	Xenograft Target	Repotrectinib dose And schedule	TGI%
NIH3T3	SDC4-ROS1 WT	15 mg/kg BID	139%
		50 mg/kg BID	169%
	CD74-ROS1 G2032R	15 mg/kg BID	64%
		75 mg/kg BID	91%
Ba/F3	CD74-ROS1 WT	15 mg/kg BID	197%
		75 mg/kg BID	200%
	CD74-ROS1 G2032R	15 mg/kg BID	99%
		75 mg/kg BID	200%
Karpas299	NPM-ALK	15 mg/kg BID	59%
		50 mg/kg BID	94%
NIH3T3	EML4-ALK v1 WT	15 mg/kg BID	90%
		50 mg/kg BID	141%
Ba/F3	EML4-ALK v1 WT	15 mg/kg BID	74%
		75 mg/kg BID	154%
	EML4-ALK v1 G1202R	15 mg/kg BID	56%
		75 mg/kg BID	99%
KM12	TPM3-TRKA	15 mg/kg BID	113%
		75 mg/kg BID	111%
NIH3T3	LMNA-TRKA WT	3 mg/kg BID	100%
		15 mg/kg BID	128%
	LMNA-TRKA G595R	3 mg/kg BID	56%
		15 mg/kg BID	97%
		60 mg/kg BID	123%

BID = twice daily. TGI = tumor growth inhibition. NIHN3T3 = murine fibroblast cells. Ba/F3 = murine pro-B cell line. Karpas299 = human T cell lymphoma. KM12 = cell lines of the NCI-60 panel which represents different cancer types.

We also note that the Figure 3B is mislabeled. Figure 3B is showing results for Ba/F3 CD74-ROS1 G2032R xenograft model.

Secondary Pharmacology

The Applicant's Position:

The off-target effect of repotrectinib was evaluated in a panel of 44 proteins involved in key physiological activities. The initial screen at 10 µM resulted in 50% inhibition in ligand binding or enzymatic activity against three targets: human adenosine A_{2A} receptor (50.3%), Ca^{2+} channel (L, dihydropyridine site; 69.8%), and human LCK (81.9%). The inhibitory effect of repotrectinib on these molecules was further evaluated by measuring IC_{50} values and other kinetic

parameters. Repotrectinib inhibited ligand binding of adenosine A_{2A} receptor and Ca^{2+} channel with IC_{50} values of 6.3 µM and 3.5 µM, respectively; these correspond to 87-fold and 48-fold multiples of the mean C_{max} of unbound repotrectinib observed (0.072 µM) after administration of repotrectinib at the intended clinical dose (160 mg BID). Repotrectinib inhibited LCK activity with an IC_{50} value of 0.11 µM, which corresponds to a 1.5-fold multiple of the mean clinical C_{max} of unbound repotrectinib. Inhibition of LCK has the potential to cause immunosuppression and increase the risk of infection, but a low incidence of lymphopenia has been reported in patients treated with repotrectinib (< 2%) and there is no evidence of increased immunosuppression or incidence of infection for this class of drugs and patient population.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusions on the secondary pharmacology of repotrectinib, with additional pertinent details below. The Cmax of unbound repotrectinib was calculated by the FDA clinical and nonclinical team to be 0.092 µM at the recommended dose of 160 mg BID; thus, the inhibition of adenosine A_{2A} receptor, Ca^{2+} channel, and LCK were at concentrations 68-, 38-, and 1.2-fold higher than the unbound Cmax in patients. Additional secondary kinase targets inhibited by repotrectinib at clinically relevant concentrations are listed in Table 5.

Table 5. Secondary Kinase Targets for Repotrectinib at Clinically Relevant Concentrations

Target	Repotrectinib IC_{50} (nM)	Target	Repotrectinib IC_{50} (nM)
JAK2	1	TXK	3.2
ARK5	4.5	SRC	5.3
DDR1	5.7	FAK	7
SNARK	13	HCK	16.4
LCK	18.6	JAK1	18.8
TYK2	21.6	TYK1	21.8
DDR2	23	ACK1	24.1
EPHA1	25	BLK	32.3
GRK7	35.2	PYK2	29.9
RET	47.1	JAK3	49.9
EPHA8	50.2		

Safety Pharmacology

Inhibition of the hERG potassium channel by repotrectinib was investigated using a stably transfected CHO cell line expressing the hERG mRNA at concentrations up to 30 µM. The IC_{50} value for the inhibitory effect of repotrectinib on hERG potassium current was 18 µM, which corresponds to a 249-fold multiple to the clinical mean C_{max} of unbound repotrectinib (0.072 µM). The inhibition of human Nav1.5 sodium channel and hCav1.2 calcium channel by repotrectinib was minimal (≤ 15% and 35% inhibition, respectively, at 30 µM). ECG

examinations were performed on cynomolgus monkeys in the 28- and 91-day toxicology studies, and no qualitative or quantitative ECG changes were observed with repotrectinib.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusions on the safety pharmacology of repotrectinib, with additional pertinent details below. Cmax of unbound repotrectinib was calculated by the FDA clinical and nonclinical team to be 0.092 µM, thus the 18 µM IC_{50} for hERG channel inhibition corresponds to a 196-fold multiple.

5.4. ADME/PK

The Applicant's Position:

Absorption

The dose-normalized oral bioavailability of repotrectinib ranged from 32% to 38% in fasted male mice, was 44.7% and 61.4% in fasted male and female rats, respectively, 25.3% in fasted male beagle dogs, and 13.5% in fasted female cynomolgus monkeys. Peak plasma levels of repotrectinib were generally observed between 2- and 4-hours post dose. In female rats, C_{max} and AUC values were higher compared to males. In rats, accumulation after repeated administration was dependent on dose, with about 2- to 4-fold increases over the range of 5 mg/kg to 30 mg/kg, but, at doses ≥ 100 mg/kg, the exposures decreased after multiple dosing. There were no notable or only slight increases in exposure in monkeys after repeated dosing.

Distribution

Repotrectinib-related radioactivity exhibited rapid (by 1 hour–post--dose) and widespread distribution in most tissues based on quantitative whole-body autoradiography after a single oral dose of [^{14}C]-repotrectinib to pigmented Long-Evans rats. The distribution patterns of radioactivity into tissues in males and females were comparable; however, in most female tissues, exposures to radioactivity were at least 2-fold higher than the exposures in male tissues. The tissues with the highest radioactivity exposures in both sexes were pigmented skin, uveal tract, liver, renal cortex, and kidneys, whereas distribution of radioactivity into non-circumventricular CNS tissue (protected by blood-brain barrier) was very low. Repotrectinib is highly protein bound in plasma; the protein unbound fraction was approximately 4.6%, 4.2%, 5.1%, 7.9%, and 7.4% in human, mouse, rat, dog, and monkey, respectively.

Metabolism

After administration of a single dose of [^{14}C]-repotrectinib, unchanged compound was the predominant circulating component in rat and monkey plasma. Repotrectinib is metabolized through several metabolic pathways which includes (i) oxidations at the linker between the ether oxygen and amide nitrogen atoms of repotrectinib and further dehydrogenation or dehydration and glucuronidation; (ii) hydroxylation at the substructure that includes the fluoro-benzene and the methyl moiety in the C13 position and further glucuronidation; and (iii) amide hydrolysis/oxidative ring opening as well as further glucuronidation. Oxidative metabolism,

likely mediated by CYP3A4, appears to be the primary route for metabolism of repotrectinib followed by glucuronidation of the oxidative metabolites. All metabolites formed in humans were also formed in rat and/or monkey, confirming the suitability of these species for nonclinical safety testing.

Excretion

Across species (monkey and rat), fecal excretion is the major route of elimination of repotrectinib and its metabolites, whereas urinary excretion is a minor route of elimination.

Drug–Drug Interactions (DDIs)

Treatment of human hepatocytes with repotrectinib caused increases in the mRNA expression of CYP2B6, CYP3A4, CYP2C8, CYP2C9, and CYP2C19. In pooled human liver microsomes, there was no reversible inhibition of repotrectinib on CYP1A2, CYP2B6, CYP2D6, or CYP3A4 (midazolam) activities (IC_{50} values > 50 µM), and at high concentrations (IC_{50} values ≥ 5.72 µM), repotrectinib inhibited CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (testosterone). However, based on the observed exposure of repotrectinib from clinical studies, the compound has little potential to cause DDI by inhibiting the activity of these CYP enzymes systemically due to potential induction effects. Repotrectinib showed a low potential to cause DDI via inhibition of OATP1B3, OAT1, OAT3, OCT2, and MATE1, but may have the potential to inhibit P-gp and BCRP, as well as OATP1B1 and MATE2-K at clinically relevant concentrations. Of the UGT isoforms evaluated, repotrectinib was shown to inhibit UGT1A1 but showed a low potential to cause DDI by this mechanism.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusions on pharmacokinetics.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

General toxicology studies for repotrectinib included single- and repeat-dose toxicity studies up to 3 months in duration. The rat and monkey were selected as the appropriate species for toxicity studies based on similar metabolic profiles to human and the ability to achieve adequate systemic exposures. Furthermore, the protein sequences of ROS1, ALK, and NTRK1-3 are well conserved across rat, monkey, and human.

In single-dose studies conducted in both rats and monkeys, acute oral administration of repotrectinib was well tolerated up to 1000 mg/kg/day. In repeat-dose toxicology studies including the 28- and 91-day definitive toxicity studies, the main target organs were the skin and CNS in rat, bone marrow in rat and monkey, and GI tract in monkey.

Table 6. Rat Studies (Study 00219)

TPX-0005: A 28-Day Oral Toxicity Study in Rats with a 28-Day Recovery Module 4.2.3.2 Key findings: • Main target organs were skin (scabs/ulcers), bone marrow (hypocellularity), and CNS (ataxia) • Early mortalities/moribundity were observed at the mid- and high-dose groups in males and high-dose group in females GLP compliance: Yes						
Methods						
Dose and frequency of dosing:	M: 0, 30, 50, 100, and 300 mg/kg/day once daily for 28 days F: 0, 6, 20, and 60 mg/kg/day once daily for 28 days					
Route of administration:	Oral					
Formulation/vehicle:	[redacted] (b) (4) /1% Tween-80 in deionized water					
Species/strain:	Rat/Crl:CD®(SD)					
Number/sex/group:	16					
Age:	6 weeks					
Satellite groups:	Toxicokinetics; 3-6/sex/group					
Toxicokinetics						
Sex	Male			Female		
Daily dose (mg/kg)	30	100/50*	300	6	20	60
C_{max} (ng/mL)						
Day 1	986	1710/NA	1890	333	1070	1990
Day 28	1490	NA/1560	NA	775	1800	NA
$AUC_{0\text{-}24h}$ (ng·h/mL)						
Day 1	7040	20600/NA	22300	2140	7280	15600
Day 28	15100	NA/17100	NA	4940	15500	NA

Abbreviations: $AUC_{0\text{-}24}$ = Area under the plasma concentration-time curve from time 0 to 24 hours post-dose; C_{max} = maximum plasma concentration; CNS = central nervous system; GLP = good laboratory practice; NA = not applicable.
** Due to mortality, animals were placed on a dosing holiday beginning on Day 20; dosing resumed on Day 22 at 50 mg/kg/day.*

Table 7. Rat Studies (Study 00272)

TPX-0005: A 91-Day Oral Toxicity Study in Rats with a 28-Day Recovery Period Module 4.2.3.2 Key findings: • Main target organs were skin (scabs/ulcers), bone marrow (hypocellularity), and CNS (ataxia) • Early mortalities/moribundity were observed in high-dose group males and females that led to dose reductions; clinical signs associated with the early deaths consisted of decreased body weight and appetite, ataxia, thin appearance, tremors, hypersensitivity to touch, weakness and/or skin abrasions GLP compliance: Yes	
Methods	
Dose and frequency of dosing:	M: 0, 5, 15, and 50/40 mg/kg/day once daily for 91 days F: 0, 5, 15, and 40/30 mg/kg/day once daily for 91 days
Route of administration:	Oral
Formulation/vehicle:	[redacted] (b) (4) /1% Tween-80 in deionized water
Species/strain:	Rat/Crl:CD®(SD)
Number/sex/group:	15 or 20
Age:	6.5 weeks
Satellite groups:	Toxicokinetics; 4-8/sex/group
Toxicokinetics	

Sex	Male			Female		
Daily dose (mg/kg)	5	15	50/40*	5	15	40/30**
C_{max} (ng/mL)						
Day 1	81.1	281	934	120	962	1980
Day 91	352	954	1630	660	2410	2040
$AUC_{0\text{-}24h}$ (ng·h/mL)						
Day 1	637	2170	7980	1050	7140	15600
Day 91	2710	7190	17300	4300	20500	22000

Abbreviations: $AUC_{0\text{-}24}$ = Area under the plasma concentration-time curve from time 0 to 24 hours post-dose; C_{max} = maximum plasma concentration; CNS = central nervous system; GLP = good laboratory practice.
** Beginning on Day 21, all males at 50 mg/kg/day were placed a dose holiday. Dosing resumed on Day 25 at 40 mg/kg/day.*
*** Beginning on Day 18, all females at 40 mg/kg/day were placed on a dose holiday. Dosing resumed on Day 25 at 30 mg/kg/day.*

Table 8. Monkey Studies (Study 00229)

TPX-0005: A 28-Day Oral Toxicity Study in Cynomolgus Monkeys with a 28-Day Recovery
Module 4.2.3.2
Key findings:

- Main target organs of bone marrow (decreased red cell mass, reticulocytes, and increased platelets) and GI tract (watery feces)
- No adverse, treatment-related effects on ECG parameters were observed at any dose level
- One high-dose animal euthanized early with a high incidence of watery feces and decline in body weight; a definitive cause of death not determined, but the animal had a marked increase in platelet count and depleted body fat compared to other high-dose animals

GLP compliance: Yes

Methods						
Dose and frequency of dosing:	0, 10, 30, and 100 mg/kg/day once daily for 28 days					
Route of administration:	Oral					
Formulation/vehicle:	(b) (4) 1% Tween-80 in deionized water					
Species/strain:	Monkey/cynomolgus					
Number/sex/group:	4-6					
Age:	2-4 years					
Satellite groups:	Toxicokinetics; all animals					
Toxicokinetics						
Sex	Male			Female		
Daily dose (mg/kg)	10	30	100	10	30	100
C_{max} (ng/mL)						
Day 1	194	287	356	63.5	145	396
Day 28	212	257	259	137	243	248
$AUC_{0\text{-}24h}$ (ng·h/mL)						
Day 1	1930	2420	4750	962	1670	3660
Day 28	2070	2690	3820	1560	2150	2850

Abbreviations: $AUC_{0\text{-}24}$ = Area under the plasma concentration-time curve from time 0 to 24 hours post-dose; C_{max} = maximum plasma concentration; ECG = electrocardiogram; GLP = good laboratory practice.

Table 9. Monkey Studies (Study 00357)

TPX-0005: A 91-Day Oral Toxicity Study in Monkeys with a 28-Day Recovery Period Module 4.2.3.2 Key findings: • Main target organs were GI tract (emesis, watery feces, minimal subacute/chronic inflammation and/or minimal to mild mucosal gland hyperplasia in the large intestines) and bone marrow (decreased red cell mass and reticulocyte counts and increased platelet counts) • No adverse, treatment-related effects on ECG parameters were observed at any dose level GLP compliance: Yes						
Methods						
Dose and frequency of dosing:	0, 5, 15, and 50 mg/kg/day once daily for 91 days					
Route of administration:	Oral					
Formulation/vehicle:	(b) (4) /1% Tween-80 in deionized water					
Species/strain:	Monkey/cynomolgus					
Number/sex/group:	4-6					
Age:	2-4 years					
Satellite groups:	Toxicokinetics; 4-6/sex/group					
Toxicokinetics						
Sex	Male			Female		
Daily dose (mg/kg)	5	15	50	5	15	50
C_{max} (ng/mL)						
Day 1	46.7	110	300	54.6	121	166
Day 91	94.4	189	294	100	173	267
AUC_{0-24h} (ng·h/mL)						
Day 1	548	1110	3000	706	1490	1650
Day 91	855	1630	3910	1040	2020	2390

Abbreviations: AUC_{0-24} = Area under the plasma concentration-time curve from time 0 to 24 hours post-dose; C_{max} = maximum plasma concentration; GI = gastrointestinal; GLP = good laboratory practice.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusions on toxicology, with additional pertinent details below. While we acknowledge that a single dose of repotrectinib was tolerated at doses up to 1000 mg/kg, results from repeat-dose studies in rats and monkeys demonstrated that doses ≥60 mg/kg caused mortalities. Major target organs in the rat 28-day and 91-day repeat-dose toxicology studies included the skin, bone marrow, thymus, some lymphoid tissue, and the CNS. The Applicant attributed tremors, ataxia, and some skin toxicities to rambunctious play among animals; however, reports of other inhibitors of ALK, ROS, and TRKs include incidences of neural toxicity, and clinical findings in patients treated with repotrectinib suggest that these effects are related to repotrectinib. Major target organs in the 28-day and 91-day repeat-dose toxicology study in monkey included bone marrow, GI tract, some lymphoid tissue, and thymus. One monkey in the 91-day study dosed at 15 mg/kg was euthanized in extremis on Day 72 due to dehydration secondary to enteritis/bacterial infection. Considering the GI toxicity and histopathology findings observed in monkeys in the 91-day study, repotrectinib likely played a role in the clinical condition of the animal. Histopathology findings in the 91-day studies are included in Table 10 for rats and Table 11 for monkeys. At the highest dose in the rats, 1/15 rats showed mild increased bilateral germ cell debris in the testes

(not observed in recovery animals) and at the highest dose in the monkey 1/4 males showed mild fibrous hypoplasia of the testes (no recovery animals necropsied). These findings were considered incidental due to the low occurrence thus were not included in the label. There were no findings in reproductive organs in either the rat or monkey 28-day toxicity study or the 7-day dose-range finding studies. Exposure at the tolerated dose in female rats (15 mg/kg/day for 91 days) was ~3-fold higher compared to the human exposure at the recommended repotrectinib dose of 160 mg BID (20500 vs. 7210 ng*h/mL, respectively); however, the exposure in male rats at the tolerated dose of 15 mg/kg/day for 91 days was comparable patients at the recommended dose (7190 vs. 7210 ng*h/mL, respectively). The exposure in monkeys at the highest dose tested in both the 90-day and 28-day toxicology studies (100 and 50 mg/kg/day, respectively) was 2- to 3-fold lower than exposures observed in patients at the recommended dose.

Table 10. Histopathology Findings in Rats Treated With Repotrectinib for 91 Days (Study 00272)

Dose (mg/kg)		0 mg/kg		5 mg/kg		15 mg/kg		50/40 mg/kg	40/30 mg/kg
Sex		M	F	M	F	M	F	M	F
# animals (main, recovery)		15,5	15,5	15	15	15	15	15,5	15,5
Skin									
Erosion/ulcer	Mild	-	-	1*	2*	1*	2*	7	7,1
	Moderate	-	-	1*	1*	-*	-*	2	-
	Marked	-	-	-*	-*	1*	-*	5	5
Spleen									
Decreased lymphocytes, generalized	Minimal	-	-	2	2	1	4	3	2
	Mild	-	-	-	1	3	3	7	4
	Moderate	-	-	-	-	-	1	5	7
	Marked	-	-	-	-	-	-	-	2
Thymus									
Decreased lymphocytes, generalized	Minimal	-	-	-	-	2	-	4	5
	Mild	-	-	-	-	-	-	-	2
	Moderate	-	-	-	-	-	-	-	3
Lymph node, mandibular									
Decreased lymphocytes, generalized	Minimal	-	-	-	-	-	-	1	5
Lymph node, mesenteric									
Decreased lymphocytes, generalized	Minimal	-	-	-	-	-	-	5	8
Bone marrow, femur									
Increased number, megakaryocytes	Minimal	-	-	1	7	2	3	6	8
Bone marrow, sternum									
Increased number, megakaryocytes	Minimal	-	-	4	9	10	9	6	9
Pancreas									
Secretory depletion, acinar cell	Minimal	-	-	-	-	-	-	1	-
Hemorrhage/pigment/inflammation/fibrosis, islets	Minimal	1	-	-	-	-	-	1	-
	Mild	1	-	-	-	-	-	4	-
	Moderate	-	-	-	-	-	-	1	-
Testes									
Germ cell debris, increased bilateral	Mild	-	na	-	na	-	na	1	na

Dose (mg/kg)		0 mg/kg		5 mg/kg		15 mg/kg		50/40 mg/kg	40/30 mg/kg
Sex		M	F	M	F	M	F	M	F
# animals (main, recovery)		15,5	15,5	15	15	15	15	15,5	15,5
Mammary gland									
Adenocarcinoma, malignant, primary	na	-	-	-	-	-	-	-	1

'-' indicates no findings. *According to the study report Table L, only 1 male and 2 females were examined for skin findings at the 5 and 15 mg/kg dose level without explanation, thus numbers likely underrepresent findings of skin toxicity. na - not applicable. Table includes findings in early death animals.

Table 11. Histopathology Findings in Monkeys Treated With Repotrectinib for 91 Days (Study 00357)

Dose (mg/kg)		0 mg/kg		5 mg/kg		15 mg/kg		50 mg/kg	
Sex		M	F	M	F	M	F	M	F
# animals (main, recovery)		4,2	4,2	4	4	4	4	4,2	4,2
Large intestine, cecum									
Hyperplasia, mucosal	Minimal	-	-	1	-	1	2	1	-
	Mild	-	-	-	-	-	-	2	-
	Moderate	-	-	-	-	-	1*	-	-
Infiltration, mononuclear cell	Minimal	1	-,1	2	3	3	1	3,1	3
	Mild	-	-	-	-	-	1	1	-
Inflammation, subacute/chronic	Minimal	-	-,1	2	1	1	1	1,1	-
	Moderate	-	-	-	-	-	1*	-	-
Mineralization	Minimal	-	-	-	-	1	-	-	-
Large intestine, colon									
Hyperplasia, mucosal	Minimal	-	-	2	-	1	2	1	-
	Mild	-	-	-	-	-	1*	-	-
Infiltration, mononuclear cell	Minimal	-,1	-,1	2	3	3	2	4,1	3
	Mild	-	-	-	-	-	1	-	-
Inflammation, subacute/chronic	Minimal	-	-	1	-	-	2	2	-,1
	Mild	-	-	-	-	-	1*	-,1	-
Hemorrhage	Minimal	-	-	-	-	-	-	-	-,1
Large intestine, rectum									
Hyperplasia, mucosal	Minimal	-	-	1	-	1	3*	1	1
Infiltration, mononuclear cell	Minimal	-	-	1	2	3	4*	4,1	-
	Mild	-	-	1	-	-	-	-	-
Hypertrophy/hyperplasia, goblet cell	Minimal	-	-	-	-	-	-	-	1
Inflammation, subacute/chronic	Minimal	-	-	-	1	-	-	-	1
	Marked	-	-	-	-	-	1*	-	-
Ulcer	Mild	-	-	-	-	-	-	-	1
Small intestine, jejunum									
Bacterial colonies	Minimal	-	-	-	-	-	1*	-	-
Hyperplasia, mucosal	Minimal	-	-	-	-	-	1*	-	-
Inflammation, subacute/chronic	Minimal	-	-	-	-	-	1*	-	1
Atrophy, villus	Minimal	-	-	-	-	1	-	-	-
Small intestine, ileum									
Atrophy, villus	Moderate	-	-	-	-	-	1*	-	-
Hyperplasia, mucosal	Mild	-	-	-	-	-	1*	-	-

Dose (mg/kg)		0 mg/kg		5 mg/kg		15 mg/kg		50 mg/kg	
Sex		M	F	M	F	M	F	M	F
# animals (main, recovery)		4,2	4,2	4	4	4	4	4,2	4,2
Inflammation, subacute/chronic	Mild	-	-	-	-	-	1*	-	-
Small intestine, duodenum									
Infiltration, mononuclear cell	Minimal	-,2	4,2	1	3	-	2*	3,2	2,1
	Mild	-	-	1	-	1	-	-	-
Thymus									
Depletion, lymphoid, cortex	Minimal	1	1,1	-	-	-	3	-	1
	Mild	-	-	-	-	-	-	3	1
	Moderate	-	-	-	-	-	-	-	1
	Marked	-	-	-	-	1	1*	-	-
GALT									
Decreased lymphocytes, generalized	Minimal	-	-	-	-	1	-	-	1
	Mild	-	-	-	-	-	1*	-	-
Lymph node, mandibular									
Depletion, lymphoid, germinal center	Minimal	-	-	-	-	2	-	-	-
	Mild	-	-	-	-	1	-	-	-
	Moderate	-	-	-	-	-	1*	-	-
Erythrocytosis/erythrophagocytosis, sinus	Minimal	-	-	-	-	-	1*	-	-
Histiocytosis, sinus	Mild	-	-	-	-	-	1*	-	-
Hyperplasia, lymphoid follicular	Minimal	-	-	-	1	-	1	-	-
	Mild	-	1	-	1	-	-	-	1
Lymph node, mesenteric									
Hyperplasia, lymphoid, paracortex	Minimal	-	-	-	1	-	-	-	-
Leukocytosis, sinusoidal	Minimal	-	-	-	-	-	1*	-	-
Decreased germinal centers	Mild	-	-	-	-	-	1*	-	-
Adrenal gland									
Mineralization	Minimal	-	1	1	-	1	2*	-	2
	Mild	-	-	-	-	1	-	-	-
Hypertrophy, diffuse, cortical	Minimal	-	-	-	-	1*	-	-	-
	Mild	-	-	-	1	-	-	-	-
Epididymides									
Infiltration, mononuclear cell	Minimal	-	na	1	na	-	na	-	na
Mineralization	Minimal	-	na	-	na	1	na	-	na
Eyes									
Infiltration, mononuclear cell	Minimal	-	-	-	-	1	-	1	-
Heart									
Degeneration/necrosis, myofiber	Minimal	-	2	1	1	1	-	-	2
Nerve, sciatic									
Degeneration, axonal/myelin	Minimal	-	-	-	-	-	-	1	1
Seminal vesicles									
Infiltration, mononuclear cell	Minimal	-	-	-	-	-	-	1	-
Skin									
Ulcer	Minimal	-	-	-	-	1	-	-	-
Inflammation, subacute/chronic	Minimal	-	-	-	-	-	-	1	-
	Moderate	-	-	-	-	1	-	-	-
Spleen									

Dose (mg/kg)		0 mg/kg		5 mg/kg		15 mg/kg		50 mg/kg	
Sex		M	F	M	F	M	F	M	F
# animals (main, recovery)		4,2	4,2	4	4	4	4	4,2	4,2
Hyperplasia, focal lymphoid	Minimal	1	-	-	-	2	-	2	-
	Mild	-	-	-	-	1	-	-,1	-
Adhesion/inflammation/fibrosis, capsule	Minimal	-	-	-	-	-	1	-	-
Depletion, lymphoid, follicular	Moderate	-	-	-	-	-	1*	-	-
Stomach									
Degeneration/necrosis, myofiber	Minimal	-	-	-	-	-	-	-	1
Dilatation/inflammation, mucosal gland	Minimal	-	-	-	-	-	1	-	-
Testes									
Hypoplasia, fibrous	Mild	-	na	-	na	-	na	1	na
Bone marrow, sternum									
Decreased cellularity, hematopoietic	Minimal	-	-	-	1	-	-	-	-
	Mild	-	-	-	-	-	1*	-	-
Tongue									
Degeneration/regeneration, myofiber	Minimal	-	-	-	-	1	-	-	-
Trachea									
Metaplasia, squamous	Minimal	-	-	-	-	-	-	1	-
Brain									
Infiltration, mononuclear cell, perivascular	Minimal	-	-	-	2	-	-	-	1

'-' indicates no findings. *Includes findings in early death animal. na - not applicable.

5.5.2. Genetic Toxicology

The Applicant's Position:

Repotrectinib was evaluated in a battery of genotoxicity studies. Repotrectinib was negative for mutagenicity in the Ames assay. In the mammalian cell micronucleus assay in TK6 cells, repotrectinib was positive for the induction of micronuclei in both non-activated S9-activated test systems. Subsequent CREST staining indicated that repotrectinib induced micronuclei by an aneugenic mechanism of action. An aneugenic mechanism of action was further supported in two in vivo mammalian erythrocyte micronucleus assays conducted in rats that demonstrated a threshold for induction of micronuclei at > 100 mg/kg (nominal dose); this corresponded to exposures that were 4.1-fold higher for C_{max} and 4.3-fold higher for AUC than the anticipated human exposures at 160 mg BID.

Table 12. In Vitro Studies

Study Number	00270	00271
Study Title	Bacterial Reverse Mutation Assay	In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells
eCTD Location	4.2.3.3.1	4.2.3.3.1
Study Type	Reverse mutation assay	Clastogenicity and aneugenicity
Test System	Bacterial Ames Test: *S. typhimurium* TA98, TA100, TA1535, T A1537; *E. coli* WP2 *uvrA* Test articles: 15.0, 50.0, 150, 500, 1500, or 5000 µg repotrectinib per plate	Lymphocytic TK6 cells Test articles: 0.1-14 µg/mL repotrectinib
GLP Compliance	Yes	Yes
Test Validity	Yes	Yes
Evaluations	Reverse mutations in the presence or absence of S9 mix	Frequency of micronucleated cells in the presence or absence of S9 mix
Findings	Repotrectinib did not induce reverse mutations in any of the strains with or without S9 and was considered negative for mutagenicity.	Repotrectinib was positive for the induction of micronuclei with and without S9. Repotrectinib induced micronuclei by an aneugenic mechanism of action.

Table 13. In Vivo Studies

Study Number	00248	00388
Study Title	In Vivo Mammalian Erythrocyte Micronucleus Assay in Rats	TPX-0005: In Vivo Mammalian Erythrocyte Micronucleus Assay in Male Sprague-Dawley Rats
eCTD Location	4.2.3.3.2	4.2.3.3.2
Study Type	Clastogenicity	Clastogenicity
Test System	Rat Test articles: 0, 500, 1000, or 2000 mg/kg oral repotrectinib	Rat Test articles: 0, 20, 50, or 100 mg/kg oral repotrectinib
GLP Compliance	Yes	Yes
Test Validity	Yes	Yes
Evaluations	Incidence of induction of micronucleated polychromatic erythrocytes (PCEs) in bone marrow	Incidence of induction of micronucleated PCEs in bone marrow
Findings	Repotrectinib was positive for the induction of micronucleated PCEs at all doses tested.	Repotrectinib was negative for the induction of micronucleated PCEs at all doses tested.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusions that repotrectinib is genotoxic. In vitro, repotrectinib was negative for genotoxicity in the AMES assay and positive for genotoxicity in the micronucleus assay. In vivo, repotrectinib was positive for genotoxicity in male rats for micronucleated PCEs in bone marrow at doses ≥500 mg/kg. We do not consider safety exposures provided by the Applicant relevant as the drug is genotoxic. Additionally, it is unclear how these values were calculated as toxicokinetic data was not collected in Study

00248 and the toxicokinetic data collected in Study 00388 is invalid due to all dose groups failing the formulation analysis.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted nor are any planned with repotrectinib in accordance with ICH S9.

The FDA's Assessment:

The FDA agrees that carcinogenicity studies are not needed to support the use of repotrectinib for the currently proposed indication per ICH S9.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

No fertility, early embryonic, prenatal, or postnatal development studies have been conducted nor are any planned with repotrectinib in accordance with ICH S9. In a preliminary embryo-fetal development study, teratogenic effects (fetal external malformation of malrotated hindlimbs) were observed with repotrectinib at estimated maternal exposures approximately 3-fold higher than the clinical exposures. The effects of repotrectinib on juvenile rats was investigated in dose range-finding and definitive repeat-dose toxicology studies. Similar to adult rats, CNS and bone marrow findings were observed in juvenile rats; however, the CNS effects in juvenile rats were much more severe than what was observed in adult rats at similar exposures and resulted in acute mortality and early euthanasia. Systemic exposure to repotrectinib appeared to be age-dependent with terminal exposures (C_{max} and AUC) up to 80% lower than at Day 1 of dosing.

Table 14. Embryo Fetal Development Studies

Study 00397	
An Oral (Gavage) Dose Range-Finding Study of the Effects of TPX-0005 on Embryo/Fetal Development in Rats Module 4.2.3.5.2 Key findings: • Maternal effects included scabbing/abrasions in cervical and thoracic regions and increased body weight gain at 12 mg and 20 mg/kg • Fetal external malformation of malrotated hindlimbs was observed in 3 fetuses at the highest dose levels (12 mg and 20 mg/kg) • Decreased fetal body weights were observed at 12 mg and 20 mg/kg GLP compliance: No	
Methods	
Dose and frequency of dosing:	0, 2, 6, 12, or 20 mg/kg/day once daily from gestation Days 6-17
Route of administration:	Oral
Formulation/vehicle:	(b) (4) /1% Tween-80 in deionized water
Species/strain:	Rat/Sprague Dawley
Number/sex/group:	5F
Age:	8 to 10 weeks

Table 15. Juvenile Toxicity Studies (Study 00480)

A 4-Week Oral (Gavage) Dose Range-Finding Juvenile Toxicity Study of TPX-0005 in Sprague Dawley Rats, with a Toxicokinetic Phase Module 4.2.3.5.4 Key findings: • Lower mean body weight gains were observed at 3 mg/kg • Severe CNS toxicity was observed at 10 mg and 30 mg/kg, and animals were found dead or euthanized on PND 13-15. Clinical findings included ataxia, hypoactivity, labored respiration, decreased respiration rate, cool body or extremities, and/or splayed hindlimbs • Systemic exposure to TPX-0005 appeared to be age-dependent; PND 40 exposures (C_{max} and AUC) were approximately 65%-80% lower compared to PND 12 GLP compliance: No	
Methods	
Dose and frequency of dosing:	0.1, 0.3, 1, 3, 10, or 30 mg/kg/day once daily from postnatal day (PND) 12 to PND 40
Route of administration:	Oral
Formulation/vehicle:	(b) (4) /1% Tween-80 in deionized water
Species/strain:	Rat/Sprague Dawley
Number/sex/group:	10
Toxicokinetics:	30/sex

Table 16. Applicant Table

Study 00481
An Oral (Gavage) Juvenile Toxicity Study of TPX-0005 in Sprague Dawley Rats, with a Recovery and a Toxicokinetic Phase

Study 00481

Module 4.2.3.5.4
Key findings:

- Decreased body weight, food consumption, and femur length as well as increased platelet counts were observed at the high dose of 3 mg/kg
- Body weight at the age of attainment of vaginal patency was lower and statistically significant at 1 mg and 3 mg/kg
- There were no test article-related effects on the age or body weight at attainment of balanopreputial separation or age at attainment of vaginal patency nor any effects on auditory startle responsiveness, motor activity, and learning and memory (Biel maze) up to the highest dose of 3 mg/kg
- Systemic exposure to TPX-0005 appeared to be age-dependent; PND 70 exposures (C_{max} and AUC) were approximately up to 60% lower compared to PND 12

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0.3, 1, or 3 mg/kg/day once daily from postnatal days (PND) 12 to PND 70
Route of administration:	Oral
Formulation/vehicle:	(b) (4) /1% Tween-80 in deionized water
Species/strain:	Rat/Sprague Dawley
Number/sex/group:	20
Toxicokinetics:	30/sex

Toxicokinetic Data

Sex	Male			Female		
Daily Dose (mg/kg)	0.3	1	3	0.3	1	3
C_{max} (ng/mL)						
PND12	9.74	79.3	310	13.2	89.0	366
PND70	7.40	31.8	113	60.0	33.3	174
AUC_{tlast} (ng·h/mL)						
PND12	119	622	2300	132	698	2080
PND70	58.7	290	880	154	310	1260

*Abbreviations: AUC = plasma concentration-time curve; AUC_{last} = area under the plasma concentration-time curve from time 0 to time of last measurable concentration; C_{max} = maximum plasma concentration; GLP = good laboratory practice; PND = postnatal. *p < 0.05; **p < 0.01*

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion. The pregnancy index was 100 at all dose levels and in the control group and all pregnancies at all dose levels contained 100% viable fetuses. Repotrectinib had no statistically significant effect on litter size. At 20 mg/kg/day, the number of late resorptions was significantly higher than controls (0.6 vs.0, respectively; p<0.05) and post implantation loss increased with an increase in dose but without statistical significance. Repotrectinib at doses ≥6 mg/kg/day led to skin toxicity consisting of thoracic and/or cervical scabbing in treated pregnant dams (Table 17). Repotrectinib given to pregnant

rats at doses ≥12 mg/kg/day caused embryofetal toxicity in the form of malformations and at a dose of 20 mg/kg/day caused decreased fetal body weight greater than 10% (Table 18). The Applicant states that the findings occurred at estimated maternal exposures approximately 3-fold higher than the clinical exposures; however, no toxicokinetic data was collected in the embryofetal development study (Study 00397) to use for comparison to clinical exposure in patients. Based on body surface area doses that caused embryofetal toxicity were 0.3 times that of the intended clinical dose of 160 mg BID.

Table 17. Maternal Findings in Dams Treated With Repotrectinib on GDs 6-17 (Study 00397)

Dose (mg/kg/day)	0	2	6	12	20
Number of females on study	5	5	5	5	5
Number with scabbing; thoracic/cervical region	0	0	3	2	3
Pregnancy index	100	100	100	100	100
Females with viable fetuses at GD21	5	5	5	5	5
Liter size	11.4	12.8	11.6	12.4	10
Number of viable fetuses	11.4	12.8	11.6	12.4	10
Number on non-viable fetuses	0	0	0	0	0
Number of early + late resorptions	0.2	0.6	1.0	0.8	1.4
Number of early resorptions	0.2	0.4	1	0.8	0.8
Number of late resorptions	0	0	0.2	0	0.6*
Post implantation loss (%)	2	4.5	6.9	5.8	11.4

*p<0.05

Table 18. Embryofetal Findings After Treatment of Pregnant Dams With Repotrectinib on GDs 6-17 (Study 00397)

Dose (mg/kg/day)		0	2	6	12	20
Body Weights*						
Fetal weights (Males)		-	-4%	-5%	-6%	-11%
Fetal weights (Females)		-	-6%	-6%	-7%	-13%
External Malformations						
Number of litters examined		5	5	5	5	5
Number of fetuses examined		57	64	55	62	50
Hind limbs- Entire, malrotated-malformation	Number of fetuses (%total fetuses)	0	0	0	2 (3.2)	1 (2)
	Number of liters (%total liters)	0	0	0	2 (40)	1 (20)

*Body weight values are percent change compared to control values.

The FDA generally agrees with the Applicant's conclusion for juvenile toxicology, with additional pertinent details below. In the dose-range finding study (Study 00480), treatment of juvenile rats from postnatal day (PND) 12 to 40 with oral once daily repotrectinib doses of 0.1, 0.3, 1, 3, 10, or 30 mg/kg/day led to 30% and 45% death at 10 and 30 mg/kg/day, respectively between PND 13-15. Severe CNS toxicity, including ataxia, hypoactivity, labored respiration, decreased respiration rate, cool body/extremities, and splayed hindlimbs, was observed in early decedents leading to early euthanasia or animals found dead. All surviving animals in the 10 and 30 mg/kg/day dose groups were euthanized on PND13 or 14. Juveniles dosed with 3 mg/kg/day showed significantly less body weight gain compared to controls throughout the study (up to 13% less weight gain vs. controls). No body weight data was available for the 10 and 30 mg/kg/day groups. There were no macroscopic pathology or organ weight changes at the up to 3 mg/kg/day; the 10 and 30 mg/kg/day groups were not necropsied. No microscopic observations were conducted.

In the definitive juvenile toxicology study (Study 00481), juvenile rats were dosed once daily with repotrectinib at 0.3, 1, or 3 mg/kg from PND12-70. No CNS findings occurred at these dose levels. Mean body weights were up 7 and 12% lower in males and females treated with 1 and 3 mg/kg/day, respectively, compared to controls by the end of the dosing period and continued to be lower during the recovery period (up to 10 and 16%, respectively). Both groups also had decreased mean food consumption during the dosing and recovery periods compared to controls. Hematology findings were limited to reversible increased platelets in the 3 mg/kg/day group for males and females (21 and 26%, respectively, vs. controls on Day 71). Repotrectinib at 3 mg/kg/day led to significantly decreased femur lengths (Table 19). No additional microscopic changes were noted. Toxicokinetic analyses showed exposure was up to 60% lower on PND70 compared to PND12 in both males and females (Table 20).

Table 19. Femur Length in Juvenile Rats Treated Daily With Oral Repotrectinib

Sex	Males				Females			
Dose mg/kg/day	**0**	**0.3**	**1**	**3**	**0**	**0.3**	**1**	**3**
Dosing Phase								
Femur length (mm)	37.21	36.95	36.88	35.96*	33.74	33.45	33.43	35.52*
Recovery Phase								
Femur length (mm)	40.23	39.63	39.7	38.81*	35.24	35.29	34.49	34.42

*p<0.01

Table 20. Toxicokinetic Data in Juvenile Rats Treated Orally Once Daily With Repotrectinib on PND 12-70

Dose mg/kg/day	AUC_{0-24} ng*hr/mL		C_{max} ng/mL	
	PND12	**PND70**	**PND12**	**PND70**
Males				
0.3	119	58.7	9.74	7.4
1	622	290	79.3	31.8

3	2300	880	310	113
Females				
0.3	132	154	13.2	60
1	698	310	89	33.3
3	2080	1260	366	174

5.5.5. Other Toxicology Studies

The Applicant's Position:

Repotrectinib was not phototoxic in an in vivo rat study in Long-Evans pigmented rats up to and including the limit dose of 1000 mg/kg for three consecutive days followed by a single exposure to UVR approximately 4 hours postdose.

Table 21. Applicant Table

Study Number	00240
Study Title	A Multiple Dose Phototoxicity Study to Determine the Effects of Oral Gavage Administration of TPX-0005 on Eyes and Skin in Pigmented Rats
eCTD Location	4.2.3.7.7
Study Type	Phototoxicity
Test System	Female Long-Evans rats
GLP Compliance	Yes
Key Findings • No test article-related clinical observations or body weight changes were observed • No skin reactions in the pigmented or non-pigmented sites or ophthalmic observations	

The FDA's Assessment:

The FDA agrees with the Applicant's conclusion.

X _____ X _____

Primary Reviewer: Stephanie L. Aungst, PhD Supervisor: Claudia P. Miller, PhD

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and the

tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC. The Applicant is seeking approval of repotrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC). The Applicant's proposed dosing regimen is 160 mg orally once daily for 14 days, followed by an increase to 160 mg twice daily, with or without food.

The Clinical Pharmacology key review questions focused on the appropriateness of the proposed recommended dosing regimen for the general patient population, and on determination of the drug-drug interaction potential for repotrectinib as a victim and a perpetrator.

Based on the FDA review, the proposed recommended dosing regimen of 160 mg QD for 14 days followed by an increase to 160 mg BID is acceptable with a favorable benefit:risk profile. Specifically, there were positive trends for ORR and OS with repotrectinib exposures in patients who were both TKI naïve and TKI pretreated. The proposed recommended dosage was also supported by statistically significant relationships that were identified for steady state repotrectinib exposures, i.e., $C_{max,ss}$ and/or $C_{avg,ss}$, and multiple safety endpoints including dizziness (Grade 2 and above).

The current submission included inadequate clinical drug interaction study data and insufficient PBPK based modeling data to adequately evaluate the drug interaction potential for repotrectinib as a victim or a perpetrator. As a result, FDA issued two PMRs and two PMCs to evaluate the effects of specific strong and moderate CYP3A4 inhibitor and inducer, specific P-gp inhibitor, and dual moderate CYP3A4 and P-gp inhibitor on repotrectinib exposure, and the effect of repotrectinib on exposures of substrates of CYP2B6, 2C8, 2C9, and 2C19, and the effect of repotrectinib on exposures of substrates of MATE2-K, P-gp, OATP1B1, and BCRP, respectively.

In addition, the current submission did not address the potential impact of moderate and severe hepatic impairment. As a result, FDA issued one PMR to evaluate the effect of moderate and severe hepatic impairment on repotrectinib exposure and adverse reactions.

6.1.1. Recommendations

This NDA is approvable from a clinical pharmacology perspective, provided the Applicant and the FDA reach an agreement regarding the labeling language. The key review issues with specific recommendations/comments are summarized below.

Table 22. Key Clinical Pharmacology Review Issues by FDA

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	An ongoing Phase 1/2, multicenter, open-label, dose-escalation and expansion study (TRIDENT-1), pooled efficacy and safety data from the Phase 1 and Phase 2 portions in patients with ROS1-positive NSCLC: pooled EXP-1 for TKI-naiive patients and pooled EXP-4 for patients received 1 prior ROS1+ TKI therapy and no prior chemotherapy or immunotherapy.
General Dosing instructions	The recommended dosage of repotrectinib is 160 mg once daily (QD) for 14 days, followed by an increase to 160 mg twice daily (BID), without regard to food.
Dosing in patient subgroups (intrinsic factors)	• No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST). The recommended dosage for use in patients with moderate (total bilirubin >1.5 to 3 times ULN and any AST) or severe (total bilirubin > 3 times ULN with any AST) hepatic impairment has not been established. • No dose adjustment is recommended for patients with mild to moderate renal impairment (Creatine Clearance [CLcr] 30 to < 90 mL/min, as estimated by Cockcroft-Gault). The recommended dosage of olutasidenib has not been established in patients with severe renal impairment (CLcr 15 to 29 mL/min as estimated by Cockcroft-Gault), kidney failure (CLcr <15 mL/min, as estimated by Cockcroft-Gault), and patients on dialysis. • No dose adjustment is recommended based on age, sex, or body weight.
Drug-drug interactions	• Avoid concomitant use with strong or moderate CYP3A4 inhibitors or inducers, P-gp inhibitors. • Avoid concomitant use with certain CYP3A sensitive substrates. If unavoidable, (b) (4)
QTc Assessment	• Analysis of ECG data was conducted from 398 patients in TRIDENT01 study, who received repotrectinib at dosages ranging from 40 mg to 240 mg once daily or twice daily under fasted or fed conditions. Results showed that repotrectinib does not cause a large mean increase in the QTc interval < 20 ms at the recommended dosage of 160 mg QD followed by 160 mg BID, with or without food.

Bridge between the to-be-marketed and clinical trial formulations	• The to-be-marketed formulation, i.e., 40 mg capsule, was used for relevant clinical pharmacology studies and for pivotal cohort in the target patient population.

6.1.2. Post-Marketing Requirements and Commitments

The rationale and descriptions of post-marketing requirements (PMR) and commitments (PMC) are summarized in the table below. The PMRs and PMCs are issued to address the hepatic impairment and drug interaction potential for repotrectinib as a victim and as a perpetrator.

Table 23. Summary of Post-Marketing Requirements and Commitments

Post-Marketing Requirement-1	
PMR Rationale	The result of the mass balance evaluation shows that 89% of the total radioactivity recovered was found in the feces, indicating that hepatic elimination is the major elimination pathway. The risk of hepatic impairment to increase repotrectinib plasma exposure, leading to increased adverse reactions, has not been ruled out and additional data is needed to determine the appropriate dosage of repotrectinib in patients with moderate and severe hepatic impairment.
PMR Description	Conduct a clinical pharmacokinetic trial in non-cancer hepatically impaired subjects to evaluate the effect of moderate and severe hepatic impairment on the single dose pharmacokinetics and safety of repotrectinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling." In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trial, to evaluate the effect of hepatic impairment on multiple dose pharmacokinetics of repotrectinib to determine an appropriate dosage of repotrectinib and to identify and assess the potential serious risk of increased drug toxicity in patients with moderate and severe hepatic impairment. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled "Physiologically Based Pharmacokinetic Analyses - Format and Content."
Post-Marketing Requirement-2	
PMR Rationale	Repotrectinib is primarily metabolized by CYP3A4 and a P-gp substrate in vitro. In the single dose study in healthy subjects, repotrectinib drug exposure (AUC) increased by 5.9-fold when coadministered with a strong CYP3A and P-gp

	inhibitor (itraconazole). The risk of concomitant use of a specific strong CYP3A or moderate CYP3A inhibitor, P-gp inhibitor, or a dual P-gp and moderate CYP3A inhibitor to increase repotrectinib plasma exposure, leading to increased adverse reactions, has not been ruled out.
PMR Description	Conduct a clinical pharmacokinetic trial to evaluate the effects of multiple doses of a specific strong CYP3A inhibitor and a specific P-gp inhibitor, respectively on the single-dose pharmacokinetics and safety of repotrectinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions." In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trial, to evaluate the effects of a specific strong CYP3A inhibitor, a specific moderate CYP3A inhibitor, a specific P-gp inhibitor, and a dual P-gp and moderate CYP3A inhibitor, respectively on the multiple-dose pharmacokinetics of repotrectinib to address the potential for increased drug toxicity with appropriate dosage recommendations of repotrectinib when concomitantly used with these inhibitors. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."
Post-Marketing Requirement-3	
PMR Rationale	In vitro studies revealed that repotrectinib is an inhibitor of MATE2-K, P-gp, OATP1B1, and BCRP. The risk of concomitant use of repotrectinib to increase plasma exposure of MATE2-K, P-gp, OATP1B1, and BCRP substrates, leading to increased adverse reactions, has not been ruled out.
PMR Description	Conduct a clinical pharmacokinetic trial to evaluate the effect of multiple doses of repotrectinib on the single dose pharmacokinetics of a substrate of MATE2-K, P-gp, OATP1B1, and BCRP, respectively to address the potential for increased drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions".
Post-Marketing Commitment-1	
PMC Rationale	Repotrectinib is primarily metabolized by CYP3A4 and a P-gp substrate in vitro. In the single dose study in healthy subjects, repotrectinib drug exposure (AUC) decreased by 92% when coadministered with a strong CYP3A and P-gp inducer (rifampin). The risk of concomitant use of a moderate CYP3A inducer to decrease repotrectinib plasma exposure, leading to reduced efficacy, has not been ruled out.

PMC Description	Conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trials with specific CYP3A and P-gp inhibitors, to evaluate the effect of multiple doses of a moderate CYP3A inducer on the multiple-dose pharmacokinetics of repotrectinib to assess the magnitude of decreased drug exposure with appropriate dosage recommendations of repotrectinib when concomitantly used with moderate CYP3A inducers. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."
Post-Marketing Commitment-2	
PMC Rationale	In vitro studies revealed that repotrectinib is an inducer of CYP2B6, CYP2C8, CYP2C9, and CYP2C19. The risk of concomitant use of repotrectinib to decrease plasma exposure of CYP substrates has not been ruled out.
PMC Description	Conduct a clinical pharmacokinetic trial with repeat doses of repotrectinib on the single dose pharmacokinetics of a substrate of CYP2B6, CYP2C9, and CYP2C19, respectively to assess the magnitude of decreased drug exposure. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions". In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study to predict impact of repotrectinib on the magnitude of decreased drug exposure of CYP2C8 substrates. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Repotrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and the 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 has demonstrated a dose-dependent suppression of phosphorylation of the targeted oncogenic fusion proteins, their downstream signal effectors, and inhibition of cell proliferation of several human cancer cell lines expressing the targeted fusion oncogenes ROS1,

TRKA, TRKB, TRKC, and corresponding mutations. Repotrectinib binds inside the boundary of the ATP-binding pocket and avoids steric interference from both solvent front and gatekeeper mutations.

Repotrectinib inhibits ROS1 and ROS1^{G2032R} with biochemical IC_{50} values of 0.07 and 0.46 nM, respectively, and 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 CD74–ROS1, LMNA–TRKA, TEL–TRKB, TEL–TRKC or corresponding solvent-front substitutions (ROS1G2032R, ROS1D2033N, TRKA^{G595R}, TRKB^{G639R}, TRKC^{G623R}, TRKC^{G623E}) with IC_{50} values ranging from < 0.2 to 8.4 nM.

In cancer patients, following administration of repotrectinib 160 mg single dose under modified fasted conditions (no food and beverage 1 hour before and 2 hours after dosing), the geometric mean (%CV) of C_{max} and AUC_{inf} were 714 ng/mL (46.7%) and 10000 ng·h/mL (45.5%), respectively. Following single-dose administration of repotrectinib at dose range 40 mg to 240 mg, the increases in C_{max} and AUC_{last} were approximately dose proportional. Following administration of repotrectinib 160 mg QD under modified fasted conditions, the steady state geometric mean (CV%) of C_{max} and AUC_{0-24} were 433 ng/mL (51.1%) and 4500 ng·h/mL (72.7%), respectively.

Following administration of repotrectinib 160 mg QD under fed condition, the steady state geometric mean (CV%) of C_{max} and AUC_{0-24} were 747 ng/mL (18.7%) and 6150 ng·h/mL (24.6%), respectively. For subjects who were able to titrate to 160 mg BID regimen, the steady state geometric mean (CV%) of C_{max} and AUC_{0-24} were 713 ng/mL (32.5%) and 7210 ng·h/mL (40.1%), respectively.

Absorption

The median (minimum, maximum) repotrectinib T_{max} was 3.0 hours (1.0 to 7.8 hours) following a single oral 160 mg dose and 2.0 hours (1.4 to 4.0 hours) following 160 mg twice a day oral dose at steady state under modified fasted conditions. The mean (CV%) absolute bioavailability of repotrectinib is 45.7% (19.6%).

Distribution

Repotrectinib was 95.4% bound to human plasma proteins. The blood to plasma ratio was 0.56, in vitro. The mean (CV%) steady state Vd_{ss} was 264 L (22.3%) following a single intravenous dose.

Elimination

Following an IV administration in healthy subjects, repotrectinib exhibited low CL with a mean (CV%) of 7.04 L/h (14.0%) which is comparable with that estimated based on the population PK model of 7.06 L/h. Based on the population PK analysis, the single dose terminal $t_{1/2}$ was estimated to be 55.5 hours for healthy subjects and 50.6 hours for cancer patients, and the steady-state terminal $t_{1/2}$ was estimated to be 41.2 hours for healthy subjects and 35.4 hours for cancer patients.

Metabolism

Repotrectinib is primarily metabolized by CYP3A4 to form oxidative metabolites followed by secondary glucuronidation. No metabolite exceeded 10% of total circulating drug-related radioactivity. There were no major/disproportionate or unique human metabolites.

Excretion

Following the administration of a single oral 160 mg dose of radiolabeled repotrectinib, the mean recovery was 93.7%. Fecal excretion was the predominant route of elimination, with a mean of 88.8% (50.6% as unchanged) of the dose recovered in feces. On average, 4.84% (0.56% as unchanged) of dose was recovered in the urine.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the clinical pharmacology program supports the use of repotrectinib for the treatment of ROS1-positive NSCLC.

The clinical pharmacology program in the current NDA submission includes the following assessments supported by a total of seven clinical trials with six trials in healthy subjects and one trial in patients with cancer:

Dose selection/dose confirmation:

- TPX-0005-01: a Phase 1/2, first-in-human, single arm study of repotrectinib in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1, pivotal trial)

Mass balance, absolute bioavailability:

- TPX-0005-09: a single dose, nonrandomized, 2-part, fixed sequence crossover study to evaluate the absolute bioavailability of oral repotrectinib to-be-marketed formulation and IV ^{14}C]repotrectinib (Part 1) and the excretion and mass balance, PK, and metabolism of [^{14}C]repotrectinib (Part 2) in healthy male subjects

Drug interaction:

- TPX-0005-10: a two-part, fixed-sequence study of multiple dose itraconazole and rifampin on the PK of single dose repotrectinib (to-be-marketed capsule formulation) in healthy male subjects;
- TPX-0005-01 Phase 1 substudy: a single arm study of multiple dose repotrectinib (to-be-marketed capsule formulation) on the PK of single dose midazolam in patients with cancer;

Food effect, relative BA/BE:

- TPX-0005-08: a single dose, randomized, 2-way crossover PK and relative bioavailability study of (b) (4) capsule formulation versus suspension formulation in healthy male subjects;
- TPX-0005-11: a single dose, 2-way crossover food effect study of to-be-marketed capsule formulation in healthy male subjects;

- TPX-0005-12: a single dose, randomized, 3-way crossover PK and relative bioavailability study of to-be-marketed capsule formulation versus (b) (4) tablet formulations in healthy male subjects;
- TPX-0005-14: a single dose, randomized, 3-way crossover bioequivalence and food effect study of to-be-marketed capsule formulation versus (b) (4) capsule formulation in healthy male subjects;

See FDA assessment of hepatic impairment and drug-drug interaction potential in Section 6.2.2.2. More details are in Sections 6.3.2.3 and 6.3.2.4 respectively.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The repotrectinib proposed dosing regimen is 160 mg orally QD for 14 days, then increase to 160 mg BID with or without food until disease progression or unacceptable toxicity. 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 and with the potential to titrate up to 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 at Day 15 approximately one half of 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.

The clinical results of TRIDENT-1 Phase 2 study as well as the accompanying exposure-response (E-R) analysis further support the 160 mg QD/BID dosing regimen in the target population.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the proposed dosage of repotrectinib 160 mg QD for 14 days then increase to 160 mg BID, is supported by a favorable efficacy-safety profile in TRIDENT-1 Phase 2, as well as additional PK information in the indicated patient population.

(1) Efficacy:

The efficacy of repotrectinib at the proposed dosage was established in a total of 127 pooled patients with ROS1-positive NSCLC in TRIDENT-1 Phase 1 and 2, with regard to the primary efficacy endpoint of confirmed ORR:

- In the pooled EXP-1 cohort in patients who were TKI-naïve (N=71), the confirmed ORR was 79%, including 4 CR and 52 PR. The median time to response (TTR) was 1.8 months,

duration of response (DOR) was 27.4 months, lesion reduction rate was 100%.

- In the pooled EXP-4 cohort in patients who received 1 prior TKI treatment therapy but no chemo- or immunotherapy, the confirmed ORR was 38%, including 3 CR and 18 PR. Specifically, the cORR was 39% in 46 patients who received prior treatment of crizotinib and 22% in 9 patients who received prior treatment of entrectinib, respectively. The median time to response (TTR) was 1.8 months, duration of response (DOR) was 17.8 months, lesion reduction rate was 88%.
- Exposure-response analysis showed that in both TKI-naïve and TKI-pretreated patients in the pooled EXP-1 and pooled EXP-4 cohorts, there were positive trends observed for ORR and OS with repotrectinib exposures ($C_{avg,ss}$ and $C_{max,ss}$), respectively. However, the exposure-response analysis was limited as the majority of the data were from only one dose level, i.e., the proposed dosage, and the results should be interpreted with caution. See Appendix 19.4.3.1 for details.
- Additional exposure-response modeling and simulation as conducted and revealed a maximal ORR at around the exposure achieved at the dosage of 160 mg BID.

(2) Safety:

The overall safety in the 264 patients with ROS1-positive NSCLC treated at the proposed dosage also revealed a generally manageable profile:

- A total of 48% (128/254) patients had TEAEs leading to dose interruption, 35% (93/254) had TEAEs leading to dose reduction, and 8.3% (22/264) had TEAEs leading to dose discontinuation. The relative dose intensity was greater than 75%.
- The most common adverse reactions (≥20%) reported were dizziness, dysgeusia, paresthesia, constipation, ataxia, dyspnea, cognitive disorders, fatigue, and nausea. The CNS toxicity, e.g., dizziness, was considered a class effect for ROS1 and NTRK inhibitors. In general, the TEAEs resolved or improved with standard of care symptomatic measures, dose modifications or drug discontinuations.
- Exposure-response analysis identified a statistically significant relationship between repotrectinib exposure (either C_{max}, C_{avg}, or both) for 11 out of the 15 safety endpoints evaluated (grade ≥ 2 dizziness, headache, muscular weakness, ataxia, AST increased, ALT increased, paresthesia, anemia, constipation, dysgeusia, and dizziness). Particularly, repotrectinib C_{max} was significantly associated with an increased probability of grade ≥ 2 dizziness. See Appendix 19.4.3.3 for details.
- E-R modeling and simulation also predicted a comparable incidence rate of Grade 2 and greater dizziness around the exposure achieved at the dosage of 160 mg BID (17%) versus that following 160 mg QD dosage (14%).

In addition, a dose-response relationship for dizziness was noted in the Phase 1 dose escalation portion at repotrectinib doses ranging from 40 mg to 240 mg QD, and 160 mg to 200 mg BID under fasted condition (Phase 1a). Although the MTD was not met in Phase 1 under fasted or fed conditions, 3 DLTs were reported with 2 as Grade 3 dizziness (160 mg BID and 240 mg QD, 1 each) and dosages higher than 160 mg BID were not recommended based on the safety profile

observed in Phase 1.

(3) PK:

Repotrectinib has time dependent PK with auto-induction of CYP3A4. At the steady state, (e.g., on Day 15 following once daily dose), the drug exposure was approximately half of single dose exposure. As such, FDA agrees with the Applicant that up-titration from QD to BID schedule on Day 15 could maintain the drug exposure initially reduced due to auto-induction. Of note, the median TTR for both TKI-naïve and TKI-pretreated patients was 1.5 months in the currently indicated patient population from the TRIDENT-1 study.

(4) Food Effect:

The food effect study in TRIDENT-1 Phase 1b revealed a moderate food effect when taking repotrectinib with a standard high fat meal compared to taking it under modified fasted condition. Taking repotrectinib without regard to food in Phase 2 compared to Phase 1a (fasted condition) showed an overall comparable safety profile. As a result, taking repotrectinib without regard to food is acceptable given lack of a clinically meaningful difference compared to taking it under fasted condition. See Section 6.3.2.4 for detailed assessment.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No dose adjustment is required based on age, race, or sex, in patients with mild and moderate renal impairment or those with mild hepatic impairment. Repotrectinib has not been evaluated in patients with severe renal impairment or patients with moderate or severe hepatic impairment. A dedicated study is ongoing in moderate to severe hepatic impairment. Since renal excretion is a minor elimination pathway (4.84% of administered drug), a dedicated renal impairment study is not planned.

Coadministration of repotrectinib with moderate or strong CYP3A4 inhibitors, strong CYP3A4 inducers, sensitive CYP3A4 substrates or sensitive CYP2B6 substrates should be avoided. Recommendations made in the proposed labelling are considered adequate and sufficient to warrant correct use of repotrectinib with other concomitant medications.

The FDA's Assessment:

1. **Dosage recommendation for intrinsic factors:**

FDA agrees that no dosage adjustment is required based on age, race, or sex, in patients with mild and moderate renal impairment or those with mild hepatic impairment. For the lack of assessment in patients with moderate or severe hepatic impairment, a post-marketing requirement (PMR) will be issued for the study of the impact of hepatic impairment on the PK of repotrectinib and potential increased toxicity.

2. Concomitant medication Instruction

(1) Repotrectinib as a victim:

(b) (4)

Given that repotrectinib is a P-gp substrate and primarily metabolized by CYP3A4 in vitro, and the drug-interaction study with a strong CYP3A4 and P-gp inhibitor (itraconazole) substantially increased repotrectinib AUC by 5.9-fold, the potential impact of a P-gp inhibitor or moderate CYP3A inhibitor on the PK of repotrectinib could not be ruled out. Therefore, FDA recommends that concomitant use of both strong and moderate CYP3A inhibitors and P-gp inhibitors should be avoided for concomitant medication with repotrectinib. Post-marketing studies should be conducted to adequately address the in vivo potential of specific P-gp, strong and moderate CYP3A inhibitor and dual P-gp and moderate CYP3A inhibitor, respectively on PK of repotrectinib and inform the dosage recommendations for concomitant use.

Similarly, given that the drug-interaction study with a strong CYP3A4 and P-gp inducer (rifampin) substantially decreased repotrectinib AUC by 92%, the potential impact of a moderate CYP3A inducer on the PK of repotrectinib could not be ruled out. Therefore, FDA recommends that both strong and moderate CYP3A inducers should be avoided for concomitant medication with repotrectinib. Post-marketing studies should be conducted to adequately address the in vivo potential of a specific moderate CYP3A inducer on the PK of repotrectinib and inform the dosage recommendations for concomitant use medications.

(2) Repotrectinib as a perpetrator:

FDA agrees with the Applicant's recommendation to avoid co-administration with sensitive CYP3A substrates, given the potential induction effect of repotrectinib based on the drug-interaction study.

(b) (4) The assessment of repotrectinib induction potential on CYP2B6 substrates was conducted based on physiologically-based PK (PBPK) modeling. However, the PBPK model could not adequately evaluate the potential effect of repotrectinib on CYP2B6 substrates, given that the (b) (4) model, has not been adequately validated. As a result, there is lack of adequate information to support (b) (4) Additionally, PBPK modeling analysis suggest that the potential interaction of repotrectinib with CYP2C8, 2C9, and 2C19 substrates could not be ruled out. A post-marketing study should be conducted to adequately address the in vivo potential of repotrectinib on the PK of CYP2B6, 2C8, 2C9, and 2C19 substrates.

6.2.2.3. Outstanding Issues

The Applicant's Position:

None.

The FDA's Assessment:

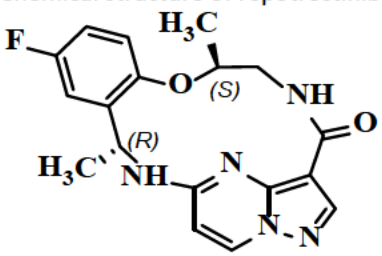
FDA determined that there are outstanding issues related to the adequacy of DDI assessment (Section 6.3.2.4) and hepatic impairment assessment (Section 6.3.2.3). Four PMRs and two PMCs to address hepatic impairment and the DDI potential of repotrectinib with specific strong and moderate CYP3A inhibitors, specific P-gp inhibitors, dual P-gp and moderate CYP3A inhibitors, moderate CYP3A inducers, substrates of CYP2B6, 2C8, 2C9, 2C19, and substrates of MATE2-K, P-gp, OATP1B1, and BCRP.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A general overview of repotrectinib ADME and clinical PK information are presented in the table below.

Table 24. Applicant Table

Physiochemical Properties		
Chemical Structure and Molecular Weight	Chemical structure of repotrectinib:  Molecular weight: 355.37 g/mol LogP: 3.49	
Aqueous Solubility	Repotrectinib is a neutral compound and exhibits pH-independent aqueous solubility of 0.006 mg/mL to 0.008 mg/mL across the physiological pH-range, which is practically insoluble. The solubility of repotrectinib in biorelevant media at 37° C were 0.102 mg/mL in fed state simulated intestinal fluid (FeSSIF) at pH 5.0, and 0.017 mg/mL in fasted state simulated intestinal fluid (FaSSIF) at pH 6.5.	
	Solvent	**Solubility (mg/mL)**
	N,N-Dimethylformamide	95.3
	Ethanol	11.1
	Methanol	15.0
	Tetrahydrofuran	8.13
	Isopropyl alcohol	5.95
	1,4-Dioxane	2.81
	Dichloromethane	4.41
	Acetonitrile	1.59
	Ethyl acetate	1.09
	Methyl tert-butyl ether	0.062

	Water	0.004
	Source: Module 3 Table 3.2.S.3.1.2-1	
Pharmacology		
Mechanism of Action	Repotrectinib is an oral ATP-competitive small molecule inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and the TRK, TRKA, TRKB, and TRKC (encoded by the NTRK genes NTRK1, NTRK2, and NTRK3, respectively). Repotrectinib has demonstrated a dose-dependent suppression of phosphorylation of the targeted oncogenic fusion proteins, their downstream signal effectors and inhibition of cell proliferation of many human cancer cell lines expressing the targeted fusion oncogenes as it binds inside the boundary of the ATP-binding pocket and avoids steric interference from both solvent front and gatekeeper mutations. Repotrectinib inhibits ROS1 and ROS1^{G2032R} with biochemical IC_{50} values of 0.07 and 0.46 nM, respectively and inhibits TRKA/B/C with biochemical IC_{50} values of 0.83, 0.05 and 0.10 nM, respectively.	
Active Moieties	Repotrectinib	
QT/QTc Prolongation	Dedicated cardiac safety and concentration – QTc analyses were conducted based on data from 398 subjects in Phase 1a, Phase 1c and Phase 2 of TRIDENT 1 study. Repotrectinib had no clinically significant effects on heart rate, PR interval, or QRS duration in either Phase 1 or Phase 2 of the study. Repotrectinib had no clinically significant effects on QT interval corrected for heart rate (QTc) based on the results of the primary concentration-QTc analysis as well as the by-time point, time averaged, and categorical outlier analyses. A linear mixed-effect model was used to evaluate the relationship between repotrectinib plasma concentration and ΔQTcF (change-from-baseline in QTcF) based on the ECG data from Phase 1a, 1c and 2 of the TRIDENT 1 study. The individual and pooled analyses all resulted in negative slopes for the relationship between repotrectinib and QTcF, with model predicted QTc increase predicted to be below 10 msec for the highest exposures reached in all cohorts of each the study. The largest predicted ΔQTcF effects in the 2 highest dose groups with food in pooled analysis were 4.8 msec (90% CI: 3.9 to 5.7) and 3.6 msec (90% CI: 2.7 to 4.5) for the 160 mg QD/BID dosing regimen used in the Phase 2 portion of the study and the 160 mg QD (fed) group in Phase 1c. Based on the predicted ΔQTcF at the geometric mean peak repotrectinib concentration, an effect on ΔQTcF exceeding 20 msec can be excluded within the full observed range of plasma concentrations of repotrectinib up to ~3750 ng/mL (> 5-fold of observed steady state mean C_{max} of 747 ng/mL at 160 mg QD).	
General Information		
Bioanalysis	In the pivotal study TPX-0005-01 (TRIDENT-1), plasma repotrectinib concentrations were measured using validated LC-MS/MS methods.	
Healthy Volunteers vs. Patients	PK Exposures in healthy subjects and subjects with advanced solid tumors were similar based on population PK analysis.	
Drug exposure at steady state-following the therapeutic dosing regimen	Following administration of repotrectinib 160 mg QD (Phase 1a dose escalation) under modified fasted conditions (no food and beverage 1 hour before and 2 hours after dosing), the steady state- geometric mean (CV%) of C_{max} and AUC_{0-24} were 433 (51.1%) ng/mL and 4500 ng·h/mL (72.7%), respectively. Following administration of repotrectinib 160 mg QD under fed condition (Phase 1c dose escalation), the steady state- geometric mean (CV%) of C_{max} and AUC_{0-24} were 747 (18.7%) ng/mL and 6150 ng·h/mL (24.6%), respectively. For subjects who were able to titrate to	

<table>
<tr><td></td><td>160 mg BID, the steady state geometric mean (CV%) of C_{max} and AUC_{0-24} were 713 ng/mL (32.5%) and 7210 ng·h/mL (40.1%), respectively.</td></tr>
<tr><td>Minimal effective dose or exposure</td><td>Not determined.</td></tr>
<tr><td>Maximal tolerated dose or exposure</td><td>In the TRIDENT-1 study, patients with advanced solid tumors were treated with repotrectinib up to doses of 240 mg QD and 200 mg BID. The MTD was not determined.</td></tr>
<tr><td>Dose Proportionality</td><td>Following a single dose administration of repotrectinib at 40 mg, 80 mg, 160 mg and 240 mg, the increases in exposure (C_{max} and AUC_{last}) were approximately dose proportional.
<table>
<tr><th>Parameter</th><th>N</th><th>Dose Range</th><th>Intercept Estimate</th><th>Intercept 90% CI</th><th>Slope Estimate</th><th>Slope 90% CI</th></tr>
<tr><td>C_{max} (ng/mL)</td><td>40</td><td>(40 mg to 240 mg)</td><td>2.651</td><td>(1.528, 3.775)</td><td>0.783</td><td>(0.553, 1.012)</td></tr>
<tr><td>AUC_{last} (ng·h/mL)</td><td>40</td><td>(40 mg to 240 mg)</td><td>5.150</td><td>(3.767, 6.533)</td><td>0.803</td><td>(0.521, 1.085)</td></tr>
<tr><td>AUC_{inf} (ng·h/mL)</td><td>35</td><td>(40 mg to 240 mg)</td><td>5.722</td><td>(4.334, 7.110)</td><td>0.697</td><td>(0.411, 0.984)</td></tr>
</table>
Source: Module 2.7.2 Section 3.1.4</td></tr>
<tr><td>Accumulation</td><td>The geometric mean (CV%) accumulation ratio (AUC_{0-24}) at steady state in cohorts of 40 mg QD, 80 mg QD, 160 mg QD, and 240 mg QD under modified fasted condition were 1.19 (44%), 1.12 (69%), 0.67 (35%), and 0.54 (69%), respectively.
Accumulation ratios were lower at higher doses (160 mg and 240 mg QD), most likely due to a net auto-induction of CYP3A4 and potentially P-gp, which became more pronounced with increasing repotrectinib doses.</td></tr>
<tr><td>Variability</td><td>In multiple dose studies in subjects with advanced solid tumors, the inter-subject variability (CV%) at steady state- ranged from 29.1% to 51.7% for C_{max} and 20.5% to 72.7% for AUC_{0-24} under modified fasted condition (TRIDENT-1 Phase 1a). Under TRIDENT-1 Phase 1c fed condition, the inter-subject variability (CV%) at steady state ranged from 18.7% to 54.7% for C_{max} and 24.6% to 81.9% for AUC_{0-24}.</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Bioavailability</td><td>The mean (CV%) absolute bioavailability of repotrectinib is 45.7% (19.6%) under fasted condition.</td></tr>
<tr><td>T_{max}</td><td>The median (range) repotrectinib T_{max} was 3.0 hours (1.0 to 7.8 hours) following a single oral 160 mg dose and 2.0 hours (1.4 to 4.0 hours) following 160 mg twice a day oral dose at steady state in patients with advanced solid tumors.</td></tr>
<tr><td>Relative Bioavailability</td><td>In study TPX-0005-08, results showed comparable oral bioavailability between repotrectinib 160 mg oral suspension and 160 mg (b) (4) capsule formulation under fasted conditions, except 90% CI lower bound for C_{max} fell just below the 80-125% boundary which is not considered clinically significant.
<table>
<tr><th>Parameter (Unit)</th><th>Treatment A Suspension (Test, N = 11) Geometric LSM</th><th>Treatment B Capsule (Reference, N = 14) Geometric LSM</th><th>GMR Test/Reference (%)</th><th>90% CI (%)</th></tr>
<tr><td>AUC_{last} (ng·h/mL)</td><td>8810</td><td>9130</td><td>96.5</td><td>90.0, 103.4</td></tr>
</table></td></tr>
</table>

	AUC_{inf} (ng·h/mL)	9665	9946	97.2	91.1, 103.6
	C_{max} (ng/mL)	453.6	483.3	93.9	78.4, 112.3

Source: Module 2.7.1 Section 2.1.1

Food Effect (Fed/Fasted)

In the TRIDENT-1 study, effects of a high-fat meal were evaluated in a pilot sub-study (Phase 1b). A modest but not clinically significant food effect (AUC_{inf} and C_{max} under fed conditions were 123% and 115% of modified fasted conditions, respectively) was observed where modified fasted conditions were defined as no food and beverage 1 hour before and 2 hours after dosing.

Parameter (Unit)	N/n	Fasted (Reference) Geometric LSM	Fed (Test) Geometric LSM	GMR Test/Reference (%)	90% CI (%)
AUC_{last}/Dose (ng·h/mL/mg)	28/24	66.41	84.26	127.4	(114.4, 141.9)
AUC_{inf}/Dose (ng·h/mL/mg)	28/21	74.12	91.13	123.0	(110.0, 137.4)
C_{max}/Dose (ng/mL/mg)	28/24	4.869	5.603	115.1	(96.9, 136.7)

Source: Module 2.7.1 Section 2.3.1

In a dedicated food effect study in healthy subjects (TPX-0005-11), food effects were demonstrated where an overnight fast of at least 10 hours was implemented. AUC_{inf} and C_{max} of repotrectinib with high fat meal was 156% and 249% of fasted conditions.

Parameter (Unit)	Fasted - Reference (N = 14) Geometric LSM	Fed – Test (N = 14) Geometric LSM	GMR Test/ Reference (%)	90% CI (%)	Intrasubject CV (%)
AUC_{last} (ng·h/mL)	9970.5	16189	162.36	141.28, 186.59	20.87
AUC_{inf} (ng·h/mL)	10707	16721	156.17	136.76, 178.34	19.90
C_{max} (ng/mL)	498.2	1240	248.93	209.83, 295.32	25.78

Source: Module 2.7.1 Section 2.3.2

The difference in food effect on C_{max} was likely due to the modified fasted conditions used in cancer patients on the TRIDENT-1 study versus the overnight fasted conditions used in healthy subjects.

Acid-reducing Agent Effect	Repotrectinib is a neutral compound where pKa cannot be experimentally determined. Solubility of repotrectinib at 37°C is pH independent ranging from 0.008 mg/mL at pH 1.2 to 0.006 at pH 7.4. Therefore, acid reducing agents are not expected to affect the bioavailability of repotrectinib.
Distribution	
Volume of Distribution	The mean (CV%) steady state volume of distribution (Vd_{ss}) was 264 L (22.3%) following a single intravenous dose.

Plasma Protein Binding	The plasma protein binding of repotrectinib was studied in vitro. Repotrectinib was highly plasma protein bound in pooled human plasma with binding of 95.41% (4.59% unbound). Repotrectinib preferentially binds to HSA and to a lesser extent to AGP, and binding HSA and AGP was not concentration dependent
Blood to Plasma Ratio	The mean blood-to-plasma ratios of repotrectinib at concentrations of 0.1 µM, 1 µM and 10 µM were 0.60, 0.56 and 0.50, respectively, suggesting accumulation of repotrectinib to blood cells was limited and was not concentration dependent.
Elimination	
Half-life	Based on the population PK analysis, the single dose terminal $t_{1/2}$ was estimated to be 55.5 hours for healthy subjects and 50.6 hours for cancer patients, and the steady state terminal $t_{1/2}$ was estimated to be 41.2 hours for healthy subjects and 35.4 hours for cancer patients.
Clearance	Following an IV administration in healthy subjects, repotrectinib exhibited low CL with a mean (CV%) of 7.04 L/h (14.0%) which is comparable with that estimated based on the population PK model of 7.06 L/h
Metabolism	
Primary Metabolic Pathway(s)	Based on in vitro phenotyping studies, repotrectinib is primarily metabolized by CYP3A4. Following a single oral administration of [^{14}C]-repotrectinib to 7 healthy male human subjects, unchanged repotrectinib accounted for the majority (84.3%) of systemically available radioactivity in the cross-subject AUC pooled plasma extract. Circulating metabolites included M1/M3 (glucuronide conjugates of hydrated [+O, +2H] repotrectinib), M2 (glucuronide conjugate of a hydroxylated metabolite of repotrectinib), M5, and M9 (hydroxylated metabolites of repotrectinib). No metabolite exceeded 10% of total circulating drug-related radioactivity. All detected human metabolites had been previously detected in rat and/or non-human primate plasma and/or excreta, and there were no major/disproportionate or unique human metabolites.
Inhibitor/ Inducer	Coadministration of itraconazole (a strong CYP3A4 inhibitor) with a single 80 mg dose repotrectinib increased repotrectinib AUC_{inf} by 5.9-fold and C_{max} by 1.7-fold compared to repotrectinib administered alone. PBPK simulations (b) (4) Coadministration of 160 mg repotrectinib once a day for 14 days followed by twice a day dosing for 7 days reduced AUC_{inf} by 69% and C_{max} by 48% of a single oral dose of midazolam (a CYP3A4 substrate) compared to midazolam administered alone, suggesting repotrectinib is a moderate CYP3A4 inducer. In vitro data suggest that at the clinically relevant concentrations, repotrectinib is a potential inhibitor of CYP2C8 and CYP2C9 systemically, and CYP3A4 in the intestine. Repotrectinib also has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19 based on hepatocyte induction data. The repotrectinib PBPK model (b) (4) (b) (4)

	 (b) (4)
Excretion	
Primary Excretion Pathway(s) (%dose) ±SD	In healthy subjects (Study TPX-0005-09) following 160 mg single oral dose of [^{14}C]-repotrectinib, mass balance was achieved with overall cumulative recovery of radioactivity at 93.7%. Fecal excretion was the predominant route of elimination, with a mean of 88.8% of the dose recovered in feces and 4.84% recovered in urine. Approximately 51% (50.6% in feces, 0.56% in urine) of the administered dose was excreted as unchanged repotrectinib and the remainder was eliminated by metabolism.

Abbreviations: AGP = human alpha-1-acid glycoprotein; ATP = adenosine triphosphate; AUC_{0-24} = AUC from time 0 to 24 hours post-dose; AUC_{last} = area under the plasma concentration-time curve from time 0 to time of last measurable concentration; BCRP = breast cancer resistance protein; BID = twice a day / twice daily; CI = confidence interval; C_{max} = maximum plasma concentration; CV = coefficient of variation; CYP = cytochrome P450; DDI = drug-drug interaction; FeSSIF = fed state simulating intestinal fluid; FaSSIF = fasted state simulating intestinal fluid; hPXR = human pregnane X receptor; HSA = human serum albumin; LC-MS/MS = liquid chromatography with tandem mass spectrometry; MATE = multidrug and toxin extrusion protein; NTRK = neurotrophin receptor kinase; OAT = organic anion transporter; OCT = organic cation transporter; PBPK = physiologically based pharmacokinetic modeling and simulation; P-gp = P-glycoprotein; PK = pharmacokinetic(s); PXR = pregnane X receptor; PK = pharmacokinetic(s); QD = once a day / once daily; T_{max} = time to reach maximum (peak) observed plasma drug concentration; TRK = tropomyosin receptor kinase; TRKA = tropomyosin receptor kinase A; TRKB = tropomyosin receptor kinase B; TRKC = tropomyosin receptor kinase C; UGT = uridine 5'-diphospho-glucuronosyltransferase; Vd_{ss} = steady state volume of distribution.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Data:

The integrated efficacy analysis from the TRIDENT-1 study (pooled EXP-1 and EXP-4) demonstrated robust clinical activity in *ROS1*-positive NSCLC population.

In *ROS1*-positive NSCLC TKI-naive subjects (pooled EXP-1), the confirmed ORR by BICR was 78.9% (n = 56 of 71; 95% CI: 67.6, 87.7), including 4 (6%) CRs and 52 (73%) PRs. The onset of response was rapid (median TTR was 1.8 months) and the responses were durable (median DOR was 27.4 months and median PFS was 31.1 months). Median PFS was 31.1 months (95% CI: 24.6, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 12 months was 79.7% (95% CI: 69.8, 89.6). The median OS was not reached at the time of the data cutoff date.

In R*OS1*-positive NSCLC patients pretreated with one TKI and no chemotherapy (pooled EXP-4), the confirmed ORR by BICR was 37.5% (N = 21 of 56; 95% CI: 24.9, 51.5) with 3 subjects (5.4%) achieving a CR and 18 subjects (32.1%) achieving a PR. The onset of response was rapid (median TTR was 1.8 months) and the responses were durable (median DOR was 17.8 months and median PFS was 9.0 months). Median PFS was 9.0 months (95% CI: 7.3, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 9 months was 55.1% (95% CI: 40.5, 69.7). The estimated median OS was 25.1 months (95% CI: 17.9, NE).

To support the clinical efficacy observed with repotrectinib, exposure-response analysis was performed based on data from pooled EXP-1 (*ROS1* TKI-naïve) and EXP-4 (1 prior *ROS1* TKI and no prior chemotherapy or IO) population in the TRIDENT-1 study. The analysis showed a statistically significant relationship between repotrectinib C_{maxss} and ORR with the probability of an objective response increasing with increasing C_{maxss}. The model predicted ORR increased with dose and dosing frequency and approached to the plateau around 160 mg BID dose. In general, the BID dose regimen is predicted to have higher probability of ORR than the QD dose regimen. For TKI-naïve patients, the median predicted ORR were 81.9% and 86.5% for 160 mg QD and 160 mg BID, respectively. For TKI pretreated patients, the median predicted ORR were 37.8% and 44.0% for 160 mg QD and 160 mg BID, respectively.

The Applicant's Position:

The efficacy results from TRIDENT-1, along with clinical pharmacology program collectively provide adequate evidence for the effectiveness of repotrectinib in *ROS1*-positive NSCLC patients who are either ROS1 TKI-naïve or have been pretreated with 1 prior ROS1 TKI.

The FDA's Assessment:

FDA generally agrees with the Applicant that the integrated results from TRIDENT-1 provide evidence of effectiveness of repotrectinib at a dosage of 160 mg once daily for 14 days followed by an increase to 160 mg twice daily in patients with ROS1-positive NSCLC who are either ROS1 TKI-naïve or have been pretreated with 1 prior ROS1 TKI.

6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Data:

The PK of repotrectinib was well-described by a 2-compartment model with first-order absorption, non-linear elimination and a time-dependent induction clearance. PK simulation showed that repotrectinib AUC following 160 mg QD was reduced by approximately one half at steady state compared to the first dose due to auto-induction of CYP3A4. Increasing 160 mg QD dosing to BID dosing after 14 days would compensate the PK exposure loss due to auto-induction and maintain effective repotrectinib exposure throughout the treatment duration.

Exposure-response analysis showed a statistically significant relationship between repotrectinib C_{maxss} and ORR with the probability of an objective response increased with increasing C_{maxss}.

The model predicted ORR increased with dose and dosing frequency and approached a plateau around 160 mg BID dose. In general, the BID dose regimen has higher probability of ORR than the QD dose regimen. For TKI-naïve patients, the median predicted ORR are 81.9% and 86.5% for 160 mg QD and 160 mg BID, respectively. For TKI-pretreated patients, the median predicted ORR are 37.8% and 44.0% for 160 mg QD and 160 mg BID, respectively.

E-R analysis for safety demonstrated a statistically significant E-R relationship between C_{max} and grade ≥ 2 dizziness. In addition, age was found to be a significant covariate. As age increased, the model predicted probability of grade ≥ 2 dizziness increased, which is consistent with clinical findings. The probability of grade ≥ 2 dizziness increased with the dose and dosing frequency, though the absolute rates were relatively low. The median predicted probability of grade ≥ 2 dizziness at 160 mg QD and 160 mg BID doses were 13.8% and 17.1%, respectively, suggesting the proposed clinical dose regimen is generally well tolerated.

In summary, the E-R safety and efficacy simulations demonstrated that the proposed clinical dose regimen of 160 mg QD/BID achieved maximal ORR with relatively low incidence rate of grade ≥ 2 dizziness. Taking into consideration the overall benefit/risk assessment, the cumulative data support the 160 mg QD/BID dose regimen of repotrectinib as the optimal dose for adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.

The Applicant's Position:

The proposed dosing regimen of 160 mg QD/BID is supported by clinical efficacy and safety data as well as the population PK and E-R analyses.

The FDA's Assessment:

FDA generally agrees with the Applicant that the proposed repotrectinib dosing regimen of 160 mg QD/BID is supported by clinical efficacy and safety data as well as the population PK and E-R analyses.

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:

Population PK profiles of repotrectinib in healthy subjects and subjects with advanced solid tumors were adequately described by the population model. Age, sex, race, ethnicity, renal impairment (mild and moderate), hepatic impairment (mild), subject status (healthy vs with cancer) were not significant covariates affecting repotrectinib exposure. Additional covariates associated with cancer subjects such as ECOG score (0 and 1), cancer type (NSCLC and other), cancer histology (adenocarcinoma, sarcoma, squamous, non-classified), and tumor genetic mutation (*ALK*, *ROS1*, or *NTRK*) were evaluated and were not significantly associated with the variability of repotrectinib exposure.

In the population PK analysis, consistent with the principle of allometry, body weight (range 39.5 to 169 kg) was identified as a covariate associated with CL, V2 (central volume of distribution), and V3 (peripheral volume of distribution). On average, a subject with 93.4 kg (90th percentile) body weight had 22.4% higher CL and 31.0% higher V2 and V3 than a subject with a median body weight of 71.3 kg. A subject with 53 kg (10th percentile) body weight had 19.9% lower CL and 25.7% lower V2 and V3 than a subject with a median body weight of 71.3 kg. The exposure difference at 90th and 10th percentile of body weight were within inter-subject variability observed in TRIDENT-1, thus no dose adjustment based on body weight is warranted.

Hepatic impairment may affect the PK of repotrectinib. In the population PK analysis, 52 subjects (9.9%) with mild hepatic impairment as classified based on the NCI criteria, were included in the analysis. No statistically significant effect of mild hepatic impairment on key PK parameters was evident and therefore, no dose adjustment is recommended for subjects with mild hepatic impairment. No data is available in subjects with moderate and severe hepatic impairment. A study of subjects with varying degrees of hepatic impairment including moderate, severe hepatic impairment and demographically matched normal hepatic function is ongoing (TPX-0005-15).

Renal excretion of repotrectinib was low. Approximately, 4.84% of total administered dose (0.56% excreted as unchanged drug) was excreted renally. Due to the low renal excretion, renal impairment is not expected to have a relevant effect on the PK of repotrectinib and was evaluated as a part of the population PK analysis. Renal impairment was not identified as a significant covariate affecting the PK of repotrectinib. Subjects with mild and moderate renal impairment had similar exposure compared to the subjects with normal renal function. Therefore, no dose adjustment is required for subjects with mild or moderate renal impairment.

The Applicant's Position:

Repotrectinib dose adjustment is not required for subjects with mild or moderate renal impairment. Dose adjustment is also not required for subjects with mild hepatic impairment. Repotrectinib has not been evaluated in subjects with severe renal impairment or moderate or severe hepatic impairment. Based on population PK analysis, no dose adjustment is required for the intrinsic factors age, sex, race, ethnicity, and subject status. Body weight was identified as a covariate, but exposure differences were within inter-subject variability and thus no dose adjustment is considered warranted.

The FDA's Assessment:

FDA generally agrees with the Applicant that no dose adjustment is required for intrinsic factors of age, sex, race, ethnicity, subject status, ROS1 status and mild to moderate renal impairment.

1. **Hepatic impairment**

In the mass balance study (TPX-0005-09) in healthy subjects, 89% of the total 93.7% recovered dose was found in the feces with 50.6% unchanged, indicating that hepatic elimination is the

main elimination pathway for repotrectinib.

While the effect of mild hepatic impairment was addressed by population PK analysis, no clinical data are available for subjects with moderate or severe hepatic impairment. As a result, a post-marketing study should be conducted to address the potential impact of moderate and severe hepatic impairment on PK of repotrectinib.

In order to address the impact of HI on PK and safety of repotrectinib, the Applicant proposed an alternative approach of conducting a single dose repotrectinib study in healthy subjects with hepatic impairment, followed by PBPK modeling approach to predict the multiple dose repotrectinib PK in patients with hepatic impairment. Considering the recruitment challenges for the ongoing HI study TPX-0005-15 for the multiple dose repotrectinib study in patients with moderate and severe HI, FDA does not object to the Applicant's proposal. However, it is still uncertain at this stage that whether the modeling approach can be applied to extrapolate the single dose PK data to multiple dose PK data for repotrectinib in patients with hepatic impairment. It is the Applicant's risk that at the time of final report submission, the modeling approach may not be accepted, or the predicted results may not be used to inform labeling.

2. Body weight

In the population PK model, baseline body weight is allometrically scaled on clearance and volume of distribution. However, it is not considered clinically meaningful, with 85% - 113% of CL for 10^{th} -90^{th} percentile of BW compared to patients with median BW. See Appendix 19.4.2 for more details.

3. ROS1 Fusion Partner

Multiple ROS1 fusion partners have been reported in NSCLC. Patients in the TRIDENT-1 study had ROS1 status prospectively assessed using local next-generation sequencing (NGS) or quantitative polymerase chain reaction (qPCR) tests, or using a centralized NGS clinical trial assay (Repotrectinib CTA) when local results were based on fluorescence in situ hybridization (FISH). Patients enrolled using local NGS and qPCR were retrospectively assessed for ROS1 fusion partner using the Repotrectinib CTA. Eighteen patients did not have fusion partner results available because of enrollment based on local qPCR testing that did not report the specific fusion partner combined with either an invalid Repotrectinib CTA result (N = 12; 7 TKI-Naïve and 5 TKI-Pretreated patients) or lack of a fusion detected by the Repotrectinib CTA (N = 6; 4 TKI-Naïve and 2 TKI-Pretreated patients). A total of 10 unique ROS1 fusion partners were identified across the TKI-Naïve pooled EXP-1 (N = 71) and TKI-Pretreated EXP-4 (N = 56) cohorts. In addition, 2 patients were found to have multiple ROS1 fusion partners (TKI-Naive: SDC4-ROS1 & DKK3-ROS1; TKI-Pretreated: CD74-ROS1 & LRIG3-ROS1). Responses were observed across most ROS1 fusion partner subgroups containing more than a single patient (Table 25,Table 26), with the exception of the TKI-pretreated SDC4-ROS1 subgroup (N = 8). However, TKI-naïve patients with SDC4-ROS1 fusions did show response to repotrectinib (5/9, 56%) and there is no clear mechanistic rationale for lack of response in this subgroup.

Table 25. Best Overall Response by Fusion Partner in ROS1 TKI-Naive Patients With ROS1-Positive NSCLC (Pooled EXP-1) (N = 71) at the 19-Dec-2022 DCO

	Best Overall Response					
Fusion Partner	CR	PR	SD	PD	Missing	Total
CD74-ROS1	4 (15.4)	19 (73.1)	2 (7.7)	1 (3.8)	0 (0.0)	26
EZR-ROS1	1 (7.1)	12 (85.7)	1 (7.1)	0 (0.0)	0 (0.0)	14
SDC4-ROS1	1 (11.1)	4 (44.4)	2 (22.2)	1 (11.1)	1 (11.1)	9
SLC34A2-ROS1	1 (14.3)	4 (57.1)	2 (28.6)	0 (0.0)	0 (0.0)	7
LDLR-ROS1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1
MSN-ROS1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	1
MYH9-ROS1	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
Multiple	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
Not Detected	0 (0.0)	8 (72.7)	2 (18.2)	0 (0.0)	1 (9.1)	11
QC Failure by Central Lab	0 (0.0)	4 (57.1)	2 (28.6)	0 (0.0)	1 (14.3)	7

Abbreviations: CR = complete response; DCO=Data cutoff; EXP = expansion cohort; PD = progressive disease; PR = partial response; SD = stable disease.
Fusion partners detected either by local or central testing.
Best response of Not Evaluable (NE) is suppressed due to no subjects having best response of this category.

Source: Applicant response to FDA IR received 26 July 2023.

Table 26. Best Overall Response by Fusion Partner in ROS1 TKI-Pretreated Patients With ROS1-Positive NSCLC (Pooled EXP-4) (N = 56) at the 19-Dec-2022 DCO

	Best Overall Response						
Fusion Partner	CR	PR	SD	PD	NE	Missing	Total
CD74-ROS1	2 (8.7)	6 (26.1)	10 (43.5)	4 (17.4)	0 (0.0)	1 (4.3)	23
EZR-ROS1	1 (10.0)	5 (50.0)	4 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	10
SDC4-ROS1	0 (0.0)	0 (0.0)	5 (62.5)	2 (25.0)	1 (12.5)	0 (0.0)	8
SLC34A2-ROS1	0 (0.0)	3 (50.0)	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	6
TPM3-ROS1	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
Multiple	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1
Not Detected	0 (0.0)	4 (57.1)	0 (0.0)	3 (42.8)	0 (0.0)	0 (0.0)	7
QC Failure by Central Lab	0 (0.0)	3 (60.0)	0 (0.0)	2 (40.0)	0 (0.0)	0 (0.0)	5

Abbreviations: CR = complete response; DCO=Data cutoff; EXP = expansion cohort; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.
Fusion partners detected either by local or central testing.

Source: Applicant response to FDA IR received 26 July 2023.

4. Baseline Resistance Mutations in TKI-pretreated patients

Patients in the pooled EXP-4 cohort that had received 1 prior ROS1 TKI were assessed for ROS1 resistance mutations at baseline using either a local (tissue-based) or central (plasma-based ctDNA) NGS assay prior to treatment with repotrectinib (Table 27). Resistance mutations status was unknown for 7 patients because of QC failure by the central lab (N = 1) or because testing

was not performed by the central lab (N = 6). Resistance mutations were identified in 8/49 (16%) TKI-pretreated patients assessed and consisted of 6 solvent front mutation (G2032R), 1 gatekeeper mutation (L2026M), and 1 other mutation (S1986F/Y) that has been reported to impact the alphaC helix of the kinase domain [PMID: 2740124]. Responses (PR) were observed across resistance mutation subgroups, and were higher in patients with resistance mutations (ORR 75%) as compared to patients without resistance mutations (ORR 29%) or to patients with resistance mutation status unknown (ORR 43%).

Table 27. Best Overall Response by Resistance Mutation and Fusion Partner in ROS1 TKI-Pretreated Patients With ROS1-Positive NSCLC (Pooled EXP-4) (N = 56) at the 19-Dec-2022 DCO

Resistance Mutation	Fusion Partner	Beast Overall Response					
		CR	PR	SD	PD	NE	Total
Mutation Positive (N = 8)							
G2032R	CD74-ROS1	0	3 (60)	1 (20)	1 (20)	0	5
	SLC34A2-ROS1	0	1 (100)	0	0	0	1
L2026M	EZR-ROS1	0	1 (100)	0	0	0	1
S1986F/Y	EZR-ROS1	0	1 (100)	0	0	0	1
Mutation Negative (N = 41)							
	CD74-ROS1	2 (12)	3 (18)	8 (47)	3 (18)	1 (6)	17
	EZR-ROS1	1 (14)	2 (29)	4 (57)	0	0	7
	SDC4-ROS1	0	0	4 (67)	1 (17)	1 (17)	6
	SLC34A2-ROS1	0	1 (25)	3 (75)	0	0	4
	TPM3-ROS1	0	0	1 (100)	0	0	1
	Multiple (CD74-ROS1, LRIG3-ROS1)	0	0	1 (100)	0	0	1
	Not Detected	0	1 (50)	0	1 (50)	0	2
	QC Failure by Central Lab	0	2 (67)	0	1 (33)	0	3
Mutation Status Unknown (N = 7)							
	CD74-ROS1	0	1 (50)	0	0	0	2*
	SDC4-ROS1	0	0	1 (50)	1 (50)	0	2
	EZR-ROS1	0	1 (50)	0	0	0	1
	QC Failure by Central Lab	0	1 (50)	0	1 (50)	0	2

* 1 patient with Best Overall Response = Missing.

Source: Reviewer analysis using TRIDENT-1 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

The effect of a high-fat meal on repotrectinib PK was first evaluated in a pilot sub-study in TRIDENT-1 at 40 mg, 80 mg, and 160 mg dose levels. A modest but not clinically significant food effect (AUC_{inf} and C_{max} GMRs under fed conditions were 123% and 115% of fasted conditions, respectively) was observed where modified fasted conditions were applied (no food and beverage 1 hour before and 2 hours after dosing). Given the findings from the pilot food-effect study, the TRIDENT-1 protocol was updated with the food instruction for repotrectinib to be administered with or without food in Phase 2. In a dedicated food effect study in healthy subjects, food effects were demonstrated in healthy subjects where a standard overnight fast of at least 10 hours was implemented. AUC_{inf} and C_{max} GMRs of repotrectinib with high fat meal were 156% and 249% of fasted conditions for [redacted] (b) (4) capsules (TPX-0005-11). The difference in food effect was likely due to the modified fasted conditions used with cancer patients in the TRIDENT-1 study versus the overnight fasted conditions (at least 10 hours) used in healthy subjects.

Simulation using a population PK model showed that the GMRs of AUC_{inf} and C_{max} after a single 160 mg dose of repotrectinib under fed conditions were 138% and 256% of the fasted conditions, respectively, which is consistent with the results from the food-effect study in healthy subjects (TPX 0005-11). The predicted mean GMRs of AUC_{inf} and C_{max} under fed conditions were 126% and 102% of the modified fasted conditions, respectively, which is in alignment with the results from the pilot food-effect study in subjects with advanced solid tumors. These results demonstrated that the food effect on PK of repotrectinib was adequately described by the population PK model.

Following multiple doses of 160 mg BID repotrectinib, the predicted geometric mean AUC_{24} and C_{max} at steady state under fed conditions were 139% and 164% of the fasted conditions, respectively. While the GMR of AUC did not change at steady state (139% compared to 138% after single dose), the GMR of C_{max} at steady state is predicted to be attenuated to 164% (compared to 256% after single dose). The impact of food effect on efficacy and safety was further evaluated with E-R analysis in subjects with advanced solid tumors. The median probability of achieving an objective response or experiencing grade ≥ 2 dizziness was numerically higher under fed and modified fasted conditions versus fasted conditions but was overlapping among the different fed conditions.

In summary, the totality of the clinical data, population PK and exposure-response evaluations support that repotrectinib can be administered without regard to food.

Drug Interactions with Repotrectinib as a Victim (CYP3A4 inhibition)

Coadministration of itraconazole (a strong CYP3A4 inhibitor) with a single 80 mg dose repotrectinib increased repotrectinib AUC_{inf} by 5.9-fold and C_{max} by 1.7-fold compared to repotrectinib administered alone (Study TPX-0005-10). Based on PBPK modeling results (b) (4)

Drug Interactions with Repotrectinib as a Victim (CYP3A4 induction)

Coadministration of rifampin (a strong CYP3A4 inducer) with a single 160 mg repotrectinib dose reduced repotrectinib AUC_{inf} by 92% and C_{max} by 79% (Study TPX-0005-10). Based on PBPK modeling results (b) (4)

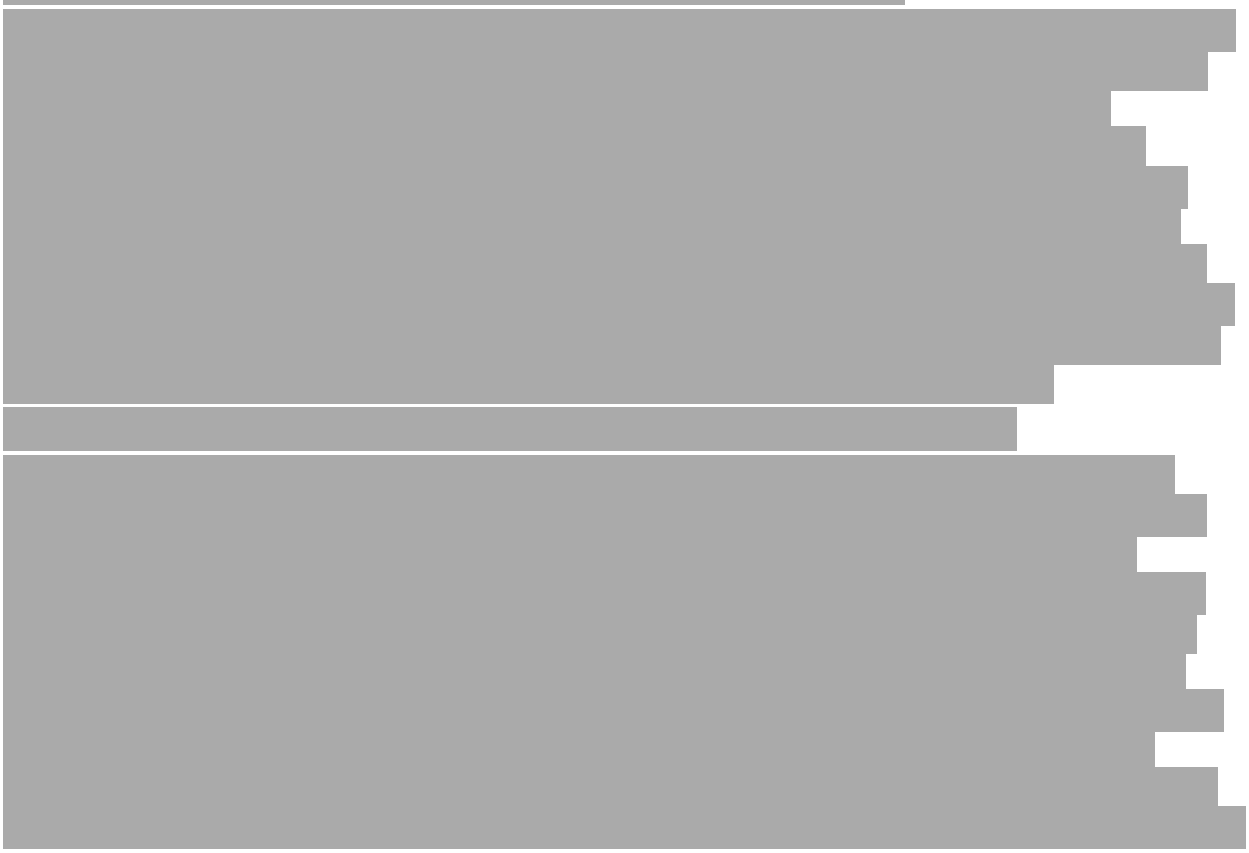
Drug Interaction with Repotrectinib as a Perpetrator (CYP3A4)

Coadministration of 160 mg repotrectinib QD for 14 days followed by BID dosing for 7 days reduced AUC_{inf} by 69% and C_{max} by 48% of a single oral dose of midazolam (a CYP3A4 substrate) compared to midazolam administered alone, suggesting repotrectinib is a moderate CYP3A4 inducer (TRIDENT-1 DDI sub-study).

Drug Interaction with Repotrectinib as a Perpetrator (Other Major CYP Isoforms)

The repotrectinib PBPK model was used (b) (4)

(b) (4)



The Applicant's Position:

Repotrectinib can be taken with or without food. Acid-reducing agents such as proton pump inhibitors, H2 receptor antagonists, and antacids are not expected to affect the bioavailability of repotrectinib.

Coadministration of repotrectinib with a strong or a moderate CYP3A4 inhibitor should be avoided as it increases repotrectinib exposure, which may increase the incidence and severity of adverse reactions of repotrectinib. Coadministration of repotrectinib with a strong CYP3A4 inducer should be avoided as it decreases repotrectinib plasma concentrations, which may decrease efficacy of repotrectinib.

Avoid concomitant use of repotrectinib with certain CYP3A4 substrates, for which minimal concentration changes may lead to serious therapeutic failures. If concomitant use is unavoidable, increase the CYP3A4 substrate dosage in accordance with approved product labeling.

(b) (4)

(b) (4)

The FDA's Assessment:

FDA agrees with the Applicant on the assessment and management strategy for the administration of repotrectinib with regard to food. However, FDA does not agree that the drug-drug interaction assessment is adequate.

1. **Food drug interaction**

Based on the dedicated food effect study in healthy subjects, taking repotrectinib with a high fat meal significantly increased repotrectinib drug exposure compared to the overnight fasted condition.

However, in the pilot food effect study in TRIDENT-1 Phase 1b in patients with solid tumors, following a standard high-fat meal at repotrectinib dosage range of 40 mg, 80 mg, or 160 mg QD, the overall increase was only 15%, 27%, and 23% for dose normalized C_{max}, AUC_{last}, and AUC_{inf}, respectively compared to modified fasted condition (no food 1 hour before or 2 hours after the dosing). Of note, the Applicant's proposed (b) (4) is different from FDA recommendation (b) (4)

A further comparison of the PK and safety was conducted at the recommended repotrectinib dosage of 160 mg QD/BID under a modified fasted condition (TRIDENT-1 Phase 1a), fed (Phase 1c), and with or without food (TRIDENT-1 Phase 2). As shown in the table below, the results show that the single dose PK after the first-dose was generally consistent for the Phase 1b food effect substudy, the 160 mg QD/BID first dose under fed condition (Phase 1c) and the first dose without regard to food (midazolam substudy, Phase 2). For the safety profile, the TEAEs were generally comparable overall among the three different food administration conditions.

Based on the overall consideration of the PK, safety, and patient compliance, the proposed recommendation for repotrectinib administration without regard to food appears acceptable.

Table 28. Overall Summary of TRIDENT-1 PK and Adverse Events Data by Dose and Food Guidance

	Modified Fasting Phase 1a		With Standard Meal Phase 1c		Without Regard to Food	
	160 mg QD	160 mg BID	160 mg QD	160 mg QD/BID	Midazolam Substudy RP2D 160 mg QD/BID	Phase 2 RP2D 160 mg QD/BID [a]
Single Dose PK Data						
N	**18**		**18**		**10**	**315**
C_{max} (ng/mL)	714 (46.7)		851 (50.0)		796 (37.1)	784 (32.3) [a]
AUC_{inf} (ng·h/mL)	10000 (45.5)		NR		NR	12200 (37.5) [a]
AUC_{0-24} (ng·h/mL)	6870 (59.0)		7740 (43.1)		8090 (39.3)	7420 (29.2) [a]

Safety Data						
N	**23**	**12**	**6**	**12**	**10**	**341**
All subjects with TEAEs, n (%)	23 (100.0)	12 (100.0)	6 (100.0)	12 (100.0)	10 (100.0)	339 (99.4)
TEAEs leading to discontinuation of study drug, n (%)	4 (17.4)	1 (8.3)	1 (16.7)	2 (16.7)	2 (20.0)	27 (7.9)
TEAEs leading to dose reduction, n (%)	0 (0.0)	5 (41.7)	1 (16.7)	5 (41.7)	3 (30.0)	186 (54.5)
TEAEs leading to drug interruption	8 (34.8)	6 (50.0)	2 (33.3)	5 (41.7)	6 (60.0)	130 (38.1)
Grade ≥ 3 TEAEs, n (%)	15 (65.2)	6 (50.0)	5 (83.3)	8 (66.7)	7 (70.0)	166 (48.7)
Grade 3–4 TEAEs, n (%)	15 (65.2)	6 (50.0)	4 (66.7)	8 (66.7)	6 (60.0)	150 (44.0)
Fatal TEAEs, n (%)	0 (0.0)	0 (0.0)	1 (16.7)	3 (25.0)	1 (10.0)	16 (4.7)
SAEs, n (%)	11 (47.8)	5 (41.7)	5 (83.3)	7 (58.3)	7 (70.0)	107 (31.4)

[a] The PK data was generated by PK simulation.

Source: Applicant's response to ClinPharm IR dated 25MAY2023.

2. Drug-drug interaction

Repotrectinib as a victim:

FDA does not agree that the assessment of the DDI potential of repotrectinib as a victim with CYP3A and P-gp modulators is adequate. Post-marketing studies of clinical DDI studies followed by PBPK modeling studies are needed to ensure an adequate assessment of the effects of CYP3A and P-gp modulators on the PK of repotrectinib.

Repotrectinib is a P-gp substrate and primarily metabolized by CYP3A4 in vitro. Concomitant use with itraconazole (a dual P-gp and strong CYP3A4 inhibitor) significantly increased the single dose repotrectinib systemic exposure by 5.9-fold for AUC_{inf} and 1.7-fold for C_{max}, while concomitant used with rifampin (a dual P-gp and strong CYP3A4 inducer) significantly reduced the single dose repotrectinib systemic exposure by 92% for AUC_{inf} and 79% for C_{max}, indicating that a clinically significant impact of moderate CYP3A and/or P-gp inhibitors or inducers on the PK of repotrectinib could not be ruled out.

The Applicant subsequently utilized PBPK modeling (b) (4)

(b) (4)

Based on the above considerations, labeling will recommend avoiding concomitant use of repotrectinib with strong or moderate CYP3A inhibitors or inducers, and P-gp inhibitors. Furthermore, in order to inform the dosage recommendations for repotrectinib when concomitantly taking it with CYP3A and/or P-gp inhibitors or inducers, FDA recommends a total of 1 PMR and 1 PMC assessment by conducting DDI studies with a specific strong CYP3A inhibitor and a specific P-gp inhibitor, respectively to quantify the contribution of CYP3A and P-gp on the single dose PK of repotrectinib, followed by PBPK modeling studies to evaluate the impact of specific strong and moderate CYP3A inhibitors, specific moderate CYP3A inducers, specific P-gp inhibitors, and dual P-gp and moderate CYP3A inhibitors on the multiple dose PK of repotrectinib.

FDA agrees with the Applicant that acid reducing agents (ARAs) are not likely to alter the PK of repotrectinib, given that repotrectinib is a neutral compound with pH-independent solubility at pH 1.2 to 7.4.

Repotrectinib as a perpetrator

FDA does not agree that the PBPK modeling assessment is adequate for evaluating the DDI potential of repotrectinib as a perpetrator with substrates of CYP2B6, 2C8, 2C9, and 2C19. Postmarketing clinical DDI studies are needed to ensure an adequate assessment of the effect of repotrectinib on the PK of these substrates.

(b) (4)

.

Based on the above considerations, PBPK modeling analysis was considered inadequate to

(b) (4)

efer to Section 19.4.4 for detailed information about the PBPK analysis.

Based on FDA guidance In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions, *"the Sponsor may first carry out an in vivo study with a sensitive index substrate of the CYP with the largest R or AUCR value. If this in vivo study shows no interaction, in vivo evaluations of other CYPs with lower potencies (e.g., smaller R or AUCR) are not needed."*

The in-vitro measured induction potency of repotrectinib on CYP450 enzymes under the same test conditions is listed in the table below. Based on the assessment, repotrectinib has the following rank order from most potent to least potent induction: CYP2B6 > CYP2C9 ≈ CYP2C8 > CYP2C19.

Table 29. Comparison of In-Vitro Measured Induction Potency of Repotrectinib on CYP450 Enzymes and the Predicted Drug Interactions

CYP Enzymes	Human Hepatocytes mRNA Fold change at Clinically Relevant Concentration	Emax	EC50	Imax,u	R3 Static Model	AUCR by PBPK
CYPB6	5.77, 16.9, 28.9	54	2.47	0.0966	0.06	(b) (4)
CYP2C8	1.38, 1.77, 2.61, 2.73	1.78	0.309	0.0966	0.43	
CYP2C9	1.29, 1.64, 2.21, 2.93	NC	NC	0.0966	0.43	
CYP2C19	1.12, 1.23, 1.64, 2.07	2.26	2.77	0.0966	0.63	

Source: Response to FDA comments received 04 Oct 2023.

Given the same induction mechanism through pregnane X receptor for the CYP2C enzymes and the similar in-vitro induction potency between CYP2C8 and CYP2C9, repotrectinib DDI with the CYP2C8 substrate could potentially be assessed from the observed clinical DDI with the CYP2C9 substrate by applying the in-vivo induction information to the PBPK model.

Based on the above considerations, a PMC DDI study is needed to address the effect of repotrectinib on exposures of substrates of CYP2B6, 2C9, and 2C19. The PMC study for CYP2C8 substrate could be conducted by PBPK modeling prediction by using the results of the DDI study with CYP2B6, 2C9, and 2C19 substrates.

FDA agrees with the Applicant to avoid co-administration with sensitive CYP3A4 substrates, given the potential induction effect of repotrectinib based on substudy in TRIDENT-1 Phase 1 with midazolam.

FDA does not agree that the repotrectinib interaction with transporter substrates is adequately addressed, given that the (b) (4) is still ongoing and no results are available up to date. FDA agrees with the Applicant's proposal to include this study as a PMR study for assessment of repotrectinib effect on exposures of substrates of MATE2-K, P-gp, OATP1B1, and BCRP.

FDA agrees that the repotrectinib interaction potential with UGT1A1 is low at clinically relevant concentrations.

X	X
Primary Reviewer	Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 30. Listing of Clinical Trials Relevant to this NDA

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: 120 mg QD – 160 mg	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	Subjects 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
			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 subjects with *ROS1*+ and *NTRK*+ solid tumors	oral administration; 28-day cycles 160 mg QD/BID[b]	Primary[c]: cORR (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: 342 (341 dosed) *ROS1+* NSCLC (EXP-1 to EXP-4): 257 (256 dosed) *NTRK+* Solid Tumors (EXP-5, EXP-6): 85 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: TRK TKI-naïve	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
							EXP-6: TRK TKI-pretreated	
		Studies to Support Safety						
TPX-0005-13 (TRIDENT-2)	NCT05071183	Phase 1b/2 multicenter, open-label, dose escalation (Phase 1), expansion (Phase 2)	Repotrectinib with trametinib in 28-day cycles Route: Oral	MTD, RP2D efficacy, and PK	Until disease progression, intolerable toxicity, death, or withdrawal from treatment	Phase 1 (dose escalation): 6 Ongoing[d]	Subjects With *KRAS*-Mutant Advanced Solid Tumors	5 centers 1 country (USA)
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: 19 Phase 1: 10 Completed Phase 2: 9 Ongoing[d]	Pediatric and young adult subjects with advanced or metastatic solid tumors, primary central nervous system (CNS) tumors, or ALCL with *ALK*, *ROS1*, or *NTRK* alterations	28 centers 6 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
		Other studies pertinent to the review of efficacy or safety (eg, clinical pharmacological studies)						
TPX-0005-08	NA	Phase 1, open-label, randomized, 2-period, 2-sequence crossover	160mg single dose Route: Oral	BA of 2 oral formulations, safety	NA	Healthy volunteers: 14	NA	1 center 1 country (USA)
TPX-0005-09	NA	Phase 1, single-center, open-label, 2-period, single-sequence, crossover	160mg single dose (^{14}C) Route: Oral	Mass balance, PK, metabolism, excretion, safety	NA	Healthy volunteers: 7	NA	1 center 1 country (USA)
TPX-0005-10	NA	Phase 1, two-part, open-label, fixed-sequence	Part 1: 80-160 mg Part 2: 160 mg Route: Oral	PK: DDI Itraconazole, rifampin, safety	NA	Male healthy volunteers: 30 (Part 1: 16; Part 2: 14)	NA	1 center 1 country (USA)
TPX-0005-11	NA	Phase 1, open-label, randomized, two-period, two-treatment crossover	160 mg Route: Oral	PK: food effect, safety	NA	Male healthy volunteers: 14	NA	1 center 1 country (USA)
TPX-0005-12	NA	Phase 1, open-label, randomized, balanced, single oral dose, 3-period crossover	4x40 mg or 1x 160 mg Route: Oral	PK: relative BA capsule formulations safety	NA	Male healthy volunteers: 17	NA	1 center 1 country (USA)

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
TPX-0005-14	NA	Phase 1, open-label, randomized, three-period, four-treatment crossover	160 mg [redacted] (b) (4) Formulation 1 capsule 160 mg vs clinical 40 mg capsule Route: Oral	PK: BE, safety	NA	Male healthy volunteers: 36	NA	1 center 1 country (USA)

Abbreviations: ALCL = anaplastic large cell lymphoma; BA = bioavailability; BCR = clinical benefit rate; BE = bioequivalence; BICR = Blinded Independent Central Review; BID = twice daily; cORR = confirmed overall response rate; 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; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; Pt = platinum; QD = once daily; RP2D = Recommended Phase 2 Dose; 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 subject 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 20 June 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 subjects with NSCLC whose tumors are *ROS1*-positive. For the integrated analysis plan, subject data were pooled from Phase 1 and Phase 2 of the TRIDENT-1 study. All *ROS1*-positive NSCLC subjects who initiated treatment on and before 15 October 2021 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 *ROS1*-positive NSCLC subjects, including the following EXP cohorts for the primary efficacy analysis:

- Pooled EXP-1 (TKI-naïve *ROS1*-positive NSCLC): 71 subjects (8 from Phase 1 and 63 from Phase 2)
- Pooled EXP-4 (TKI-pretreated: *ROS1*-positive NSCLC with 1 prior TKI and no prior platinum-based chemotherapy): 56 subjects (3 from Phase 1 and 53 from Phase 2)

Efficacy data for the *ROS1*-positive NSCLC subject populations below are presented as supportive, as these cohorts have yet to meet the protocol-defined total subject population:

- Pooled EXP-2 (TKI-pretreated: *ROS1* positive NSCLC with 1 prior TKI and 1 prior line of platinum-based chemotherapy): 26 subjects (3 from Phase 1 and 23 from Phase 2)
- Pooled EXP-3 (TKI-pretreated: *ROS1* positive NSCLC with 2 prior TKIs and no prior platinum-based chemotherapy): 18 subjects (1 from Phase 1 and 17 from Phase 2).

The primary safety dataset supporting the assessment of safety of repotrectinib comprises pooled results of 444 subjects from Phase 1 and Phase 2 of TRIDENT-1, including all subjects who received at least 1 dose of repotrectinib.

Preliminary safety data from the combination therapy study TRIDENT-2 (TPX-0005-13; n = 6) and the pediatric monotherapy study CARE (TPX-0005-07, n = 19), and safety data from supportive clinical pharmacology studies in healthy volunteers provide supportive evidence for the assessment of the repotrectinib safety profile.

Given the seriousness of the disease in this rare patient population as well as the high unmet medical need in the ROS1 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 patients with locally advanced or metastatic *ROS1*-positive NSCLC.

The FDA's Assessment:

FDA agrees with the Applicant's description of the integrated efficacy dataset, comprised of pooled EXP-1 and pooled EXP-4. Please refer to Section 8.2 regarding the 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)

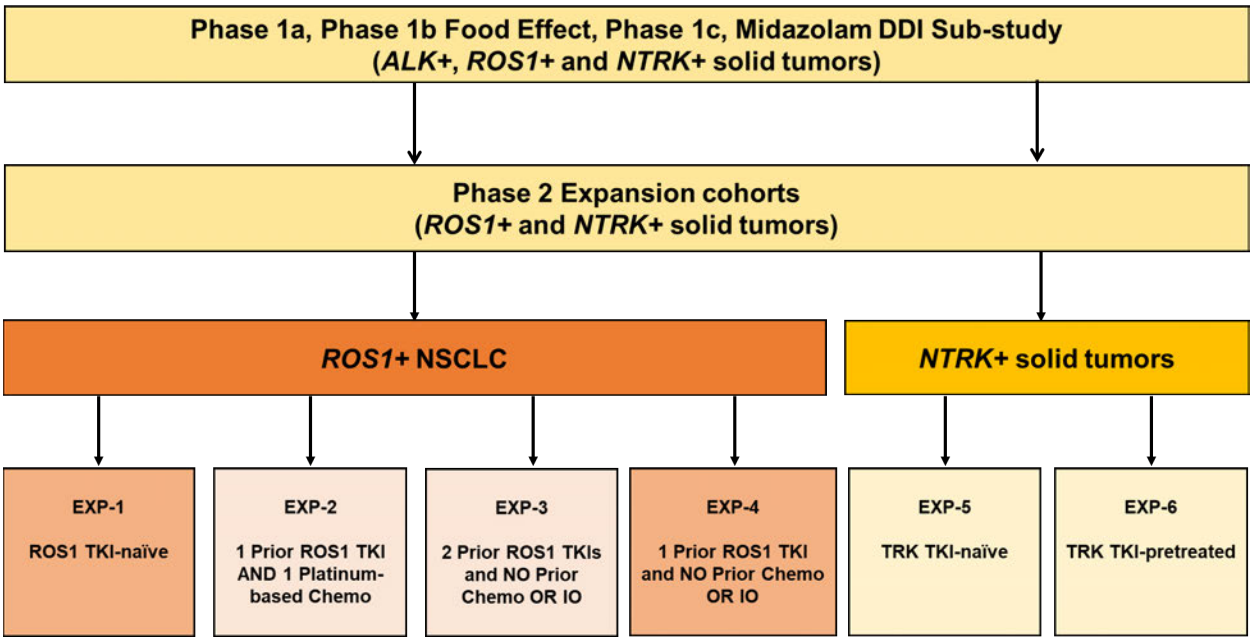
8.1.1.1. Trial Design

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 subjects 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 4. 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.
Source: Module 5.3.5.2, TPX-0005-01 Phase 1 CSR, Section 9.1.

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:

FDA generally agrees with the Applicant's description of the clinical trial design. FDA notes that the efficacy population consists of ROS1 positive NSCLC patients who have received distinct prior lines of therapy. Pooled cohorts EXP-1 and EXP-4 of TRIDENT-1 included patients who demonstrated a histologically or cytologically confirmed diagnosis of locally advanced or metastatic ROS1 positive NSCLC, with ROS1 fusion detected by Clinical Laboratory Improvement Amendments (CLIA) lab or equivalent.

From Phase 1 and 2 of TRIDENT-1, 71 patients with ROS1 positive NSCLC and who were TKI-naïve were grouped into the pooled cohort EXP-1 (8 from Phase 1 and 63 from Phase 2). The included Phase 1 patients were treated at the following doses: 240 mg QD, n=1; 40 mg QD, n=1; 80 mg QD, n=2, 160 mg QD, n=2; 120 mg QD with Food, n=1; and 160 mg QD/BID with Food, n=1. All other patients in the pooled EXP-1 cohort received the RP2D (160 mg orally once daily for 14 days, then increased to 160 mg twice daily).

An additional 56 TKI-pretreated patients with ROS1 positive NSCLC who received 1 prior TKI and no prior platinum-based chemotherapy from Phase 1 and 2 of Trident-1, were included in the pooled EXP-4 cohort (3 from Phase 1 and 53 from Phase 2). The 3 patients from Phase 1 received the following doses: 120 mg QD with Food, n=1; 160 mg QD with Food, n=1; and 160 mg BID, n=1. All other patients in the pooled EXP-4 cohort received the RP2D (160 mg orally once daily for 14 days, then increased to 160 mg twice daily).

Inclusion of patients who did not receive the RP2D was considered reasonable in this instance since the patients represent a small percentage of the efficacy population and their inclusion augments the sample size to improve the understanding of effectivity in this rare indication.

Eligibility Criteria

The Applicant's Description:

In Phase 1, eligible patients were male or female 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. Prior immunotherapy (eg, anti-PD-1, anti-PDL1, anti-TIM3, anti-OX40) was allowed. At the time of enrollment, all subjects 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 male or female patients 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. Locally advanced disease was defined as Stage III when the subject is not a candidate for surgery, radiation, or multi-modality therapy, and metastatic disease was defined as Stage IV per the AJCC Eighth Edition Cancer Staging Manual guidelines. At the time of enrollment, all subjects must have had archival tissue sample (or have de novo tissue sample available at the time of screening) for central laboratory confirmation of *ALK*, *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. Subjects with CNS-only measurable disease ≥ 10 mm as defined by RECIST v1.1 were eligible.

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 agrees with the Applicant's description of eligibility criteria.

8.1.1.2. Study Endpoints

The Applicant's Description:

A brief summary and description of key efficacy endpoints are provided in Table 31. Detailed methodology for summary and statistical analyses are provided in the TPX-0005-01 Integrated SAP, including full definitions and censoring rules.

Table 31. Definitions of Key Efficacy Endpoints in TRIDENT-1

Endpoint	Definition
ORR	The proportion of subjects with a 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 subjects with a ≥ 30% reduction from baseline (PR/CR) in intracranial target lesions, as assessed by modified RECIST v1.1, in the subset of subjects with baseline measurable CNS metastases by BICR.
CBR	The proportion of subjects 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 subjects 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 subject 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 subjects 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 assessment of study endpoints. FDA notes that time-to-event endpoints such as PFS and OS are difficult to interpret in this non-randomized setting.

Per the TRIDENT-1 protocol, patient imaging studies were reviewed by a BIRC. During the independent radiology review, all independent reviewers were blinded to patient name, initials, date of birth, exam date, total number of imaging timepoints, investigator site identifiers, site lesion selection for tumor assessments, site determination of tumor response, and reason for exam. As described in the Imaging Review Charter, images at each timepoint were assessed by two independent reviewers (double read) who were asked to determine an overall tumor assessment at each postbaseline timepoint according to RECIST 1.1 as described in IRC Section 5.7 Timepoint by Timepoint Radiology Review Assessment Criteria. Further, in the event of a disagreement between independent reviewers for a given patient, a process for adjudication was described in the charter.

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-0005-001). The Integrated SAP of repotrectinib is discussed here with focus on the 2 expansion cohorts used to assess the primary evidence for efficacy, ie, Pooled EXP-1 and Pooled EXP-4.

The current version of the Integrated SAP, version 3.0, was finalized on 12 December 2022. The initial SAP was updated to reflect changes in protocol amendments and add additional details to the analysis.

Patients were pooled from Phase 1 and Phase 2 of the study based on pooling criteria defined in the SAP. The pooling criteria for the primary efficacy population cohorts (Pooled EXP-1 and Pooled EXP-4) is as presented below:

- *ROS1*-positive TKI-naïve NSCLC cohort (Pooled EXP-1): includes all *ROS1*-positive NSCLC subjects in the Phase 1 and Phase 2 portions of TRIDENT-1 study who meet the following criteria:
    - Confirmation by central laboratory test for *ROS1* rearrangement per the requirement in each phase of TRIDENT-1 study protocol.
    - No prior exposure to a ROS1 TKI.
    - Started treatment at least 8 months prior to data cutoff date (6 months of follow-up for tumor assessment after first post-baseline scan).

- *ROS1*-positive TKI-pretreated NSCLC cohort (Pooled EXP-4): includes all locally advanced or metastatic *ROS1*-positive NSCLC subjects in the Phase 1 and Phase 2 portions of TRIDENT-1 study who meet the following criteria:
    - Confirmation by the central laboratory test for *ROS1* rearrangement per the requirement in each phase of TRIDENT-1.
    - Disease progression or intolerant to 1 prior line of ROS1 TKI treatment with no prior chemotherapy.
    - Started treatment at least 8 months prior to data cutoff date (6 months of follow-up for tumor assessment after first post-baseline scan).

Primary Efficacy Analysis:

- Confirmed ORR was the primary endpoint and presented for the primary efficacy analysis set for each of the primary efficacy population cohorts:
    - **Pooled EXP-1 (TKI-naïve *ROS1*-positive NSCLC):** For the primary efficacy population, 71 TKI-naïve *ROS1*-positive NSCLC subjects (8 subjects from Phase 1 and 63 from Phase 2 of TRIDENT-1) were expected to be eligible for pooling.
    - **Pooled EXP-4 (1 prior *ROS1*-positive TKI and NO Chemotherapy or Immunotherapy *ROS1*-positive NSCLC):** For the primary efficacy population, 56 *ROS1*-positive NSCLC subjects pretreated with 1 prior ROS1 TKI and no previous treatment with chemotherapy or immunotherapy (3 from Phase 1 and 53 from Phase 2 of TRIDENT-1) were expected to be eligible for pooling.

Safety Analysis:

- The Safety Analysis Set includes all subjects who are enrolled and have received any dose of repotrectinib in either the Phase 1 or Phase 2 portion of TRIDENT-1.
    - In addition, safety data are presented for the RP2D subject subpopulations receiving at least 1 dose of repotrectinib at the RP2D, and *ROS1*-positive NSCLC subjects receiving at least 1 dose of repotrectinib at the RP2D.

The primary endpoint of ORR is based on the radiologic assessments evaluated by the BICR for Phase 1 and Phase 2 of the TRIDENT-1 protocol using RECIST v1.1 and used the Efficacy Analysis Set, reported as the proportion of responders by RECIST v1.1 along with the corresponding 2-sided 95% Clopper-Pearson exact confidence interval.

DOR, as assessed by BICR per RECIST v1.1, was calculated only for the subgroup of subjects with a confirmed objective tumor response (PR or CR) and analyzed and presented graphically using the Kaplan-Meier method. If estimable, the median DOR and 95% CI for the median were constructed based on a linear transformed CI for the survival function S(t). Landmark analyses are presented for the proportion of subjects with observed DOR and 95% CI, using the Clopper-Pearson method, of at least 6, 9, 12, 18, and 24 months. The principal Kaplan-Meier assessment of DOR, for the time points at 6, 9, and 12 months, will be based on the data cutoff when the majority of responders would be at least 6 months post onset of first response, and for the 18-month and 24-month timepoints on the data cut when the majority of responders would be at least 12 months post-onset of response.

PFS based on BICR data is analyzed and presented graphically based on Kaplan-Meier methodology. The number of subjects with events and censored will be summarized. A 95% confidence interval constructed based on a linear transformed CI for the survival function S(t) using the Greenwood variance estimate is provided for the median, the first quartile, and the third quartile of PFS. The principal Kaplan-Meier assessment of PFS is conducted at the same timepoints as for DOR.

OS is also analyzed and presented graphically based on Kaplan-Meier methodology. Survival probability and 95% CI using Greenwood variance estimate and the linear transformation applied on the survival function S(t) are presented at 12, 18, and 24 months.

Subjects with a confirmed objective response (ie, CR or PR) were considered responders for the analysis of the primary endpoint. Otherwise, subjects were considered non-responders, which include PD, SD, NE, and missing. Best overall response (BOR) was based on assessments collected after the first dose of study drug until disease progression; assessments collected after the date of new cancer treatment were not considered.

In addition to the overall tumor assessment for the whole body by BICR, subjects in Phase 2 with measurable brain metastasis at baseline were to be evaluated by BICR for intracranial response per modified RECIST v1.1. Subjects in Phase 1 were not evaluated for intracranial response separately by BICR. Instead, the intracranial response and progression were calculated based on the target, non-target, and new lesions from the brain using the data for overall tumor assessment for the whole body by BICR. IC-ORR is provided as percentage along with the corresponding two-sided 95% Clopper-Pearson exact CIs.

PROs were evaluated in Phase 2 only as secondary objectives as of the data cutoff date (20 June 2022). Full details 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-subject change. For the time-to-event analyses, deterioration events were defined as a detrimental change in score relative to baseline that exceeds the prespecified thresholds for decline (10-point change) and, similarly, improvement events were defined as a beneficial change in score from baseline that exceeds the prespecified thresholds (10-point change).

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the statistical analysis plan (SAP). Please refer to Section 8.2 regarding FDA's approach to the safety analysis.

The initial version of the Integrated SAP version 1.0 was dated March 8, 2021. The second version was dated January 18, 2022. The current version 3.0 updated the efficacy analysis set by removing the criteria of having measurable disease at baseline.

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 11 times. At the time of the 20 June 2022 data cutoff, TRIDENT-1 study protocol version 12.0 (dated 14 January 2022) was in place globally. A summary of key changes relevant to the study endpoints are briefly described in Table 32. 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 32. TRIDENT-1 Protocol Amendments – Key Changes

Protocol Version Date	Description
Version 2.0 03 November 2016	• Updated statistical assumptions for primary endpoint of ORR based on treatment landscape.
Version 3.0 05 June 2018	• Added Phase 1c to investigate the administration of repotrectinib with food. • Updated the definition of the RP2D. • Updated the Sample Size Justification.
Version 4.0 02 November 2018	• Added Phase 1 secondary objective to evaluate the potential of repotrectinib to induce CYP3A using midazolam as a probe substrate. • Changed the Phase 2 secondary objective assessment to determine IC-ORR and CNS-PFS from RECIST v1.1 to RANO-BM. • Updated the Phase 2 study design to modify cohorts (total of 6 instead of 8).
Version 5.0 20 May 2019	• Added Phase 1 secondary objective to evaluate the single- and multiple-dose PK profiles of repotrectinib. • Removed Phase 2 secondary objective to assess the population PK and explore correlations between PK, response, and/or safety findings in subjects with an *ALK*, *ROS1*, *NTRK* gene rearrangements. • Defined that RP2D dose was 160 mg QD for the first 14 days and may be increased to 160 mg BID. • Modified the total number of subjects required in Phase 2 to approximately 320.
Version 6.0 07 June 2019	• No substantial changes.
Version 7.0 13 November 2019	• Modified Phase 2 Inclusion Criterion #2 allowing approved medical devices for local testing to be utilized for enrollment. • Modified Phase 2 Inclusion Criterion #7 for EXP-2 and EXP-3 to request that all subjects in Cohort 2 and Cohort 3 have been previously treated with platinum-based chemotherapy (only one line) with or without immunotherapy. • Modified Phase 2 Inclusion Criterion #7 for EXP-4 to all subjects requiring only one prior line of a ROS1 TKI and no prior lines of chemotherapy or immunotherapy. • Modified the sample size for Phase 2 EXP-4.
Version 8.0 02 January 2020	• Modified Phase 2 Inclusion Criterion #2 to remove option to utilize the Memorial Sloan Kettering Center IMPACT™ test for documentation of a *ROS1* or *NTRKI-3* gene fusion. • Modified Phase 2 Inclusion Criterion #8 to add EXP-4 to expansion cohorts requiring a washout time related to prior TKI treatment.
Version 9.0 23 March 2020	• Modified Phase 2 Inclusion Criterion #2 requirements for prospective testing, allowing NGS or qPCR tests to be utilized for enrollment.

Protocol Version Date	Description
	• Modified the Phase 2 Inclusion Criterion #8 washout time to 14 days after discontinuation of prior immunotherapy and all immune-related side effects from prior immunotherapy that must have resolved to grade ≤ 1. • Specified for the Phase 2 study that if an NGS or qPCR was used for local testing, the fusion status would be retrospectively confirmed using adequate tumor tissue by a central diagnostic laboratory test.
Version 10.0 20 October 2020	• Modified the Phase 2 Inclusion Criterion #7 for EXP-3 to remove requirement that all subjects in EXP-3 must have been previously treated with one line of platinum-based chemo/immuno-therapy. • Modified the number of subjects for Phase 2 EXP-2 and EXP-4.
Version 11.0 23 June 2021	• Modified number of subjects for enrollment in Phase 2 from approximately 320 to 365. • Updated Phase 2 Inclusion Criterion #7 for EXP-6 to add cabozantinib to prior lines.
Version 12.0 14 January 2022	• Increased the number of subjects enrolled in Phase 2 to approximately 620.

Abbreviations: CNS = central nervous system; CYP = cytochrome P450; IC-ORR = intracranial objective response rate; NGS = next-generation sequencing; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic(s); QD = once a day / once daily; qPCR = quantitative polymerase chain reaction; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; TKI = tyrosine kinase inhibitor.

The FDA's Assessment:

FDA agrees with the Applicant's summary of changes.

8.1.2. Study Results

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 was completed using good clinical practice guidelines.

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 19.2.

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 Module 1.3.4.

8.1.2.3. Patient Disposition

Data:

Table 33. Disposition in TKI-Naïve (Pooled EXP-1) and TKI-Pretreated (Pooled EXP-4) Subjects With ROS1-Positive NSCLC (Efficacy Analysis Set)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)			TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)
	With Prior Chemotherapy (N = 20)	**Without Prior Chemotherapy (N = 51)**	**Total (N = 71)**	**Total (N = 56)**
Subjects Dosed, n (%)	20 (100.0)	51 (100.0)	71 (100.0)	56 (100.0)
Subjects Ongoing Study Treatment, n (%)	9 (45.0)	36 (70.6)	45 (63.4)	19 (33.9)
Subjects Who Discontinued Study Treatment, n (%)	11 (55.0)	15 (29.4)	26 (36.6)	37 (66.1)
Radiographic Disease Progression[a]	6 (30.0)	9 (17.6)	15 (21.1)	20 (35.7)
Adverse Event	3 (15.0)	4 (7.8)	7 (9.9)	7 (12.5)
Investigator Decision	0	2 (3.9)	2 (2.8)	5 (8.9)
Withdrawal of Consent	2 (10.0)	0	2 (2.8)	4 (7.1)
Death	0	0	0	1 (1.8)
Subjects Ongoing Long-Term Follow Up, n (%)	1 (5.0)	9 (17.6)	10 (14.1)	11 (19.6)
Subjects Who Discontinued the Study, n (%)	10 (50.0)	6 (11.8)	16 (22.5)	26 (46.4)
Withdrawal of Consent	8 (40.0)	1 (2.0)	9 (12.7)	9 (16.1)
Death	2 (10.0)	5 (9.8)	7 (9.9)	17 (30.4)
Overall Duration of Follow-up, months[b]				
Median	25.46	16.13	18.07	15.54
Min, Max	11.1, 60.6	8.2, 28.1	8.2, 60.6	8.2, 52.7

Abbreviations: BICR = Blinded Independent Central Review; EXP = expansion cohort; max = maximum; min = minimum; NSCLC = non-small cell lung cancer; PI = Principal Investigator; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.
Notes: Data cutoff date of 20 June 2022.
[a] Radiographic progression includes subjects 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 subjects (TKI-naïve, N = 71; TKI-pretreated, N = 56), regardless of disposition
Source: Module 5.3.5.3 ISE Table 14.1.1.2, Table 14.1.1.3.

The Applicant's Position:

Pooled EXP-1

In Pooled EXP-1 (N = 71), 20 (28.2%) subjects were previously treated with chemotherapy and 51 (71.8%) subjects did not receive prior chemotherapy, consistent with the current preferred recommendation to use targeted therapy over front-line chemotherapy treatment regimens (NCCN 2022; Planchard 2020). As of the data cutoff date of 20 June 2022 majority of subjects (63.4%) continued on treatment, with a higher proportion of subjects without prior chemotherapy continuing treatment (70.6%) compared to subjects with prior chemotherapy (45.0%). The most frequently reported reasons for treatment discontinuation were disease progression (21.1%) followed by adverse event (9.9%). Sixteen (22.5%) subjects discontinued the study; reasons for study discontinuation were withdrawal of consent (12.7%) followed by death (9.9%).

Pooled EXP-4

In Pooled EXP-4 (N = 56) 19 (33.9%) subjects continued on treatment as of the data cutoff date of 20 June 2022. The median follow-up time was 15.5 months (range: 8.2, 52.7). Similar to the TKI-naïve population, the most frequently reported reasons for treatment discontinuation were disease progression (35.7%) followed by adverse event (12.5%). Twenty-six (46.4%) subjects discontinued the study; reasons for study discontinuation were death (30.4%) followed by withdrawal of consent (16.1%).

Overall, the disposition of the subjects 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 subjects with locally advanced or metastatic NSCLC.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition for the EXP-1 and EXP-4 pooled cohorts.

In the pooled population of TKI-naïve patients with ROS1-positive NSCLC (Pooled EXP-1, N = 71), 20 (28%) patients were previously treated with chemotherapy and 51 (72%) patients did not receive prior chemotherapy. As of the data cutoff date of June 20, 2022, a higher proportion of patients without prior chemotherapy continued treatment (71%) compared to patients with prior chemotherapy who continued treatment (45%). Reasons for treatment discontinuation included disease progression (21%), withdrawal of consent (13%), adverse events (10%), and death (10%).

The pooled EXP-4 cohort consisted of TKI-pretreated patients with ROS1-positive NSCLC and no prior immunotherapy or platinum-based chemotherapy (Pooled EXP-4, N = 56). As of June 20, 2022, 19 (34%) patients in the pooled EXP-4 (N = 56) cohort continued treatment. Reasons for treatment discontinuation included disease progression (36%), death (30%), withdrawal of consent (16%), and adverse events (13%).

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%) subjects reported an important deviation including overdose or misuse (12 [14.0%]), safety assessment deviations (4 [4.3%]), deviations to Informed Consent (2 [2%]), lab or endpoint data deviations (2 [2%]) and prohibited co-medication (1 [1%]). 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, 47 (13.8%) subjects reported at least 1 important deviation. The most commonly reported important deviation types (≥ 1% of all subjects) included informed consent (18 [5.3%]), safety assessments (13 [3.8%]), overdose or misuse (6 [1.8%]) and prohibited co-medication (6 [1.8%]). Note that the majority of deviations (> 80%) related to informed consent were due to delays in reconsenting on updated versions.

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 the reported deviations are unlikely to have significantly impacted the results of this study.

8.1.2.5. Table of Demographic Characteristics

Data:

Table 34. Key Demographics in TKI-Naïve (Pooled EXP-1) and TKI-Pretreated (Pooled EXP-4) Subjects With ROS1-Positive NSCLC (Efficacy Analysis Set)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)			TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)
	With Prior Chemotherapy (N = 20)	Without Prior Chemotherapy (N = 51)	Total (N = 71)	Total (N = 56)
Age (years)				
Mean	57.0	55.0	55.5	55.9
Median	59.0	56.0	57.0	57.0
Min, Max	32, 73	28, 80	28, 80	33, 78
Age Group, n (%)				
≥ 18 to < 65	14 (70.0)	38 (74.5)	52 (73.2)	41 (73.2)
≥ 65 to < 75	6 (30.0)	9 (17.6)	15 (21.1)	10 (17.9)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)			TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)
	With Prior Chemotherapy (N = 20)	Without Prior Chemotherapy (N = 51)	Total (N = 71)	Total (N = 56)
≥ 75	0	4 (7.8)	4 (5.6)	5 (8.9)
Sex, n (%)				
Female	12 (60.0)	31 (60.8)	43 (60.6)	38 (67.9)
Male	8 (40.0)	20 (39.2)	28 (39.4)	18 (32.1)
Race, n (%)				
Asian	16 (80.0)	32 (62.7)	48 (67.6)	27 (48.2)
White	3 (15.0)	15 (29.4)	18 (25.4)	25 (44.6)
Black or African American	0	1 (2.0)	1 (1.4)	1 (1.8)
Native Hawaiian or Other Pacific Islander	0	1 (2.0)	1 (1.4)	1 (1.8)
Not Reported	1 (5.0)	2 (3.9)	3 (4.2)	1 (1.8)
Unknown	0	0	0	1 (1.8)
Ethnicity, n (%)				
Hispanic or Latino	0	3 (5.9)	3 (4.2)	1 (1.8)
Not Hispanic or Latino	20 (100.0)	48 (94.1)	68 (95.8)	53 (94.6)
Region				
US	3 (15.0)	8 (15.7)	11 (15.5)	17 (30.4)
Asia	14 (70.0)	27 (52.9)	41 (57.7)	23 (41.1)
Other[a]	3 (15.0)	16 (31.4)	19 (26.8)	16 (28.6)

Abbreviations: EXP = expansion cohort; max = maximum; min = minimum; NSCLC = non-small cell lung cancer; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene TKI = tyrosine kinase inhibitor; US = United States.
Notes: Data cutoff date of 20 June 2022.
[a] Countries grouped to "Other" include Australia, Belgium, Canada, Germany, Spain, France, United Kingdom, Netherlands, Italy, and Poland.
Source: Module 5.3.5.3 ISE Table 14.1.3.2, Table 14.1.3.3, Table 14.1.4.2, Table 14.1.4.3, Table 14.1.7.2, Table 14.1.8, Table 14.2.1.22, Table 14.2.1.23

The Applicant's Position:

ROS1 oncogenic driver mutations are most commonly seen in younger patients, Asians, and females (Chevallier 2021; Gendarme 2022), which is reflected in the TRIDENT-1 TKI-naïve and TKI-pretreated populations by median age (57 years), prevalence of Asian subjects (TKI-naïve, 67.6%; TKI-pretreated, 48.2%), and higher proportion of females (TKI-naïve, 60.6%; TKI-pretreated, 67.9%).

Representation by race and ethnic populations were as expected and generally representative of the *ROS1*-positive NSCLC patient population, including under-represented groups of Black or African American (TKI-naïve, 1.4%; TKI-pretreated, 1.8%), Native Hawaiian or Other Pacific Islanders (TKI-naïve, 1.4%; TKI-pretreated, 1.8%), and Hispanic or Latino (TKI-naïve, 4.2%; TKI-pretreated, 1.8%) which have been reported at a prevalence ranging from 0 to 2.5% in the real-world setting (Costa 2021; Shi 2022; Liang 2014; Villanueva 2022; Zheng 2020).

Overall, the TKI-naïve and TKI-pretreated populations in TRIDENT-1 were diverse and are considered generally representative of patients that will be treated in clinical practice, based on the target indication for repotrectinib (Gendarme 2022; Costa 2021; Shi 2022).

The FDA's Assessment:

FDA generally agrees with the Applicant's description of patient demographics.

8.1.2.6. Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Data:

Table 35. Key Baseline Disease Characteristics in TKI-Naïve (Pooled EXP-1) and TKI-Pretreated (Pooled EXP-4) Subjects With ROS1-Positive NSCLC (Efficacy Analysis Set)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)			TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)
	With Prior Chemotherapy (N = 20)	Without Prior Chemotherapy (N = 51)	Total (N = 71)	Total (N = 56)
Baseline ECOG Performance Status, n (%)				
0	9 (45.0)	15 (29.4)	24 (33.8)	18 (32.1)
1	11 (55.0)	36 (70.6)	47 (66.2)	38 (67.9)
Smoking Status, n (%)				
Current	0	2 (3.9)	2 (2.8)	1 (1.8)
Former	4 (20.0)	12 (23.5)	16 (22.5)	16 (28.6)
Never	8 (40.0)	37 (72.5)	45 (63.4)	36 (64.3)
Missing	8 (40.0)	0	8 (11.3)	3 (5.4)
Histology, n (%)				
Adenocarcinoma	20 (100.0)	49 (96.1)	69 (97.2)	53 (94.6)
Adenosquamous carcinoma	0	1 (2.0)	1 (1.4)	1 (1.8)
Squamous	0	1 (2.0)	1 (1.4)	1 (1.8)
Mucoepidermal carcinoma	0	0	0	1 (1.8)
Disease at Study Entry				
Metastatic	19 (95.0)	48 (94.1)	67 (94.4)	55 (98.2)
Locally Advanced	1 (5.0)	3 (5.9)	4 (5.6)	1 (1.8)
Brain Metastasis by BICR, n (%)				
Yes	4 (20.0)	14 (27.5)	18 (25.4)	24 (42.9)
No	16 (80.0)	37 (72.5)	53 (74.6)	32 (57.1)
Prior Therapy, n (%)				
Prior TKI Therapy	0	0	0	56 (100.0)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)			TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)
	With Prior Chemotherapy (N = 20)	Without Prior Chemotherapy (N = 51)	Total (N = 71)	Total (N = 56)
Platinum-based Chemotherapy[b]	20 (100.0)	0	20 (28.2)	26 (26.0)
Immunotherapy Alone	2 (10.0)	0	2 (2.8)	0
Other Targeted Therapy	1 (5.0)	0	1 (1.4)	0
Prior lines of systemic anticancer therapy				
Median (Min, Max)	1.00 (1.0, 3.0)	0	(0, 3.0)	1.00 (1.0, 1.0)
0	0 (0.0)	51 (100.0)	51 (71.8)	0
1	16 (80.0)	0	16 (22.5)	56 (100.0)
2	2 (10.0)	0	2 (2.8)	0
≥ 3	2 (10.0)	0	2 (2.8)	0
Prior TKI Therapy, n (%)[c]				
Crizotinib	NA	NA	NA	46 (82.1)
Entrectinib	NA	NA	NA	9 (16.1)
Ceritinib	NA	NA	NA	1 (1.8)
Resistance Mutations				
Solvent Front	NA	NA	NA	6 (10.7)
Gatekeeper	NA	NA	NA	1 (1.8)
Other	NA	NA	NA	1 (1.8)
Not Detected/QC Failure	NA	NA	NA	5 (8.9)
Not tested	NA	NA	NA	43 (76.8)

Abbreviations: BICR = Blinded Independent Central Review; ECOG = Eastern Cooperative Oncology Group; EXP = expansion cohort; max = maximum; min = minimum; NA = Not Applicable NSCLC = non-small cell lung cancer; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene TKI = tyrosine kinase inhibitor.
Notes: Data cutoff date of 20 June 2022.
[a] Anatomical sites limited to brain, lung, liver, adrenal, bone, lymph node and other through medical review.
[b] All subjects received platinum-based chemotherapy.
[c] All subjects received a TKI
Source: Module 5.3.5.3 ISE Table 14.1.3.2, Table 14.1.4.2, Table 14.1.7.2, Table 14.2.1.22, Table 14.1.3.3, Table 14.1.4.3, Table 14.1.7.3, Table 14.1.8, Table 14.2.1.23

The Applicant's Position:

Pooled EXP-1

Among the subjects in Pooled EXP-1 (N = 71), the majority never smoked (63.4%) and had an ECOG performance status of 1 (66.2%) at study entry. Most subjects (94.4%) had metastatic disease, with advanced disease reported in 5.6% at study entry. Eighteen (25.4%) subjects had brain metastases at baseline as determined by BICR assessment.

Pooled EXP-4

Among the subjects in Pooled EXP-4 (N = 56), the majority of subjects never smoked (64.3%) and had an ECOG performance status of 1 (67.9%) at study entry. Fifty-five (98.2%) subjects had

metastatic disease and 1 (1.8%) locally advanced disease at study entry. Twenty-four (42.9%) subjects had brain metastases at baseline as determined by BICR assessment. Subjects were not required to be tested for resistance mutations per protocol; for those subjects that were tested (13 of 56 in EXP-4), 8 (14.3%) subjects had resistance mutations including 6 (10.7%) subjects with solvent front mutations. The majority of TKI-pretreated subjects (82.1%) were pretreated with crizotinib, which is not unexpected given the first approval of entrectinib was in August 2019 when the global TRIDENT-1 Phase 2 began enrollment (20 August 2019).

Overall, the baseline disease characteristics were as expected for the subject population 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 *ROS1*-positive NSCLC populations that would be treated in the clinic, with a high proportion of never smokers, most NSCLCs being lung adenocarcinomas, and incidence of CNS disease and SFMs (Gendarme 2022; Ou 2019).

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of baseline characteristics. Among TKI-naïve patients with ROS1 positive NSCLC (pooled EXP-1) (N = 71), 8 had measurable CNS metastases at baseline as assessed by BICR. In the pooled EXP-4 population of TKI pretreated patients with ROS1 positive NSCLC (N = 56), 8 had resistance mutations following TKI therapy. Mutations observed included: solvent front (G2032R) (CD74-ROS1, n=5 and SLC34A2-ROS1, n=1); gatekeeper (L2026M) (EZR-ROS1, n=1); and other/kinase domain (S1986F/Y) (EZR-ROS1, n=1). There were 41 patients in this group who were known resistance mutation negative. In addition, 12 patients in the pooled EXP-4 cohort had measurable CNS metastases at baseline as assessed by BICR.

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

The Applicant's Position:

Treatment Compliance

Subjects were largely compliant with treatment throughout the study, as determined by the subject 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 = 444) was 4.62 (0.1, 60.6) months and 5.5 (1, 66) cycles, respectively, with a median relative dose intensity of 95.45%.

The median duration of exposure to treatment and number of treatment cycles in TKI-naïve subjects (Pooled EXP-1) was 13.3 months (range: 0.8, 60.6) and 15 (range: 1, 66), respectively, with a median relative dose intensity of 88.5%. The median duration of exposure to treatment and number of treatment cycles in TKI-pretreated subjects (Pooled EXP-4) was 8.3 months (range: 0.5, 24.8) and 9 (range: 1, 27), respectively, with a median relative dose intensity of 87.9%.

Concomitant Medications

All concomitant medication and concurrent treatments (eg, radiation therapy) were documented at Screening and at every clinic visit. Important protocol deviations of prohibited co-medication occurred in 2 (2.2%) subjects and 6 (1.8%) subjects 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 subject safety or interpretability of the results.

Rescue Medication

Not applicable

The FDA's Assessment:

FDA agrees with the Applicant's summary of treatment compliance. In Phase 1 of TRIDENT-1, 13 patients reported deviations including overdose or misuse. One of the 13 deviations was associated with dosing compliance that led to administration of less than 90% or more than 110% of the overall expected dose. Notably, the remaining patients with deviations in Phase 1 included events such as safety assessment deviations (4 [4.3%]), deviations to Informed Consent, lab or endpoint data deviations and prohibited co-medication (2 patients each). In the Phase 2 portion of the study, overdose or misuse was reported in 6 patients and prohibited co-medication was reported in 6 patients. Prohibited concomitant medications consisted of strong CYP3A4 inhibitors and medications causing QTc prolongation.

The most frequently used therapeutic classes of concomitant medications in Phase 1 of Trident-1 were nervous system including opioids (80%), alimentary tract and metabolism (79%), and antibiotics (63%). The most frequently used therapeutic classes of concomitant medications in Phase 2 of Trident-1 were analgesics including opioids (42%), drugs for constipation (36%), acid reflux disorders (27%), antithrombotic (27%), psycholeptics (19%), and antiemetics (14%).

8.1.2.8. Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The integrated efficacy analysis focuses on the *ROS1*-positive NSCLC cohorts EXP-1 to EXP-4 with Pooled EXP-1 (TKI naïve) and Pooled EXP-4 (TKI pretreated with 1 prior TKI and no chemotherapy) as primary efficacy cohorts and Pooled EXP-2 (TKI pretreated with 1 prior TKI and platinum chemotherapy) and Pooled EXP-3 (TKI pretreated with 2 prior TKI and no chemotherapy) serving as supportive efficacy cohorts. The Efficacy Analysis Set included all locally advanced or metastatic *ROS1*-positive NSCLC subjects from Phase 1 and Phase 2 of TRIDENT-1 who met the pooling criteria (defined in Section 8.1.1).

Among subjects in Pooled EXP-1, the confirmed ORR by BICR assessment was 78.9% (N = 56 of 71; 95% CI: 67.6, 87.7), including 4 (5.6%) CRs and 52 (73.2%) PRs (Table 36). The estimated median DOR for the 56 responding subjects was 27.4 months (95% CI: 23.1, NE), with DOR ranging from 1.4+ to 35.1+ months and landmark analyses showing a probability of subjects

without a PFS event at ≥ 9 and ≥ 12 months was 88.8% (95% CI: 80.3, 97.2) and 86.1% (95% CI: 76.4, 95.8), respectively.

Among subjects in Pooled EXP-4, the confirmed ORR by BICR assessment was 37.5% (N = 21 of 56; 95% CI: 24.9, 51.5) with 3 subjects (5.4%) achieving a CR and 18 subjects (32.1%) achieving a PR. The estimated median DOR for the 21 responding subjects was 17.8 months (95% CI: 7.6, NE), with the DOR ranging from 3.7 to 17.8 months and landmark analyses showing a probability of subjects without a PFS event at ≥ 9 months was 59.6% (35.9, 83.4).

Table 36. Primary and Key Efficacy Endpoints (by BICR) in TKI-Naïve (Pooled EXP-1) and TKI-Pretreated (Pooled EXP-4) Subjects With ROS1-Positive NSCLC (Efficacy Analysis Set)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)			**TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)**
***ROS1*-positive NSCLC, TKI-Naïve**	**With Prior Chemotherapy (N = 20)**	**Without Prior Chemotherapy (N = 51)**	**Total (Pooled EXP-1) (N = 71)**	**Total (Pooled EXP-4) (N = 56)**
Key Efficacy Data				
Confirmed ORR, % (95% CI)	70.0 (45.7, 88.1)	82.4 (69.1, 91.6)	78.9 (67.6, 87.7)	37.5 (24.9, 51.5)
CR, n (%)	0	4 (7.8)	4 (5.6)	3 (5.4)
PR, n (%)	14 (70.0)	38 (74.5)	52 (73.2)	18 (32.1)
Median Time to Response, months (range)	1.71 (0.9, 5.4)	1.84 (1.6, 5.5)	1.84 (0.9, 5.5)	1.84 (1.6, 3.6)
Duration of Response (DOR)				
Events, n (%)	6 (42.9)	6 (14.3)	12 (21.4)	8 (38.1)
Median DOR, months (95% CI)	27.40 (23.10, NE)	NE (NE, NE)	27.40 (23.10, NE)	17.81 (7.56, NE)
DOR Landmark Analyses (Kaplan Meier), % (95% CI)[a]				
DOR ≥ 6 months	85.7 (67.4, 100.0)	92.5 (84.3, 100.0)	90.7 (82.9, 98.5)	79.5 (61.5, 97.5)
DOR ≥ 9 months	85.7 (67.4, 100.0)	89.9 (80.5, 99.3)	88.8 (80.3, 97.2)	59.6 (35.9, 83.4)
DOR ≥ 12 months	77.1 (54.2, 100.0)	89.9 (80.5, 99.3)	86.1 (76.4, 95.8)	59.6 (35.9, 83.4)

Abbreviations: BICR = Blinded Independent Central Review; CR = complete response; DOR = duration of response; EXP = expansion cohort; ORR = objective response rate; PR = partial response; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.

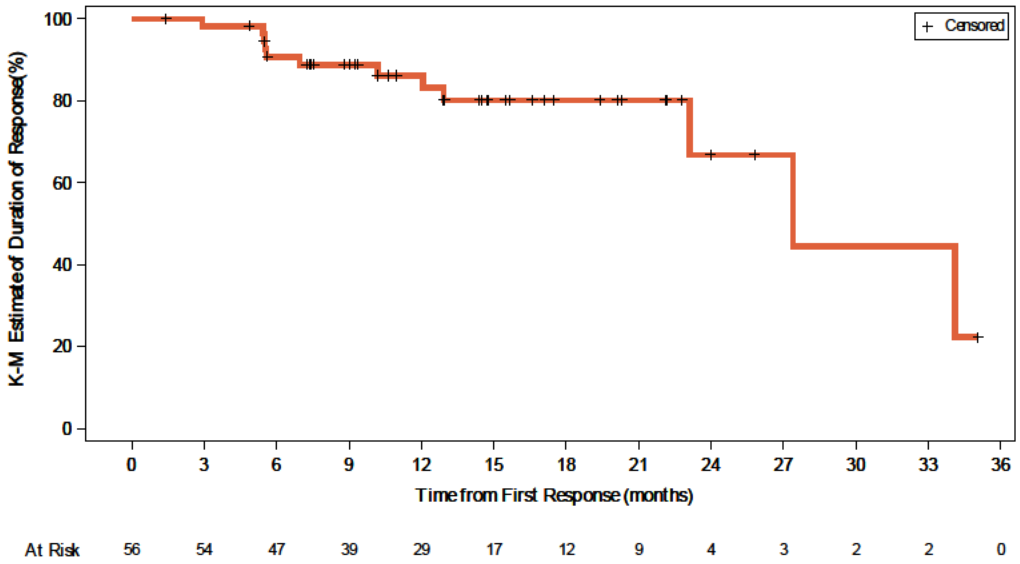
Notes: Data cutoff date of 20 June 2022.

[a] Landmark analyses up to 24 month are reported in Module 5.3.5.3 ISE Table 14.2.1.2

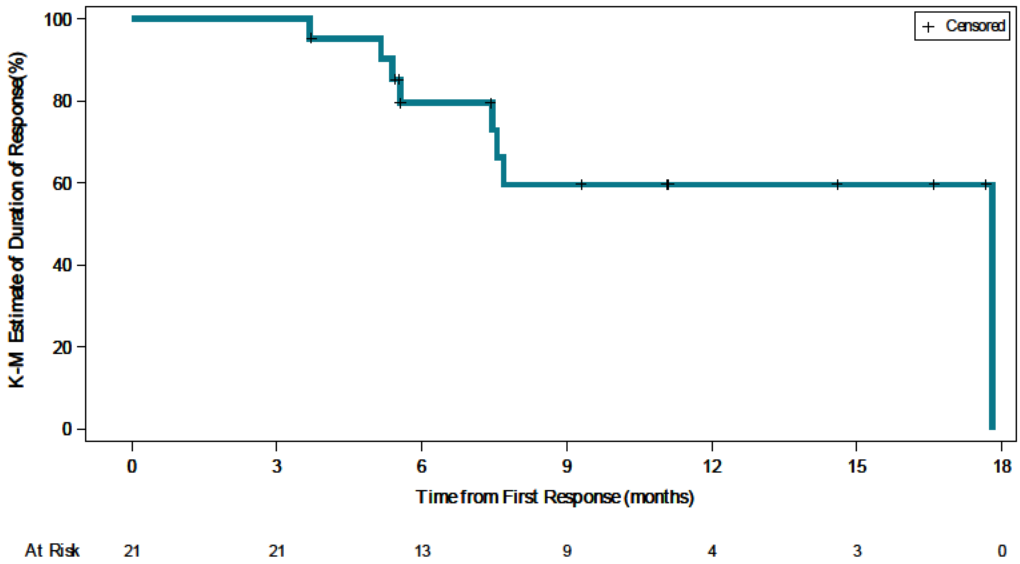
Sources: Module 5.3.5.3 ISE Table 14.1.6.2, Table 14.2.1.1, Table 14.2.3.1, Table 14.2.6.1, Table 14.1.6.3, Table 14.2.1.2, Table 14.2.3.2, Table 14.2.6.2

Figure 5. Time-to-Event Analyses (Kaplan Meier): Duration of Response (by BICR) in TKI Naïve (Pooled EXP-1) and TKI-Pretreated (Pooled EXP-4) Subjects With ROS1-Positive NSCLC (N = 71)

A. Pooled EXP-1 (N = 71)



B. Pooled EXP-4 (N = 56)



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 20 June 2022 with response assessment by BICR using RECIST v1.1.
Source: Module 5.3.5.3 ISE Figure 14.2.3.1, Figure 14.2.3.4

Pooled EXP-2

Among subjects in Pooled EXP-2 (*ROS1*-positive NSCLC pretreated with 1 prior TKI and chemotherapy), the confirmed ORR was 42.3% (N = 11 of 26; 95% CI: 23.4, 63.1), with 1 subject (3.8%) achieving a CR and 10 subjects (38.5%) achieving a PR. The estimated median DOR for the 11 responders was 8.7 months (95% CI: 4.4, NE; number of events=6) and the DOR ranged from 3.6 to 25.6+ months.

Pooled EXP-3

Among subjects in Pooled EXP-3 (*ROS1*-positive NSCLC pretreated with 2 prior TKI and no chemotherapy), the confirmed ORR was 27.8% (N = 5 of 18; 95% CI: 9.7, 53.5), with 1 subject (6%) achieving a CR and 4 subjects (22%) achieving a PR. The estimated median DOR for the 5 responders was 7.4 months (95% CI: 3.5, NE; number of events=3) and the DOR ranged from 3.5 to 25.8+ months.

The Applicant's Position:

Durable clinical responses were seen with repotrectinib in patients with *ROS1*-positive NSCLC who were TKI-naïve (Pooled EXP-1) or TKI pretreated (Pooled EXP-4). The results described above were evaluated by BICR after patients had the opportunity for at least 8 months of follow-up (6 months from first on-treatment scan) to allow for adequate characterization of DOR.

Pooled EXP-1

In the pooled population of TKI-Naïve subjects with *ROS1*-positive NSCLC (Pooled EXP-1, N = 71), treatment with repotrectinib demonstrated clinically meaningful efficacy through:

- Robust anti-tumor activity with a confirmed ORR by BICR of 78.9% (N = 56 of 71; 95% CI: 67.6, 87.7).
- Rapid onset of response (median TTR = 1.8 months; range: 0.9, 5.5).
- In subjects with post-baseline scans, deep responses were observed with most subjects (67.6%) having a reduction in the size of target lesions of at least 60% from baseline. Of note, all subjects (100%) with post-baseline scans showed a reduction in target lesions from baseline.
- Durable responses with an estimated median DOR of 27.4 months (95% CI: 23.1, NE), with landmark analyses of DOR showing a probability of subjects remaining in a response at ≥ 9 and ≥ 12 months was 88.8% (95% CI: 80.3, 97.2) and 86.1% (95% CI: 76.4, 95.8), respectively.
- Estimated median PFS of 31.1 months (95% CI: 24.6, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 9 months and ≥ 12 months was 81.3% (95% CI: 71.8, 90.9) and 79.7% (95% CI: 69.8, 89.6), respectively.
- Response irrespective of treatment with prior chemotherapy.
- Responses in subjects with locally advanced and metastatic disease (ORR of 79% (N = 53 of 67) in the metastatic population; ORR of 75% (N = 3 of 4) in the locally advanced population.

Pooled EXP-4

In the pooled population of TKI-pretreated subjects with *ROS1*-positive NSCLC (Pooled EXP-4, N = 56), treatment with repotrectinib demonstrated clinically meaningful efficacy through:

- Clinically meaningful activity with a confirmed ORR by BICR of 37.5% (N = 21 of 56; 95% CI: 24.9, 51.5).
- Rapid onset of response (median TTR was 1.8 months; range: 1.6, 3.6).
- In subjects with post-baseline scans, deep responses were observed with 37.5% of subjects having a reduction in the size of target lesions of at least 60% from baseline. Of note, most subjects (87.5%) with post-baseline scans showed a reduction in target lesions from baseline.
- Durable responses with an estimated median DOR (Kaplan-Meier) of 17.8 months (95% CI: 7.6, NE), with landmark analyses of DOR showing a probability of subjects remaining in a response at ≥ 9 months was 59.6% (35.9, 83.4).
- Estimated median PFS of 9.0 months (95% CI: 7.3, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 9 months was 55.1% (95% CI: 40.5, 69.7).
- Responses in metastatic setting and activity in the locally advanced setting (all 21 responders had metastatic disease at baseline; one subject had locally advanced disease at baseline and achieved SD as best response).

Responses achieved in subjects who have received 1 prior TKI and platinum-based chemotherapy (Pooled EXP-2) and those who have received 2 prior TKIs with no prior chemotherapy (Pooled EXP3) further support the data presented for the -TKI-pretreated *ROS1*-positive NSCLC primary efficacy analysis cohort (Pooled EXP-4).

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of ORR and DOR by BIRC. The primary data FDA reviewed in this application comes from pooled cohorts EXP-1 and EXP-4 from the TRIDENT-1 study. FDA did not independently verify other cohort results (e.g., EXP-2 and EXP-3) from TRIDENT-1. The results used to support this application were based on the original data cutoff (DCO) date of June 20, 2022, with at least 6 months of follow-up for tumor assessment after the first post-baseline scan.

In the pooled population of TKI-naïve patients with *ROS1*-positive NSCLC (Pooled EXP-1, N = 71), the confirmed ORR per RECIST 1.1 as determined by BIRC was 79% (95% CI 68, 88) for 56 responders (CR: n= 4 [6%] and PR: 52 [73%]). The median DOR was 34.1 months (95% CI 25.6, NE) Table 37. Patients treated at the RP2D accounted for 79% of the pooled EXP-1 cohort. Among the 8 patients who were treated with doses other than the RP2D, 4 demonstrated PRs, 3 demonstrated SD and one demonstrated PD.

In the pooled EXP-1 cohort, efficacy by BICR and investigator were consistent. Per investigator

at the June 20, 2022, data cutoff, ORR was 76% (N = 54 of 71; 95% CI 65, 85). The median DOR per investigator and per BICR was similar and was reported for the 56 responding patients as 27.4 months (95% CI 23.1, NE) and for the 54 responding patients as 26.7 months (95% CI 19.4, NE), respectively.

In the pooled population of TKI-pretreated patients with *ROS1*-positive NSCLC (Pooled EXP-4, N = 56), the confirmed ORR per RECIST 1.1 as determined by BIRC was 38% (95% CI 25, 52). The median DOR was as 14.8 months (95% CI 7.6, NE) in Table 37. Patients treated at the RP2D accounted for 78.6% of the pooled EXP-4 cohort. Among the 3 patients included in the pooled EXP-4 cohort not treated at the RP2D, all patients demonstrated PRs.

In the pooled EXP-4 cohort, efficacy by BICR and investigator were consistent. Per investigator at the June 20, 2022, cutoff, ORR was 39% (N = 22 of 56; 95% CI 27, 53). The median DOR as assessed by BICR vs investigator reported for the 21 responding patients was 17.8 months (95% CI 7.6, NE) and for the 22 responding patients as 9.4 months (95% CI 6.8, NE), respectively. The 95% confidence intervals for the median DORs overlapped significantly. The difference between BICR and investigator stems from selection of different target lesions and with additional follow-up, the difference in DOR is no longer substantial.

During the Application review period, the Applicant provided updated efficacy based on the DCO of December 19, 2022, which included an additional 6 months of DOR follow-up. Results from both original and updated analyses are presented in Table 37.

Table 37. FDA Primary Endpoints in Pooled EXP-1 and EXP-4 Cohorts at Primary and Updated DCOs (Efficacy Analysis Set)

	Pooled EXP-1 TKI-Naïve (N=71)		Pooled EXP-4 TKI-Pretreated (N=56)	
	Primary DCO	Updated DCO	Primary DCO	Updated DCO
ORR				
Confirmed ORR, % (95% CI)	79 (68, 88)		38 (25, 52)	
Complete Response	6	10	5	5
Partial Response	73	69	32	32
DOR				
Confirmed Responses, n	56		21	
Events, n (%)	12 (21)	15 (27)	8 (38)	11 (52)
Median DOR, months (95% CI)[a]	27.4 (23.1, NE)	34.1 (25.6, NE)	17.8 (7.6, NE)	14.8 (7.6, NE)
Range, months	1.4+, 35.1+	1.4+, 42.4+	3.7, 17.8	3.6, 22.9+
% DOR ≥12 months[b]	52	70	19	48

Abbreviations: CI = confidence interval, NE: not estimable, +: ongoing response

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

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

Impact of potential informative censoring on DOR estimation

FDA identified informative censoring as one of the potential factors impacting robustness of DOR estimates. Among the 56 responders in Pooled EXP-1, DOR was censored for 41 patients. Of the 41 patients, 6 patients received subsequent anti-cancer therapy (ACT) in the absence of disease progression per BICR before the updated DCO. Of the 6 patients, 4 had radiographic disease progression per investigator only. These 6 patients were censored at the last evaluable tumor assessment per BICR prior to the start of new ACT.

Among the 21 responders in Pooled EXP-4, DOR was censored for 10 patients. Of the 10 patients, 2 patients received subsequent ACT in the absence of disease progression per BICR before the updated DCO. Both of these patients had radiographic disease progression per investigator only and were censored at the last evaluable tumor assessment per BICR prior to the start of new ACT.

In response to an Information Request dated October 19, 2023, to evaluate the potential impact of informative censoring on DOR, the Applicant conducted sensitivity analyses by treating those patients who were censored prior to new ACT as events. Median DOR in the Pooled EXP-1 changed from 34.1 months (95% CI 25.6, NE) to 27.4 months (95% CI 23.1, NE), and remained similar in the Pooled EXP-4.

In summary, the magnitude and durability of the response rates observed for repotrectinib are

clinically meaningful for this patient population with a poor prognosis. The evidence of anti-tumor activity in patients who received one prior ROS1 TKI supports repotrectinib as a new therapeutic option for a patient population with an unmet medical need. The ORR observed in ROS1 TKI-naïve patients is comparable to the response rates observed in other approved therapies for this indication (crizotinib and entrectinib).

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 subjects 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 subjects 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 ROS1 positive NSCLC. FDA issued information requests during the review cycle to obtain clarification and additional information regarding data included in the NDA and all requests were addressed appropriately.

8.1.2.10. Efficacy Results – Secondary and Other Relevant Endpoints

Data:

Table 38. Key Secondary Efficacy Endpoints (by BICR) in TKI-Naïve (Pooled EXP-1) and TKI-Pretreated (Pooled EXP-4) Subjects With ROS1-Positive NSCLC (Efficacy Analysis Set)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)			TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)
***ROS1*-positive NSCLC, TKI-Naïve**	**With Prior Chemotherapy (N = 20)**	**Without Prior Chemotherapy (N = 51)**	**Total (Pooled EXP-1) (N = 71)**	**Total (Pooled EXP-4) (N = 56)**
Key Secondary Efficacy Data				
CBR (CR + PR + SD), % (95% CI)	90.0 (68.3, 98.8)	96.1 (86.5, 99.5)	94.4 (86.2, 98.4)	82.1 (69.6, 91.1)
Median Duration of Treatment, months (range)	15.46 (0.8, 60.6)	12.09 (1.5, 28.1)	13.27 (0.8, 60.6)	8.25 (0.5, 24.8)
Progression-Free Survival (PFS)				
Events, n (%)	7 (35.0)	13 (25.5)	20 (28.2)	28 (50.0)
Median PFS, months (95% CI)	31.11 (24.64, NE)	NE (NE, NE)	31.11 (24.64, NE)	9.03 (7.29, NE)
PFS Landmark Analyses (Kaplan Meier), % (95% CI) [b]				
PFS ≥ 6 months	100.0 (100.0,100.0)	87.6 (78.3, 96.9)	90.9 (83.9, 97.8)	67.4 (54.2, 80.6)
PFS ≥ 9 months	88.2 (72.9, 100.0)	78.9 (67.2, 90.5)	81.3 (71.8, 90.9)	55.1 (40.5, 69.7)
PFS ≥ 12 months	88.2 (72.9, 100.0)	76.7 (64.6, 88.8)	79.7 (69.8, 89.6)	44.3 (29.2, 59.4)
Overall Survival (OS)				
Death, n (%)	2 (10.0)	5 (9.8)	7 (9.9)	17 (30.4)
Median OS, months (95% CI)	44.42 (44.42, NE)	NE (NE, NE)	NE (44.42, NE)	25.13 (17.87, NE)
IC-ORR, % (n/N) [a]	50.0 (1/2)	100.0 (6/6)	87.5 (7/8)	41.7 (5/12)

Abbreviations: BICR = Blinded Independent Central Review; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DOR = duration of response; EXP = expansion cohort; NE = not evaluable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.

Notes: Data cutoff date of 20 June 2022.

[a] IC-ORR was evaluated in Phase 2 of the TRIDENT-1 study. Of the 63 TKI-naïve subjects from Phase 2, 8 subjects had measurable brain disease at baseline by BICR; of the 53 TKI-pretreated subjects in EXP-4 from Phase 2, 12 subjects had measurable disease at baseline by BICR.

[b] Landmark analyses up to 24 months are reported in Module 5.3.5.3, ISE Table 14.2.3.1, Table 14.2.3.2

Sources: Module 5.3.5.3, ISE Table 14.1.6.2, Table 14.2.1.1, Table 14.2.3.1, Table 14.2.6.1, Table 14.1.6.3, Table 14.2.1.2, Table 14.2.3.2, Table 14.2.6.2

The Applicant's Position:

Pooled EXP-1

In the pooled population of TKI-Naïve subjects with *ROS1*-positive NSCLC (Pooled EXP-1, N = 71), clinically meaningful efficacy demonstrated with the key efficacy endpoints described above were further supported by key secondary efficacy endpoints:

- CBR of 94.4% (N = 67 of 71; 95% CI: 86.2, 98.4), including 4 CRs, 52 PRs, and 11 subjects who had SD ≥ 6 weeks.
- Median duration of treatment of 13.3 months (range: 0.8, 60.6 months), with 45 (63.4%) of the 71 subjects remaining on treatment, including 42 (75.0%) of the 56 subjects with confirmed responses.
- Estimated median PFS of 31.1 months (95% CI: 24.6, NE), with PFS ranging from 0.0+ to 40.4+ months.
- Intracranial activity in 87.5% (7/8) of subjects with measurable brain metastases at baseline per BICR, including 1 CR and 6 PRs. The DOR among these 7 responding subjects ranged from 1.9 to 14.8 months at the time of the data cutoff date and 6 subjects remained on treatment in response.
- Among the 21 (29.6%) subjects with progression, the most common sites of progression were the lung (10 [47.6%]), lymph node (7 [33.3%]) and bone (5 [23.8%]). Overall, 15 (71.4%) subjects with progression continued treatment beyond progression due to sustained clinical benefits; the median time on treatment post progression was 2.1 months (range: 0.2, 32.5).

Pooled EXP-4

In the pooled population of TKI-pretreated subjects with *ROS1*-positive NSCLC (Pooled EXP-4, N = 56), clinically meaningful efficacy demonstrated with the key efficacy endpoints described above were further supported by key secondary efficacy endpoints:

- CBR was 82.1% (N = 46 of 56; 95% CI: 69.6, 91.1), including 3 CRs, 18 PRs, and 25 subjects that had SD ≥ 6.
- The median duration of treatment was 8.3 months (range: 0.5, 24.8), with 19 (33.9%) of the 56 subjects remaining on treatment including 12 (57.1%) of the 21 subjects with confirmed responses.
- Estimated median PFS of 9.0 months (95% CI: 7.3, NE), with PFS ranging from 0.0+ to 22.3 months.
- Intracranial activity in 41.7% (5/12) of subjects with measurable brain metastases at baseline per BICR. Duration of response for these 5 responding subjects ranged from 3.0 to 11.1 months at the time of the data cutoff date and 4 remained on treatment in response.
- Notably, of the 56 subjects in pooled EXP-4, 13 subjects were tested for resistance mutations and 6 (10.7%) had an SFM at baseline. Four of the 6 subjects achieved confirmed responses for a confirmed ORR of 67% (95% CI: 22, 96).

- Among the 31 (55.4%) subjects with progression, the most common sites of progression were the lung (12 [38.7%]), lymph node (11 [35.5%]) and brain (9 [29.0%]). Overall, 25 (44.6%) subjects with progression continued treatment beyond progression due to sustained clinical benefits. The median time on treatment post progression was 0.39 months (range: 0.1, 6.6).

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of secondary endpoints. FDA reviewed data from the pooled cohorts EXP-1 and EXP-4 from the TRIDENT-1 study. FDA did not independently verify results from other cohorts (e.g., EXP-2 and EXP-3) from TRIDENT-1. FDA did not independently verify the results for time-to-event endpoints such as PFS and OS; time-to-event endpoints are not interpretable in non-comparative trials and are considered exploratory only. In addition, CBR is not considered to be a clinically relevant endpoint for efficacy evaluation.

In response to an Information Request dated September 22, 2023, the Applicant clarified that the analysis of the secondary endpoints IC-ORR and IC-DOR in patients with measurable brain metastasis at baseline per BICR was performed in Phase 2 patients only, as per the BICR charter for mRECIST. In other words, the analysis was based on 63 TKI-naïve patients in EXP-1 and 53 TKI-pretreated patients in EXP-4.

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:

FDA agrees with the Applicant's position. There were 11 patients in the efficacy population who did not receive the RP2D. A sensitivity analysis demonstrated similar ORR and DOR with or without these additional patients. For non-pooled EXP-1 (N=63), the ORR was determined to be 78% (95% CI 66, 87) and DOR was NE (95% CI NE, NE), and ranged from 1.4 to 25.8 months. For non-pooled EXP-4 (N=53), the ORR was determined to be 38% (95% CI 25, 52) and median DOR was 17.8 months (95% CI 7.6, NE) and ranged 3.7 to 17.8 months. Given the consistency of the sensitivity analyses with the primary analysis, it is unlikely that inclusion of data from patients who did not receive the RP2D in the overall ORRs observed in the ROS1 TKI-naïve and ROS1 TKI-pretreated patients affects interpretation of the results.

8.1.2.12. Durability of Response

Data:

The duration of response data are presented in Section 8.1.2.10.

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:

The durability of the response data is presented in Section 8.1.2.8 in both TKI-naïve and TKI-pretreated patients.

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:

Data from the primary efficacy analysis cohorts demonstrated durable responses. In Pooled EXP-1 (TKI-Naïve *ROS1*-positive NSCLC population), the estimated median DOR (Kaplan Meier) was 27.4 months (95% CI: 23.1, NE), with landmark analyses showing a probability of subjects remaining in a response at ≥ 12 months being 86.1% (95% CI: 76.4, 95.8). In Pooled EXP4 (*ROS1*-positive NSCLC subjects previously treated with 1 prior ROS1 TKI and no chemotherapy), the estimated median DOR (Kaplan Meier) was 17.8 months (95% CI: 7.6, NE), with landmark analyses showing a probability of subjects remaining in a response at ≥ 9 months being 59.6% (95% CI: 35.9, 83.4).

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-1, median PFS was 31.1 months (95% CI: 24.6, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 12 months was 79.7% (95% CI: 69.8, 89.6). In Pooled EXP-4, median PFS was 9.0 months (95% CI: 7.3, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 9 months was 55.1% (95% CI: 40.5, 69.7).

In Pooled EXP-1 and Pooled EXP-4, median overall survival was not reached at the time of the data cutoff date.

The FDA's Assessment:

FDA notes that the analyses of PFS and OS are considered exploratory. No reliable conclusions can be made based on these results.

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.

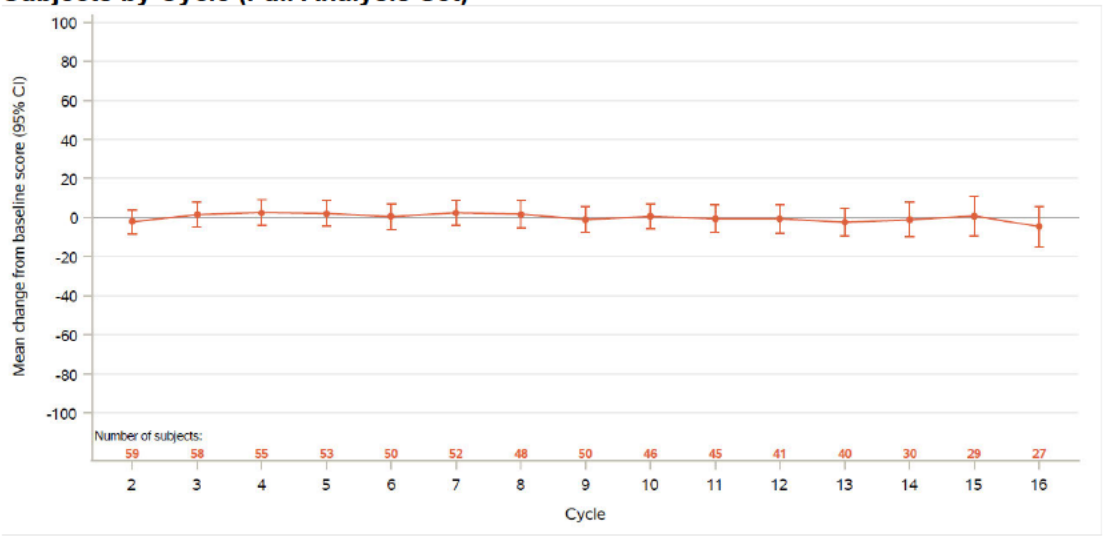
A summary of the PRO results overall and at Cycle 6 and Cycle 12 is described in the tables that follow for ROS1 TKI-naïve (EXP-1) and ROS1 TKI-pretreated (pooled EXP-2, EXP-3, EXP-4) groups.

The FAS population used for the PRO analyses included 63 subjects with *ROS1*--positive advanced NSCLC who were TKI-naïve (EXP-1) and 93 subjects with *ROS1*-positive advanced NSCLC who were TKI-pretreated (EXP-2, EXP-3, EXP-4), all of whom were dosed as of 15 October 2019 (8 months before 20 June 2022 data cutoff date). All (100%) TKI-naïve subjects and 98.9% of TKI-pretreated subjects completed baseline QLQ-C30 and LC13 assessments.

TKI-Naïve ROS1-positive NSCLC (EXP-1)

Overall, the mean change from baseline in EORTC-QLQ-C30 GHS/QOL score in ROS1 TKI-naïve (Figure 6) subjects remained stable over time at each cycle.

Figure 6. Mean Change From Baseline in EORTC-QLQ-C30 GHS/QOL Score in ROS1 TKI-Naïve Subjects 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.
Source: TRIDENT-1 Phase 2 CSR Appendix 16.6 Figure 1.1.1

The majority of subjects in the ROS1 TKI-naïve group reported stable or improved responses in many of the symptoms on the EORTC-QLQ-LC13 scale (Table 39).

Table 39. Global Health Status and Quality of Life Responder Analysis for Core NSCLC Symptoms of Dyspnea, Cough, and Pain in Chest at Cycle 6 and Cycle 12 in ROS1 TKI-Naïve Subjects (Full Analysis Set)

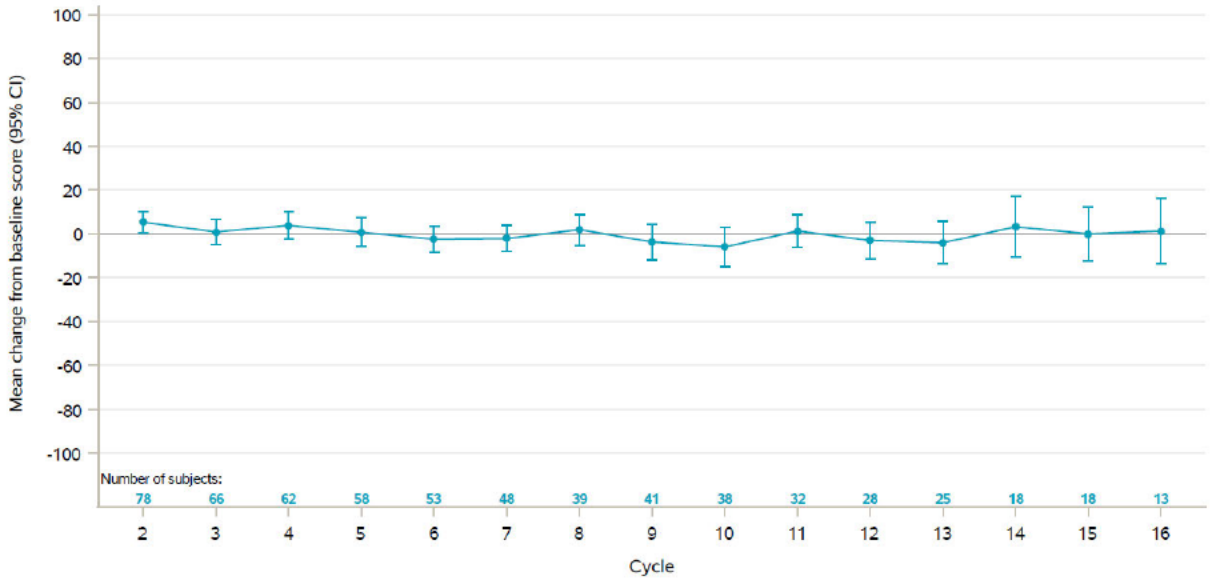
	Cycle 6			Cycle 12		
	TKI-Naïve *ROS1*-positive NSCLC (N = 50)			TKI-Naïve *ROS1*-positive NSCLC (N = 41)		
	Improved, m (%)	Stable, m (%)	Worsened, m (%)	Improved, m (%)	Stable, m (%)	Worsened, m (%)
EORTC-QLQ-C30						
GHS/QOL	15 (30.0)	23 (46.0)	12 (24.0)	11 (26.8)	16 (39.0)	14 (34.1)
EORTC-QLQ-LC13						
Dyspnea	26 (52.0)	10 (20.0)	14 (28.0)	21 (51.2)	4 (9.8)	16 (39.0)
Cough	32(62.7)	15 (29.4)	4 (7.8)	23 (56.1)	15 (36.6)	3 (7.3)
Pain in chest	22 (43.1)	27 (52.9)	2 (3.9)	18 (43.9)	20 (48.8)	3 (7.3)

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; GHS = Global Health Status; m = number of subjects in the Full Analysis Set who were expected to complete an assessment at the specified visit; NSCLC = non-small cell lung cancer; QLQ-C30 = quality of life core questionnaire; QLQ-LC13 = quality of life lung cancer module; QOL = quality of life; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.
Source: TRIDENT-1 Phase 2 CSR Appendix 16.6 Table 4.16, Table 4.17, and Table 4.23

TKI-pretreated ROS1-positive NSCLC (Pooled EXP-2, EXP-3, EXP-4)

Overall, the mean change from baseline in EORTC-QLQ-C30 GHS/QOL score in ROS1 TKI-pretreated (Figure 7) subjects remained stable over time at each cycle.

Figure 7. Mean Change From Baseline in EORTC-QLQ-C30 GHS/QOL Score in ROS1 TKI-Pretreated Subjects 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.
Source: TRIDENT-1 Phase 2 CSR Appendix 16.6 Figure 1.1.2

The majority of subjects in the ROS1 TKI-pretreated group reported stable or improved responses in many of the symptoms on the EORTC-QLQ-LC13 scale (Table 40).

Table 40. Global Health Status and Quality of Life Responder Analysis for Core NSCLC Symptoms of Dyspnea, Cough, and Pain in Chest at Cycle 6 and Cycle 12 in ROS1 TKI-Pretreated Subjects (Full Analysis Set)

	Cycle 6			Cycle 12		
	TKI-Pretreated *ROS1*-positive NSCLC (N = 53)			TKI-Pretreated *ROS1*-positive NSCLC (N = 28)		
	Improved, m (%)	Stable, m (%)	Worsened, m (%)	Improved, m (%)	Stable, m (%)	Worsened, m (%)
EORTC-QLQ-C30						
GHS/QOL	10 (18.9)	30 (56.6)	13 (24.5)	6 (21.4)	14 (50.0)	8 (28.6)
EORTC-QLQ-LC13						
Dyspnea	14 (26.9)	17 (32.7)	21 (40.4)	7 (25.0)	10 (35.7)	11 (39.3)
Cough	21(39.6)	25 (47.2)	7 (13.2)	10 (35.7)	16 (57.1)	2 (7.1)
Pain in chest	11 (20.8)	37(69.8)	5 (9.4)	3 (10.7)	22 (78.6)	3 (10.7)

Abbreviations: EORTC = European Organization for Research and Treatment of Cancer; GHS = Global Health Status; m = number of subjects in the Full Analysis Set who were expected to complete an assessment at the specified visit; NSCLC = non-small cell lung cancer; QLQ-C30 = quality of life core questionnaire; QLQ-LC13 = quality of life lung cancer module; QOL = quality of life; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.
Source: TRIDENT-1 Phase 2 CSR Appendix 16.6 Table 4.1, Table 4.16, Table 4.17, and Table 4.23

The Applicant's Position:

The majority of subjects in both ROS1 TKI-naïve and ROS1 TKI-pretreated groups reported stable or improved outcomes in many EORTC-QLQ-C30 and EORTC-QLQ-LC13 scales, with more improvement seen in the ROS1 TKI-naïve group. Meaningful improvements (≥ 10 points mean change from baseline) were reported in the EORTC-QLQ-C30 and EORTC-QLQ-LC13 symptoms scales/items, particularly in dyspnea, cough, and pain in chest for the TKI-naïve group and cough for the TKI-pretreated group. Of note, in the TKI-naïve group, results from the EORTC-QLQ-LC13 cough demonstrated large improvements (ie, 23 points or greater mean change from baseline) through the first year of treatment.

The median TDD for the EORTC-QLQ-C30 GHS/QOL was 22.97 months for the ROS1 TKI-naïve group and 21.52 months for the ROS1 TKI-pretreated group. The median TDD for the EORTC-QLQ-LC13 dyspnea was 20.73 months for the ROS1 TKI-naïve group and 10.87 months for the ROS1 TKI-pretreated group. The median TDD was not reached in EORTC-QLQ-LC13 cough and pain in chest for both the ROS1 TKI-naïve and ROS1 TKI-pretreated groups, meaning that more than half of the subjects had not reported a deterioration event.

The median TFI for the HRQOL was shortest for EORTC-QLQ-LC13 dyspnea (1.03 months) in the ROS1 TKI-naïve group and shortest for EORTC-QLQ-LC13 cough (2.89 months) in the ROS1 TKI-pretreated group. The TFI in EORTC-QLQ-LC13 cough was noticeably short (1.84 months) for the ROS1 TKI-naïve group. Median TFI was not reached for EORTC-QLQ-LC13 pain in chest for both groups. Improvement in core lung function symptoms correlated to radiological response

(median TTR of 1.8 months for both ROS1 TKI-naïve and ROS1 TKI-pretreated cohorts, presented in Section 8.2.1).

Patient-reported outcome descriptive data can complement the efficacy, tolerability, and safety data in clinical study. Preservation of HRQOL during treatment is an important therapeutic goal. Although the HRQOL analyses do not support formal statistical inferences, the results presented here in addition to the efficacy and safety results suggest that repotrectinib is a promising treatment option for patients with advanced or metastatic *ROS1*-positive NSCLC while maintaining QOL, improving key lung cancer symptoms, providing a high tumor response rate and landmark DOR.

The FDA's Assessment:

FDA considered the results of PRO endpoints presented in this section to be exploratory and therefore did not independently verify the results.

FDA does not agree with the analyses and interpretation of the results presented by the Applicant for EORTC-QLQ-C30 GHS/QOL Score. FDA recommends evaluating change from baseline for the PRO endpoints based on a specific, clinically justifiable time point, rather than change from baseline across all time points (though this can be a sensitivity analysis). An overall analysis across all timepoints on treatment may be unreliable particularly if dropouts and death are expected.

8.1.2.15. Additional Analyses Conducted on the Individual Trial

Data:

Comparison of Results of Subpopulations

Table 41. Summary of Key Subgroup Analysis of Efficacy (by BICR) in TKI-Naïve (Pooled EXP-1) and TKI-Pretreated (Pooled EXP-4) Subjects With ROS1-Positive NSCLC (Efficacy Analysis Set)

	TKI-Naïve *ROS1*-positive NSCLC (Pooled EXP-1)		TKI-Pretreated *ROS1*-positive NSCLC (Pooled EXP-4)	
Subgroup	**N**	**cORR n (%) [95% CI]**	**N**	**cORR n (%) [95% CI]**
Baseline Brain Metastasis per BICR[a]				
Yes	18	16 (88.9) [65.3, 98.6]	24	8 (33.3) [15.6, 55.3]
No	53	40 (75.5) [61.7, 86.2]	32	13 (40.6) [23.7, 59.4]
Region				
US	11	7 (63.6) [30.8, 89.1]	17	7 (41.2) [18.4, 67.1]
Asia	41	36 (87.8) [73.8, 95.9]	23	8 (34.8) [16.4, 57.3]
Other	19	13 (68.4) [43.5, 87.4]	16	6 (37.5) [15.2, 64.6]
Race				
Asian	48	39 (81.3) [67.4, 91.1]	27	9 (33.3) [16.5, 54.0]
Black or African	1	0 (0) [0, 97.5]	1	0 (0) [0, 97.5]
Native Hawaiian or Other Pacific Islander	1	1 (100) [2.5, 100.0]	1	1 (100.0) [2.5, 100.0]
White	18	14 (77.8) [52.4, 93.6]	25	10 (40.0) [21.1, 61.3]
Not Reported	3	2 (66.7) [9.4, 99.2]	1	1 (100.0) [2.5, 100.0]
Unknown	0	NA	1	0 (0) [0, 97.5]
Age				
≥ 18 to < 65	52	42 (80.8) [67.5, 90.4]	41	15 (36.6) [22.1, 53.1]
≥ 65 to < 75	15	10 (66.7) [38.4, 88.2]	10	4 (40.0) [12.2, 73.8]
≥ 75	4	4 (39.8, 100.0) [0, 60]	5	2 (40.0) [5.3, 85.3]
SFM at Baseline				
Yes	NA	NA	6	4 (66.7) [22.3, 95.7]
No	NA	NA	50	17 (34.0) [21.2, 48.8]
Prior ROS1 TKI treatment				
Crizotinib	NA	NA	46	18 (39.1) [25.1, 54.6]
Entrectinib	NA	NA	9	2 (22.2) [2.8, 60.0]

Abbreviations: cORR = confirmed objective response rate; DOR = duration of response; EXP = expansion cohort; NA = not applicable; NSCLC = non-small cell lung cancer; PFS = progression-free survival; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.
Notes: Data cutoff date of 20 June 2022.
[a] Defined as having a target and/or non-target lesion in the brain selected at baseline for RECIST v1.1
Sources: Module 5.3.5.3 ISE Table 14.2.1.3, Table 14.2.1.5, Table 14.2.1.7, Table 14.2.1.9, Table 14.2.1.13, Table 14.2.1.4, Table 14.2.1.6, Table 14.2.1.8, Table 14.2.10, Table 14.2.12, Table 14.2.1.14, Table 14.2.1.15, Table 14.2.1.20, Table 14.2.1.21.

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—1 and EXP-4, although there were some variations in confirmed ORR and median DOR across the subgroups, which was expected given the small number of subjects, confirmed clinical activity was observed across all subgroup populations with a substantial overlap in the 95% Cis across subgroups (Table 41). Notably, of the 56 subjects in Pooled EXP-4, 6 (10.7%) subjects had an SFM at baseline of which 4 achieved confirmed responses for a confirmed ORR of 66.7% (95% CI: 22.3, 95.7). Subjects 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 Applicant's position on subgroup analyses of ORR. The confirmed ORR results for the subgroup of patients ages ≥75 is 100% (95% CI 40, 100). Results for subgroup analysis by sex were omitted in Table 41. Treatment benefit was observed across subgroups based on sex. In Pooled EXP-1, an ORR of 84% (95% CI 69, 93) was observed in 43 females and an ORR of 71% (95% CI 51, 87) was observed in 28 males; in Pooled EXP-4, an ORR of 37% (95% CI 22, 54) was observed in 38 females and an ORR of 39% (95% CI 17, 64) was observed in 18 males.

FDA notes that analyses for time-to-event endpoints are not interpretable in non-comparative trials and will be considered exploratory only. CBR is not considered to be a clinically relevant endpoint for efficacy evaluation.

In the EXP-4 cohort consisting of 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 (G2032R), gatekeeper (L2026M), and other mutations (S1986F/Y). ORR in the resistance mutation population was determined to be 75% (95% CI 35, 97) and median duration of response was 17.8 months (95% CI 7.6, NE). Responses by specific resistance mutation are provided in Table 42.

Table 42. FDA Resistance Mutation Subgroup Analysis: ORR by BICR

EXP-4 (N=56)		
Resistance Mutation	**N**	**ORR %**
Yes	8	75 (35, 97)
No	48	31 (19, 46)
Solvent Front (CD74-ROS1, SLC34A2-ROS1 [G2032R])	6	67 (22, 96)
Gatekeeper (EZR-ROS1 [L2026M])	1	100 (2.5, 100)
Other Kinase Domain (EXR-ROS1 [S1986F/Y])	1	100 (2.5, 100)
Activating	0	
Not Detected/QC Fail	5	40 (5, 85)
Not Tested	43	30 (17, 46)

Regarding the response by resistance mutation in Table 42, the "other" resistance mutation observed is within the kinase domain of the protein but has an effect different from what would typically be considered as a kinase domain/activating mutation. This mutation does not directly occur within the enzyme active site but does impact the alphaC helix of the kinase domain, causing its movement with a change in the tip of the close glycine-rich region, involving the residues from 1950 to 1960 (Facchinetti 2016). It is included in the above table for completeness.

An analysis of ORR by fusion partners was performed by FDA; refer to Section 6.3.2.3 for discussion of response by fusion partner. There were no responders amongst 8 patients in the pooled EXP-4 cohort with an SDC4-ROS1 fusion. Lack of activity of repotrectinib in these 8 patients with this fusion is not supported by any biologic or mechanistic rationale. Furthermore, there were several patients with this fusion in the pooled EXP-1 cohort with objective responses in 5 of 9 patients.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The efficacy evaluation for this NDA is based primarily on the analysis of 71 TKI-naïve (pooled EXP-1) and 56 TKI-pretreated (pooled EXP-4) patients with ROS1 positive NSCLC that was locally advanced or metastatic with or without prior cytotoxic chemo- or immunotherapy.

The primary evidence of effectiveness of repotrectinib is established by the demonstration of a clinically meaningful durable ORR in the primary analysis population. The confirmed ORR by BICR per RECIST v1.1 was 79% (95% CI 68, 88) for the pooled EXP-1 cohort with a median DOR of 34.1 months (95% CI: 25.6 to NE) and 70% of responders with a response duration of ≥ 12 months. The confirmed ORR was 38% (95% CI 25, 52) for the pooled EXP-4 cohort with a median DOR of 14.8 months (7.6 to NE) and 48% of patients with a response duration of ≥ 12 months. Median DORs are reported based on the data cutoff date of December 19, 2022. In

addition, durable responses were observed in patients with resistance mutations and measurable CNS metastases. Among TKI-naïve patients, 8 had measurable CNS metastases at baseline as assessed by BICR and responses in intracranial tumors 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 and responses in intracranial tumors 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 (G2032R), gatekeeper (L2026M), and other mutations (S1986F/Y).

The totality of data suggests response rates with clinically meaningful magnitude and durability among adult patients with locally advanced or metastatic ROS1-positive NSCLC in the ROS1 TKI-naïve and ROS1 TKI-pretreated populations. Subgroup analyses also indicate activity in patients with CNS metastases and in patients with resistance mutations following prior ROS1 TKI therapy. Based on these durable responses across the populations described, an approval of repotrectinib for the treatment of patients with locally advanced or metastatic ROS1-positive NSCLC, including those who received one prior ROS1 TKI, is appropriate.

8.1.4. 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.

The FDA's Assessment:

FDA Agrees with the Applicant's position.

8.1.5. 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.

The Applicant's Position:

Based on results of Pooled EXP-1 in the pivotal TRIDENT-1 study, repotrectinib has demonstrated the following benefits in TKI-naïve subjects with *ROS1*-postivie NSCLC:

- Robust anti-tumor activity with a confirmed ORR by BICR of 78.9% (N = 56/71; 95% CI: 67.6, 87.7).
- Rapid onset of response (median TTR was 1.8 months; range, 0.9 to 5.5).

- In subjects with post-baseline scans, deep responses were observed with most subjects (67.6%) having a reduction in the size of target lesions of at least 60% from baseline, and all subjects with post-baseline scans showing a reduction in target lesions from baseline.
- Durable responses with an estimated median DOR of 27.4 months (95% CI: 23.1, NE), with landmark analyses of DOR showing a probability of subjects remaining in a response at ≥ 9 and ≥ 12 months was 88.8% (95% CI: 80.3, 97.2) and 86.1% (95% CI: 76.4, 95.8), respectively.
- Estimated median PFS of 31.1 months (95% CI: 24.6, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 9 months and ≥ 12 months was 81.3% (95% CI: 71.8, 90.9) and 79.7% (95% CI: 69.8, 89.6), respectively.
- Intracranial activity in 87.5% (7/8) of subjects with measurable brain metastases at baseline per BICR.

The magnitude of efficacy observed with repotrectinib in the *ROS1*-postivie TKI-naïve NSCLC population is favorable in context of historic benchmark data for existing approved therapies, ie, crizotinib and entrectinib (Table 43). Repotrectinib demonstrated high responses rates and improved DOR and PFS compared with historical data for therapies currently approved in the TKI-naïve setting.

Table 43. Efficacy of Repotrectinib (BICR) (Pooled EXP-1) and Historical Benchmarks in TKI-Naïve ROS1 Positive NSCLC

***ROS1*+ NSCLC, TKI-Naive**	**Repotrectinib (Pooled EXP-1) N = 71**	**Crizotinib[a] (Xalkori USPI) N = 50**	**Entrectinib[b] (Rozlytrek USPI) N = 92**	**Entrectinib[c] (Literature) N = 161**
Key Efficacy Data				
Confirmed ORR, % (95% CI)	78.9 (67.6, 87.7)	66 (51, 79)	74 (64, 83)	67 (59, 74)
CR, n (%)	4 (5.6)	1 (2)	14 (15)	14 (9)
PR, n (%)	52 (73)	32 (64)	54 (59)	94 (58)
Median Time to Response, months (range)	1.84 (0.9, 5.5)	-	-	-
DOR				
Median DOR, months (95% CI)	27.40 (23.10, NE)	18.3 (12.7, NR)	-	15.7 (13.9, 28.6)
DOR Landmark Analyses (Kaplan Meier), % (95% CI)		-	-	-
DOR ≥ 6 months	90.7 (82.9, 98.5)	-	-	83 (76, 90)
DOR ≥ 9 months	88.8 (80.3, 97.2)	-	-	75 (67, 84)
DOR ≥ 12 months	86.1 (76.4, 95.8)	-	-	63 (53, 73)

***ROS1*+ NSCLC, TKI-Naive**	**Repotrectinib (Pooled EXP-1) N = 71**	**Crizotinib[a] (Xalkori USPI) N = 50**	**Entrectinib[b] (Rozlytrek USPI) N = 92**	**Entrectinib[c] (Literature) N = 161**
Supportive Efficacy Data				
PFS				
Median PFS, months (95% CI)	31.11 (24.64, NE)	-	-	-
PFS Landmark Analyses (Kaplan Meier), % (95% CI)				
PFS ≥ 6 months	90.9 (83.9, 97.8)	-	-	77 (70, 84)
PFS ≥ 9 months	81.3 (71.8, 90.9)	-	-	66 (58, 74)
PFS ≥ 12 months	79.7(69.8, 89.6)	-	-	55 (47, 64)
IC-ORR, % (n/N)	87.5% (7/8)[e]	-	70% (7/10)	63% (35/56)
CBR (CR + PR + SD), % (95% CI)	94.4 (86.2, 98.4)	-	-	-
OS				
Death, n (%)	7 (9.9)	-	-	-
Median OS, months (95% CI)	NE (44.42, NE)	-	-	-

Abbreviations: AE = adverse event; ALT= alanine aminotransferase; AST = aspartate aminotransferase; BICR = Blinded Independent Central Review; CBR = clinical benefit rate; CR = complete response; DOR = duration of response; IC-ORR = intracranial objective response rate; n/N = number of patients (numerator/denominator); NE = not evaluable; NR = not reached; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PR= partial response; RECIST = Response Evaluation Criteria in Solid Tumors; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; USPI = United States Package Insert.

[a] Xalkori® USPI 2021; best overall response was determined by IRR using RECIST v1.1.

[b] Rozlytrek® USPI 2021; best overall response was determined by BICR using RECIST v1.1.

[c] Rozlytrek® (entrectinib) data from Dziadziuszko 2021; best overall response was determined by BICR using RECIST v1.1.

[d] IC-ORR was evaluated in Phase 2 of the TRIDENT-1 study. Of the 63 TKI naïve subjects from Phase 2, 8 (12.7%) subjects had measurable brain disease at baseline by BICR.

Sources for repotrectinib data: Module 5.3.5.3, ISE Table 14.1.6.2, Table 14.2.1.1, Table 14.2.3.1, and Table 14.2.6.1.

Considering the results in Pooled EXP-4, repotrectinib has also demonstrated benefits in TKI-pretreated subjects with *ROS1*-positive NSCLC:

- Clinically meaningful activity with a confirmed ORR by BICR of 37.5% (N = 21 of 56; 95% CI: 24.9, 51.5).
- Rapid onset of response (median TTR 1.8 months [range 1.6 to 3.6]).
- In subjects with post-baseline scans, deep responses were observed with 37.5% of subjects having a reduction in the size of target lesions of at least 60% from baseline and 87.5% of subjects showing a reduction in target lesions from baseline.
- Durable responses with an estimated median DOR (Kaplan Meier) of 17.8 months (95% CI: 7.6, NE), with landmark analyses of DOR showing a probability of subjects remaining in a response at ≥ 9 months was 59.6% (95% CI: 35.9, 83.4).
- Estimated median PFS of 9.0 months (95% CI: 7.3, NE), with landmark analyses showing that the probability of subjects without a PFS event at ≥ 9 months was 55.1% (95% CI: 40.5, 69.7).

- Intracranial activity in 41.7% (5/12) of subjects with measurable brain metastases at baseline per BICR.
- Notably, of the 56 subjects in pooled EXP-4, 6 (11%) subjects had an SFM at baseline of which 4 achieved confirmed responses for a confirmed ORR of 67% (95% CI: 22, 96).

The clinical activity demonstrated by repotrectinib in the TKI--pretreated setting is clinically meaningful in context of the available historic benchmarks (ie, pemetrexed based chemotherapy) in 2L+ setting (refer to Section 2.2).

Although there were some variations in confirmed ORR, median DOR and median PFS across subgroups in both primary efficacy populations (Pooled EXP-1 and Pooled EXP-4), which was expected given the small number of subjects, there was no evidence of a lack of efficacy in any individual subgroups and a substantial overlap in the 95% CIs across all subgroups.

Repotrectinib has also shown encouraging clinical activity, in terms of confirmed objective responses in heavily pretreated patients for which no alternate treatment exists (ORR of 42.3% [CI: 23.4, 63.1] in Pooled EXP-2 and ORR of 27.8% [9.7, 53.5] in Pooled EXP-3).

Furthermore, in a pooled analysis of all TKI-pretreated subjects with SFMs at baseline across the Pooled EXP-2, Pooled EXP-3, and Pooled EXP-4 groups, 10/17 subjects who had an SFM at baseline achieved confirmed responses for a confirmed ORR of 58.8% (95% CI: 32.9, 81.6).

The FDA's Assessment:

FDA's efficacy evaluation is based on the magnitude of the observed ORR, durability of responses, and overall benefit-risk assessment. FDA notes that analyses for time-to-event endpoints such as PFS and OS are not interpretable in non-comparative trials and will be considered exploratory only.

FDA agrees with the Applicant that the efficacy results demonstrate clinically meaningful antitumor activity of repotrectinib in both ROS1 TKI-naïve and ROS1 TKI-pretreated (1 prior ROS1 TKI with no chemotherapy or immunotherapy) patients with ROS1 positive NSCLC. The effectiveness of repotrectinib was consistent across prespecified subgroups (in patients with CNS metastasis and resistance mutations) and supported by sustained durability of responses given an additional 6 months of follow-up, providing substantial evidence of antitumor activity over time. As of the updated DCO date of December 19, 2022, the estimated median DOR was 34.1 months (95% CI 25.6, NE) in TKI-naïve patients and 14.8 months (95% CI 7.6, NE) in TKI-pretreated patients.

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 = 444), the subpopulation receiving at least 1 dose of repotrectinib at the RP2D (N = 351), and subpopulation of *ROS1*-positive NSCLC subjects receiving at least 1 dose of repotrectinib at the RP2D (N = 264) 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. Long-term treatment with repotrectinib (> 12 months) showed no evidence of increased/cumulative toxicity.

The FDA's Assessment:

FDA agrees with the Applicant's description of the TRIDENT-1 safety subpopulations. FDA's approach focused on the overall RP2D population of patients who had received at least one dose of repotrectinib at the RP2D (N=351), and on the population of patients with *ROS1*-positive NSCLC who received at least one dose of repotrectinib at the RP2D (N = 264) in the TRIDENT-1 study.

8.2.1. Safety Review Approach

Data:

The number of subjects treated with repotrectinib in the primary analysis set is presented in Table 44.

Table 44. Number of Subjects Treated With Repotrectinib in the Primary Analysis Set

Study/ISS	Phase/Indication	Design	Subjects Treated[a]	Datasets/ Population
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	CDISC (SDTM, ADaM)
TRIDENT-1 Phase 2	Phase 2; adults and youth with advanced solid tumors	Open-label, multicohort, global registrational, efficacy and safety study	341	CDISC (SDTM, ADaM)
ISS	Phase 1 and Phase 2 of TRIDENT-1	Integrated safety: Phase 1 and Phase 2 of TRIDENT-1	Overall Population: 444	CDISC (SDTM, ADaM)
			RP2D Population: 351	CDISC (SDTM, ADaM)
			ROS1-positive NSCLC at RP2D Population: 264	CDISC (SDTM, ADaM)

Abbreviations: ADaM = Analysis Data Model; DDI = drug-drug interaction; CDISC = Clinical Data Interchange Standards Consortium; ISS = integrated summary of safety; PK = pharmacokinetic; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; RP2D = recommended Phase 2 dose; SDTM = Study Data Tabulation Model

[a] Number of subjects treated is based on a data cutoff date of 20 June 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 *ROS1*-positive NSCLC comprised pooled results of

444 subjects (Safety Analysis Set) from Phase 1 and Phase 2 of the pivotal TRIDENT-1 study and includes all subjects who received at least 1 dose of repotrectinib. Data are also presented for the RP2D subpopulations, which include those subjects likely to benefit from treatment with repotrectinib based on the RP2D for the proposed indication of *ROS1*-positive NSCLC.

Data considered supportive from other clinical studies in cancer patients included available preliminary safety data from the combination therapy study TRIDENT-2 (TPX-0005-13; N = 6) and the pediatric monotherapy study CARE (TPX-0005-07, N = 19). Since subjects enrolled in the TRIDENT-2 and CARE studies are distinctly different in their baseline disease characteristics, disease histology, prior therapy, and on-study treatment in comparison to the population enrolled for the *ROS1*-positive NSCLC cohorts on the TRIDENT-1 study, the Applicant did not integrate TRIDENT-2 and CARE with the pivotal study TRIDENT 1 for the integrated safety analysis but described the preliminary data separately. In addition, safety data from supportive clinical pharmacology studies in healthy volunteers (N = 118) and limited data from Investigator Sponsored Trials (N = 13) and Single Patient Use studies (N = 24) were also considered supportive and described separately from the TRIDENT-1 data. No new significant safety concerns for repotrectinib have been identified in addition to those identified from the safety profile in TRIDENT-1.

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.

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 performance scale assessment, extensive clinical laboratory assessments (hematology, chemistry, coagulation, urinalysis, serum pregnancy tests [for WOCBP] and hypogonadism blood samples [male subjects 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 regarding FDA's approach to the safety analysis. FDA completed a comprehensive analysis and review of safety datasets and patient narratives submitted from TRIDENT-1.

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

Data:

Table 45. Extent of Exposure of Study Drug (Safety Analysis Set)

Characteristic	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Treatment duration (months)[a]			
n	444	351	264
Mean (SD)	8.08 (9.161)	7.42 (6.850)	7.60 (7.135)
Median	4.62	5.09	5.11
Min, max	0.1, 60.6	0.1, 30.6	0.1, 30.6
Subjects treated by cycle[b], n (%)			
1	444 (100.0)	351 (100.0)	264 (100.0)
2	391 (88.1)	312 (88.9)	232 (87.9)
3	327 (73.6)	266 (75.8)	200 (75.8)
4	292 (65.8)	240 (68.4)	179 (67.8)
5	247 (55.6)	205 (58.4)	155 (58.7)
6	222 (50.0)	183 (52.1)	138 (52.3)
> 6	198 (44.6)	162 (46.2)	123 (46.6)
> 12	115 (25.9)	91 (25.9)	70 (26.5)
> 15	79 (17.8)	59 (16.8)	47 (17.8)
> 18	61 (13.7)	41 (11.7)	33 (12.5)
Number of treatment cycles[c]			
n	444	351	264
Mean (SD)	9.2 (9.95)	8.5 (7.46)	8.7 (7.78)
Median	5.5	6.0	6.0
Min, max	1, 66	1, 34	1, 34
Treated at RP2D[d], n (%)			
Yes	290 (65.3)	290 (82.6)	223 (84.5)
No	54 (12.2)	54 (15.4)	36 (13.6)
NA	7 (1.6)	7 (2.0)	5 (1.9)
NA-Phase 1	93 (20.9)	0	0
Cumulative dose on study (mg)			
n	444	351	264
Mean (SD)	55040.81 (65318.436)	53778.58 (55285.708)	56180.00 (58139.984)
Median	29880.00	33600.00	34480.00
Min, max	160.0, 523200.0	160.0, 273920.0	160.0, 273920.0

Characteristic	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Relative dose intensity (%)[e]			
n	444	351	264
Mean (SD)	90.87 (57.783)	80.56 (22.725)	81.72 (21.747)
Median	95.45	91.70	92.80
Min, max	13.3, 707.8	13.3, 101.4	19.4, 101.1

Abbreviations: NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose.
Notes: Other treated subjects include subjects with ROS1-positive non-NSCLC, ALK-positive gene fusions, and any gene fusions with discordant results between local FISH test and central laboratory test. Percentages are based on the number of subjects in the Safety Analysis Set.
[a] Treatment duration (months) for repotrectinib is calculated as (date of last dose – date of first dose + 1)/30.4375. For subjects 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 subject 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 = subjects were not on treatment for at least 14 days. NA-Phase 1 = subjects in Phase 1 did not have the option to titrate at Study Day 14.
[e] Relative Dose Intensity (%) is defined as (cumulative dose on study [in mg] divided by expected cumulative dose on study) × 100, where expected cumulative dose is defined as the starting dose times number of days on treatment. The expected cumulative dose is adjusted for subjects who received a lead-in dose and for subjects starting at BID dosing who are required to take study drug QD on the first day.
Sources: Module 5.3.5.3, 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 and number of treatment cycles in the Overall population was 4.62 (0.1, 60.6) months and 5.5 (1, 66) cycles, respectively, with a median relative dose intensity of 95.45% suggestive of good overall compliance with treatment. Half (50.0%) of all subjects received up to 6 cycles of treatment and 25.9% ≥ 12 cycles that supports long term tolerability of repotrectinib. The majority (63.5%) of patients were able to titrate from 160 mg QD to 160 mg BID.

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

The FDA's Assessment:

FDA agrees with the summary of overall exposure to repotrectinib. The median (range) duration of exposure to repotrectinib and number of treatment cycles in the RP2D population (N=351) was 5.09 (0.1, 30.6) months and 6.0 (1, 34) cycles, respectively, with a median relative dose intensity of 92%. Approximately half (52%) of all patients received up to 6 cycles of treatment and 26% received ≥ 12 cycles. The majority (83%) of patients received 160 mg once

daily followed by 160 mg twice daily, while 15% of patients received repotrectinib and their dose was not subsequently titrated to 160 mg BID. Per protocol, patients were allowed to continue dosing of 160 mg once daily if they experienced unacceptable toxicity.

The median (range) duration of exposure to repotrectinib and number of treatment cycles in the ROS1 positive NSCLC population (N=264) was 5.11 (0.1, 30.6) months and 6.0 (1, 34) cycles, respectively, with a median relative dose intensity of 93%. Approximately half (52%) of all patients received up to 6 cycles of treatment and 27% received ≥ 12 cycles. The majority (85%) of patients were treated with 160 mg once daily followed by 160 mg twice daily, while 14% of patients received repotrectinib and their dose was not subsequently titrated to 160 mg BID.

8.2.2.2. Relevant Characteristics of the Safety Population

Data:

Table 46. Demographics Characteristics of Study Population (Safety Analysis Set)

Characteristic	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Age (years)			
Mean	55.2	55.7	55.3
Standard deviation	13.23	13.13	12.31
Median	56.0	56.0	56.0
Min, max	18, 93	20, 93	27, 93
Age Group, n (%)[a]			
≥ 18 to < 65	329 (74.1)	256 (72.9)	202 (76.5)
≥ 65 to < 75	88 (19.8)	72 (20.5)	47 (17.8)
≥ 75	27 (6.1)	23 (6.6)	15 (5.7)
Sex, n (%)			
Female	258 (58.1)	209 (59.5)	163 (61.7)
Male	186 (41.9)	142 (40.5)	101 (38.3)
Race, n (%)			
Asian	200 (45.0)	162 (46.2)	129 (48.9)
White	199 (44.8)	151 (43.0)	113 (42.8)
Black or African American	12 (2.7)	9 (2.6)	7 (2.7)
Native Hawaiian or Other Pacific Islander	3 (0.7)	2 (0.6)	2 (0.8)
American Indian or Alaska Native	1 (0.2)	1 (0.3)	1 (0.4)
Other	4 (0.9)	1 (0.3)	0
Not reported	22 (5.0)	22 (6.3)	9 (3.4)
Unknown	3 (0.7)	3 (0.9)	3 (1.1)

Characteristic	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Ethnicity, n (%)			
Hispanic or Latino	12 (2.7)	10 (2.8)	9 (3.4)
Not Hispanic or Latino	419 (94.4)	328 (93.4)	249 (94.3)
Missing	13 (2.9)	13 (3.7)	6 (2.3)
Region, n (%)			
US	154 (34.7)	90 (25.6)	70 (26.5)
Asia	162 (36.5)	134 (38.2)	106 (40.2)
Other[b]	128 (28.8)	127 (36.2)	88 (33.3)
Baseline ECOG performance status, n (%)			
0	152 (34.2)	123 (35.0)	89 (33.7)
1	291 (65.5)	227 (64.7)	174 (65.9)
Missing	1 (0.2)	1 (0.3)	1 (0.4)
Smoking status, n (%)			
Current smoker	9 (2.0)	9 (2.6)	4 (1.5)
Former smoker	102 (23.0)	102 (29.1)	71 (26.9)
Never smoked	230 (51.8)	230 (65.5)	181 (68.6)
Not collected[c]	103 (23.2)	10 (2.8)	8 (3.0)

Abbreviations: NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose.
Notes: Percentages are based on the number of subjects 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] Smoking status was not collected during Phase 1 of TRIDENT-1.
Sources: Module 5.3.5.3, ISS Table 14.1.3.1.1, Table 14.1.3.1.2

Table 47. Disease History of Study Population (Safety Analysis Set)

Characteristic	Overall Population (N = 444)	RP2D Populations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Tumor type, n (%)[a]			
Lung cancer, non-small cell	379 (85.4)	302 (86.0)	264 (100.0)
Histological classification, n (%)[a]			
Adenocarcinoma	385 (86.7)	305 (86.9)	255 (96.6)
Brain metastasis per BICR[b], n (%)			
Yes	106 (23.9)	77 (21.9)	77 (29.2)
Brain metastasis per Investigator[b], n (%)			
Yes	162 (36.5)	125 (35.6)	105 (39.8)

Characteristic	Overall Population (N = 444)	RP2D Populations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Stage at study entry, n (%)			
IV	426 (95.9)	334 (95.2)	250 (94.7)
Resistance mutation[c]			
Solvent front	67 (15.1)	52 (14.8)	30 (11.4)
Gatekeeper	3 (0.7)	2 (0.6)	2 (0.8)
Activating	1 (0.2)	0	0
Other	15 (3.4)	10 (2.8)	9 (3.4)
Not Detected/QC Failure	31 (7.0)	24 (6.8)	17 (6.4)
None	334 (75.2)	268 (76.4)	211 (79.9)
Type of prior systemic therapy[c], n (%)			
TKI	301 (67.8)	232 (66.1)	184 (69.7)
Chemotherapy with/without immunotherapy	213 (48.0)	133 (37.9)	81 (30.7)
Immunotherapy alone	28 (6.3)	12 (3.4)	3 (1.1)
Other targeted therapy	64 (14.4)	34 (9.7)	14 (5.3)
Other therapy	9 (2.0)	6 (1.7)	0
No prior therapy taken	76 (17.1)	75 (21.4)	62 (23.5)

Abbreviations: NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose; TKI= tyrosine kinase inhibitor.
Notes: Percentages are based on the number of subjects in the Safety Analysis Set.
[a] Reported in more than 1 subject.
[b] Brain metastasis present if target or non-target lesion selected in the brain at baseline.
[c] Subjects can be counted in more than one category.
Sources: Module 5.3.5.3, 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 subjects in the RP2D population, and subset of the RP2D population comprising *ROS1*-positive NSCLC subjects treated at the RP2D, were broadly consistent with those found in the Overall population.

Overall, the median age (56.0 years), higher proportion of females (58.1%), high proportion of never smokers (51.8%), most NSCLCs being lung adenocarcinomas (96.6%), and incidence of CNS disease (23.9% by BICR; 36.5% by Investigator) at baseline are consistent with the anticipated characteristics of patients with *ROS1*-positive NSCLC 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 patient population, including a higher proportion of Asian subjects (45.0%) and under-represented groups of Black or African American (2.7%), Native Hawaiian or Other Pacific Islanders (0.7%), and Hispanic or Latino (2.7%) which have been reported at a prevalence ranging from 0 to 2.5% in the real-world setting (Chevallier 2021; Costa 2021; Shi 2022; Liang 2014; Villanueva 2022; Zheng 2020).

The FDA's Assessment:
FDA agrees with the Applicant's position that the demographic characteristics are generally similar between the overall population, RP2D population, and the ROS1 positive NSCLC population.

8.2.2.3. Adequacy of the Safety Database

The Applicant's Position:

The population studied in TRIDENT-1 is representative of the *ROS1*-positive NSCLC population; as supported by the study population's demographic, disease, and other baseline characteristics, described above. The subject sample size 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:
FDA agrees with the Applicant's position that the safety population studied in TRIDENT-1 study adequately represents the target population, including demographics, disease, and other baseline characteristics. The safety narratives provided in the NDA submission were adequate to allow evaluation of relevant safety signals.

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 8.2.5 for further detail).

The FDA's Assessment:

FDA generally agrees with the Applicant's description of AE grading. FDA considers TEAEs to be 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.

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 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.

8.2.4. Safety Results

In the Overall safety population of TRIDENT-1, TEAEs were reported for 99.5% of subjects with treatment-related TEAEs reported for 93.7% subjects. TEAEs with fatal outcome were reported in 5.4% of subjects; none were assessed by the Investigator as treatment-related. SAEs were reported for 35.1% of subjects and were primarily driven by disease under study with 6.3% of subjects 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 (ie, individual event preferred terms [all causality]) and were typically reported at low incidences [< 2%]). Less than 10% of subjects discontinued study treatment due to a reported TEAE. Dose modifications due to reported TEAEs occurred in approximately 50% of subjects, with 34.0% requiring repotrectinib dose reduction and 45.0% interruption of repotrectinib.

Table 48. TRIDENT-1: Overall Summary of TEAEs (Safety Analysis Set)

TEAEs by Event Category	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Subjects with TEAEs, n (%)			
All Subjects with TEAEs	442 (99.5)	349 (99.4)	262 (99.2)
Leading to Discontinuation of Study Drug	43 (9.7)	29 (8.3)	22 (8.3)
Leading to Dose Modifications	226 (50.9)	194 (55.3)	144 (54.5)
SAEs	156 (35.1)	114 (32.5)	87 (33.0)
Grade ≥ 3 TEAEs	226 (50.9)	173 (49.3)	127 (48.1)
Fatal TEAEs	24 (5.4)	17 (4.8)	11 (4.2)
Subjects with TRAEs, n (%)			
All Subjects with TRAEs	416 (93.7)	334 (95.2)	248 (93.9)
Leading to Discontinuation of Study Drug	15 (3.4)	12 (3.4)	10 (3.8)
Leading to Dose Modifications	169 (38.1)	151 (43.0)	106 (40.2)
Leading to Dose Reduction	137 (30.9)	121 (34.5)	81 (30.7)
Leading to Drug Interruption	138 (31.1)	124 (35.3)	87 (33.0)
Treatment-Related SAEs	28 (6.3)	26 (7.4)	16 (6.1)
Grade ≥ 3 TRAEs	101 (22.7)	90 (25.6)	63 (23.9)
Fatal TRAEs	0	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events v4.03; NSCLC = non-small cell lung cancer; 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 subjects 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 subject is counted once for each type of event reported. For maximum grade, a subject 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.
Sources: Module 5.3.5.3, ISS Table 14.3.1.1.1 and Table 14.3.1.1.5

8.2.4.1. Deaths

Data:

Table 49. TEAEs From TRIDENT-1 With a Fatal Outcome (Safety Analysis Set)

System Organ Class Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Subjects with TEAEs with fatal outcome	24 (5.4)	17 (4.8)	11 (4.2)
Cardiac disorders	6 (1.4)	3 (0.9)	2 (0.8)
Cardiac arrest	4 (0.9)	2 (0.6)	1 (0.4)
Cardiac failure	1 (0.2)	1 (0.3)	1 (0.4)

System Organ Class Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Cardio-respiratory arrest	1 (0.2)	0	0
Infections and infestations	6 (1.4)	4 (1.1)	2 (0.8)
Pneumonia	3 (0.7)	2 (0.6)	0
Pneumonia aspiration	2 (0.5)	2 (0.6)	2 (0.8)
Sepsis	1 (0.2)	0	0
General disorders and administration site conditions	5 (1.1)	4 (1.1)	3 (1.1)
Death	2 (0.5)	2 (0.6)	2 (0.8)
Sudden death	2 (0.5)	1 (0.3)	1 (0.4)
Sudden cardiac death	1 (0.2)	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	5 (1.1)	4 (1.1)	3 (1.1)
Hypoxia	2 (0.5)	2 (0.6)	2 (0.8)
Respiratory failure	2 (0.5)	1 (0.3)	0
Dyspnoea	1 (0.2)	1 (0.3)	1 (0.4)
Blood and lymphatic system disorders	1 (0.2)	1 (0.3)	1 (0.4)
Disseminated intravascular coagulation	1 (0.2)	1 (0.3)	1 (0.4)
Nervous system disorders	1 (0.2)	1 (0.3)	0
Tremor	1 (0.2)	1 (0.3)	0

Abbreviations: NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose; TEAE = Treatment-Emergent Adverse Event; TKI= tyrosine kinase inhibitor.
Notes: Percentages are based on the number of subjects 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.
Sources: Module 5.3.5.3, ISS Table 14.3.1.19.1, Table 14.3.1.19.5

The Applicant's Position:

At the time of data cutoff date (20 June 2022), 24 (5.4%) subjects were reported with TEAEs with a fatal outcome in the Overall population, with 17 (4.8%) and 11 (4.2%) in the RP2D and *ROS1*-positive NSCLC Treated at RP2D Populations, respectively. 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, which included 37 (8.3%) deaths attributed to progressive disease that were reported as occurring within 28 days of the last dose of repotrectinib. 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 agrees with the Applicant's summary of TEAEs among the Safety Analysis Set populations (n=351 and n=264). Withdrawal from study therapy due to TEAEs was similar between the RP2D and ROS1 positive populations; occurring in 8% of patients each. In the RP2D population,

Grades 3-4 TEAEs were observed in 44% of patients, and similarly, in the ROS1 positive population, Grades 3-4 TEAEs occurred in 43% of patients. Grade 5 (fatal) TEAEs occurred in 4.8% and 4.2% of the RP2D and ROS1 positive populations, respectively (Table 49).

FDA agrees with the Applicant's position regarding on-study deaths. TEAEs with fatal outcome include the following: cardiac arrest, death, hypoxia, pneumonia, pneumonia aspiration, cardiac failure, disseminated intravascular coagulation, dyspnea, respiratory failure, sudden cardiac death, sudden death, and tremor. At the time of the initial data cutoff date, 132 patient deaths were reported in the TRIDENT-1 study, most of which were due to disease progression or their underlying disease. Twenty-four (5%) patients in the overall study population were reported to have a TEAE with fatal outcome. FDA reviewed the narratives for each of these fatal TEAEs; a brief summary is provided in Table 50 provides. Two of these 24 patients had a TEAE within 30 days of the last dose of study drug; however, the death occurred in the long-term follow up period. Thirty-eight patients were reported with deaths due to disease progression by the investigator within 30 days of the last dose of repotrectinib. One patient had a death due to unknown cause within 30 days of the last dose of repotrectinib (narrative: (b) (6)). Seventy-one patients had deaths reported in long-term follow up.

Table 50. Summary of TEAEs Reported With a Fatal Outcome

Patient ID	Disease	AE Term	Study Day
Phase 1			
(b) (6)	NSCLC	Cardio-respiratory arrest	409
	NSCLC	Cardiac arrest	308
	NSCLC	Adverse Event (Dyspnea)	85
	NSCLC	Respiratory failure	87
	NSCLC	Pneumonia	62
	Soft Tissue Sarcoma	Sepsis	37
	NSCLC	Sudden Death	12
	NSCLC	Cardiac arrest	372
	Phase 2		
	NSCLC	Heart Failure	49
	NSCLC	Sudden Death	83
	NSCLC	Dyspnea	28
	NSCLC	Pneumonia aspiration	220
	NSCLC	Pneumonia aspiration	35

(b) (6)			
	NSCLC	Hypoxia	156
	NSCLC	Heart failure	54
	NSCLC	DIC	147
	NSCLC	Cardiac arrest	23
	NSCLC	Unknown death	110
	Cholangiocarcinoma	Pneumonia	281
	Thyroid Cancer	Tremor/weakness	117
	NSCLC	Heart Failure	18
	NSCLC	Pneumonia	4
	NSCLC	Respiratory Failure	56
	NSCLC	Sudden Death	47

Source: Clinical Study Report, NDA 218213
Note: Date of onset was reported on or after the first dose of repotrectinib through 30 days after the last dose of repotrectinib.
Abbreviations: Disseminated intravascular coagulation: DIC; Non Small Cell Lung Cancer: NSCLC

Select patient narratives, including those for patients with an "unknown" cause of death are summarized below:

(b) (6) This was a 41-year-old male patient with ROS1 positive NSCLC who had previously received a ROS1 TKI. He remained on treatment for 168 days before discontinuing due to disease progression (identified radiographically). The reported cause of death 11 days after discontinuing repotrectinib was "unknown." Given the context provided in the narrative, FDA considers this death likely related to disease progression.

(b) (6): This was a 65-year-old female with NTRK+ thyroid carcinoma who experienced a TEAE of "tremor" with fatal outcome. The patient's medical history included carotid artery thrombosis, jugular vein thrombosis, dysphagia, balance disorder, and monoparesis. Her cause of death was reported as "unknown." She was assigned to 160 mg repotrectinib QD/BID and continued repotrectinib for a total of 117 days. Grade 5 tremor was reported on study day 117 resulting in study stop. The patient arrived to the emergency room due to worsening of tremor combined with a sudden decrease in muscle tone. Further review revealed that on study day 117 the patient was admitted for blood transfusion in the evening and found dead the next morning on study day 118 in the hospital. No imaging tests were performed. The differential diagnosis proposed were thrombotic events, cardiovascular events, and sepsis. No autopsy was performed, and no additional details were available. The Investigator assessed the relationship of the event to repotrectinib as not related. Although FDA considers this death as most likely due to the patient's underlying disease and

comorbidities, as the cause of death is unknown, possible contribution of study treatment cannot be ruled out.

Among the 24 patients with TEAEs with fatal outcome, 9 patients were investigated with cardiac or "sudden death" terms. These events were closely reviewed to assess the presence of underlying confounding factors and the potential relatedness of the events to repotrectinib. All patients had normal baseline QTcF values and had not experienced QTcF prolongation.

(b) (6): This patient was a 53-year-old, White male with ALK+ TKI-Pretreated NSCLC who was reported with "sudden death" on Day 9 of repotrectinib treatment. The patient had a medical history of hypertension, diabetes mellitus, obesity and hypercholesterolemia. Per the narrative, at his Cycle 1 Day 8 visit, 3 pre-dose electrocardiograms (ECG) performed during the visit revealed new atrial fibrillation with rapid ventricular response, and HR of 115 -130. The investigator informed the patient about the new finding of atrial fibrillation and provided a recommended for cardiology consultation. On Cycle 1 Day 9, the patient was found deceased at home by his spouse. The differential diagnosis for the death, provided by the Investigator, included myocardial infarction, fatal arrhythmia, other venous or arterial thromboembolic event and a medical history of the co-morbid diseases of hypertension, type 2 diabetes mellitus, and obesity. No autopsy was performed to confirm the cause of death. The death certificate reported the cause of death as lung cancer. FDA considers this event as possibly related to study drug given the timing of onset to start of therapy but multiple comorbidities listed in the medical history and those due to the patient's underlying disease are confounding factors.

(b) (6): This patient was a 42-year-old White male with ROS1-positive NSCLC. On study day 77 the patient to experienced grade 5 cardiac failure. It was reported the patient abruptly became dyspneic, experienced heart failure and passed away shortly after on the same day, while traveling internationally. An autopsy was conducted but the report was not shared with the trial site. FDA considered assessment of the cause of death, and potential relationship to repotrectinib, challenging given the lack of available detail.

In addition, FDA reviewed the narratives for the 38 patients who died within 30 days of the last dose of repotrectinib due to progressive disease as reported by the investigator for study TRIDENT-1; based on review of the narratives, FDA agreed with the assessment that death was likely related to progressive disease.

8.2.4.2. Serious Adverse Events

Data:

Table 51. Treatment-Emergent Serious Adverse Events in ≥ 2 Subjects by SOC and PT (Safety Analysis Set)

System Organ Class[a] Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Subjects with at least one SAE	156 (35.1)	114 (32.5)	87 (33.0)
Respiratory, thoracic and mediastinal disorders	57 (12.8)	42 (12.0)	33 (12.5)
Dyspnoea	17 (3.8)	12 (3.4)	10 (3.8)
Pleural effusion	13 (2.9)	10 (2.8)	9 (3.4)
Hypoxia	10 (2.3)	8 (2.3)	8 (3.0)
Pulmonary embolism	7 (1.6)	5 (1.4)	3 (1.1)
Pneumonitis	5 (1.1)	5 (1.4)	4 (1.5)
Respiratory failure	4 (0.9)	2 (0.6)	0
Asthma	2 (0.5)	2 (0.6)	2 (0.8)
Atelectasis	2 (0.5)	1 (0.3)	0
Infections and infestations	45 (10.1)	30 (8.5)	19 (7.2)
Pneumonia	25 (5.6)	18 (5.1)	9 (3.4)
Sepsis	5 (1.1)	2 (0.6)	1 (0.4)
Pneumonia aspiration	3 (0.7)	3 (0.9)	3 (1.1)
Bacteraemia	2 (0.5)	1 (0.3)	0
Pneumonia bacterial	2 (0.5)	1 (0.3)	1 (0.4)
Urinary tract infection	2 (0.5)	0	0
Nervous system disorders	25 (5.6)	16 (4.6)	12 (4.5)
Cerebrovascular accident	4 (0.9)	1 (0.3)	1 (0.4)
Syncope	4 (0.9)	4 (1.1)	2 (0.8)
Cerebral infarction	2 (0.5)	2 (0.6)	2 (0.8)
Dizziness	2 (0.5)	1 (0.3)	0
Embolic stroke	2 (0.5)	1 (0.3)	1 (0.4)
Hemiparesis	2 (0.5)	0	0
General disorders and administration site conditions	15 (3.4)	12 (3.4)	8 (3.0)
Pyrexia	6 (1.4)	5 (1.4)	3 (1.1)
Death	2 (0.5)	2 (0.6)	2 (0.8)
Sudden death	2 (0.5)	1 (0.3)	1 (0.4)
Cardiac disorders	13 (2.9)	8 (2.3)	6 (2.3)
Cardiac arrest	4 (0.9)	2 (0.6)	1 (0.4)
Pericardial effusion	4 (0.9)	3 (0.9)	3 (1.1)
Gastrointestinal disorders	12 (2.7)	8 (2.3)	4 (1.5)
Abdominal pain	3 (0.7)	3 (0.9)	2 (0.8)

System Organ Class[a] Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Nausea	2 (0.5)	0	0
Musculoskeletal and connective tissue disorders	11 (2.5)	7 (2.0)	5 (1.9)
Muscular weakness	5 (1.1)	4 (1.1)	2 (0.8)
Blood and lymphatic system disorders	8 (1.8)	6 (1.7)	5 (1.9)
Anaemia	4 (0.9)	3 (0.9)	2 (0.8)
Injury, poisoning and procedural complications	7 (1.6)	5 (1.4)	5 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.6)	4 (1.1)	4 (1.5)
Basal cell carcinoma	2 (0.5)	1 (0.3)	1 (0.4)
Vascular disorders	7 (1.6)	5 (1.4)	4 (1.5)
Embolism	3 (0.7)	2 (0.6)	1 (0.4)
Superior vena cava syndrome	2 (0.5)	2 (0.6)	2 (0.8)
Hepatobiliary disorders	4 (0.9)	1 (0.3)	0
Investigations	3 (0.7)	2 (0.6)	1 (0.4)
Blood bilirubin increased	2 (0.5)	1 (0.3)	1 (0.4)
Metabolism and nutrition disorders	3 (0.7)	2 (0.6)	2 (0.8)
Hyponatraemia	2 (0.5)	2 (0.6)	2 (0.8)
Renal and urinary disorders	3 (0.7)	2 (0.6)	2 (0.8)
Hydronephrosis	2 (0.5)	1 (0.3)	1 (0.4)

Abbreviations: NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose; SAE = Serious Adverse Event.
Notes: Percentages are based on the number of subjects 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 subjects 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 subjects, whilst all PTs within a SOC occur at incidences of < 2 subjects, explaining the absence of any PTs for those SOCs.
Sources: Module 5.3.5.3, 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 subjects) at the SOC level were Respiratory, thoracic and mediastinal disorders (12.8%), Infections and infestations (10.1%), and Nervous system disorders (5.6%). The most frequently reported SAEs (≥ 2% of subjects) in the Overall population were pneumonia (5.6%), dyspnea (3.8%), pleural effusion (2.9%) and hypoxia (2.3%). 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 agrees with the Applicant's summary of treatment-emergent SAEs. In the RP2D (N=351)

and ROS1 positive NSCLC (N=264) safety populations, SAEs occurred in 31% and 33% of patients, respectively. The most frequent serious adverse reactions (in ≥ 2% of patients) in the RP2D safety population were pneumonia (6%), dyspnea (3.4%), pleural effusion (2.8%), and hypoxia (2.3%). The most frequent serious adverse reactions (in ≥ 2% of patients) in the ROS1 positive safety population were pneumonia (5.7%), dyspnea (3.8%), pleural effusion (3.4%), and hypoxia (3%).

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 52. TEAEs Leading to Discontinuation of Study Drug in > 1 Subject (Safety Analysis Set)

System Organ Class Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Subjects with TEAEs leading to discontinuation of study drug	43 (9.7)	29 (8.3)	22 (8.3)
Grade 1	2 (0.5)	2 (0.6)	2 (0.8)
Grade 2	10 (2.3)	5 (1.4)	4 (1.5)
Grade 3	18 (4.1)	13 (3.7)	11 (4.2)
Grade 4	3 (0.7)	3 (0.9)	2 (0.8)
Grade 5	10 (2.3)	6 (1.7)	3 (1.1)
Respiratory, thoracic, and mediastinal disorders	17 (3.8)	13 (3.7)	10 (3.8)
Dyspnoea	5 (1.1)	4 (1.1)	3 (1.1)
Pneumonitis	4 (0.9)	4 (1.1)	3 (1.1)
Hypoxia	2 (0.5)	2 (0.6)	2 (0.8)
Pleural effusion	2 (0.5)	1 (0.3)	1 (0.4)
Respiratory failure	2 (0.5)	1 (0.3)	0
Nervous system disorders	6 (1.4)	4 (1.1)	3 (1.1)
Depressed level of consciousness	2 (0.5)	1 (0.3)	1 (0.4)
Infections and infestations	4 (0.9)	2 (0.6)	2 (0.8)
Pneumonia	3 (0.7)	2 (0.6)	2 (0.8)
Cardiac disorders	3 (0.7)	3 (0.9)	2 (0.8)
Cardiac arrest	2 (0.5)	2 (0.6)	1 (0.4)
Musculoskeletal and connective tissue disorders	3 (0.7)	3 (0.9)	3 (1.1)
Muscular weakness	3 (0.7)	3 (0.9)	3 (1.1)

Abbreviations: NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose; TEAE = Treatment-Emergent Adverse Event.
Notes: Percentages are based on the number of subjects 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.
Sources: Module 5.3.5.3, 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 9.7% of subjects and were consistent with the RP2D and *ROS1*-positive NSCLC treated at RP2D Populations. Discontinuations were largely driven (3.8%) 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 as 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 treatments discontinuations. In the RP2D safety population (N=351) and the ROS1 positive safety population (N=264), permanent discontinuation of repotrectinib was required in 8% of patients due to adverse reactions. Adverse reactions resulting in permanent discontinuation of repotrectinib in ≥1% of patients in both of these populations were dyspnea, pneumonitis, and muscular weakness.

8.2.4.4. Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 53. TEAEs Leading to Interruption of Study Drug in > 1% of Subjects by SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Subjects with TEAEs leading to interruption of study drug	200 (45.0)	172 (49.0)	128 (48.5)
Grade 1	11 (2.5)	7 (2.0)	5 (1.9)
Grade 2	64 (14.4)	54 (15.4)	40 (15.2)
Grade 3	107 (24.1)	97 (27.6)	72 (27.3)
Grade 4	14 (3.2)	11 (3.1)	9 (3.4)
Grade 5	4 (0.9)	3 (0.9)	2 (0.8)
Nervous system disorders	74 (16.7)	63 (17.9)	38 (14.4)
Dizziness	38 (8.6)	30 (8.5)	15 (5.7)
Ataxia	16 (3.6)	15 (4.3)	10 (3.8)
Respiratory, thoracic and mediastinal disorders	58 (13.1)	46 (13.1)	40 (15.2)
Dyspnoea	28 (6.3)	22 (6.3)	21 (8.0)
Hypoxia	8 (1.8)	6 (1.7)	6 (2.3)
Pleural effusion	8 (1.8)	7 (2.0)	6 (2.3)
Pneumonitis	5 (1.1)	5 (1.4)	5 (1.9)
Investigations	34 (7.7)	33 (9.4)	24 (9.1)

System Organ Class Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Blood creatine phosphokinase increased	9 (2.0)	9 (2.6)	8 (3.0)
Alanine aminotransferase increased	8 (1.8)	8 (2.3)	5 (1.9)
Aspartate aminotransferase increased	7 (1.6)	7 (2.0)	3 (1.1)
Neutrophil count decreased	6 (1.4)	6 (1.7)	6 (2.3)
Gamma-glutamyltransferase increased	5 (1.1)	5 (1.4)	3 (1.1)
White blood cell count decreased	3 (0.7)	3 (0.9)	3 (1.1)
Infections and infestations	31 (7.0)	27 (7.7)	17 (6.4)
Pneumonia	15 (3.4)	13 (3.7)	7 (2.7)
Musculoskeletal and connective tissue disorders	30 (6.8)	27 (7.7)	19 (7.2)
Muscular weakness	21 (4.7)	19 (5.4)	15 (5.7)
General disorders and administration site conditions	23 (5.2)	19 (5.4)	13 (4.9)
Fatigue	9 (2.0)	8 (2.3)	5 (1.9)
Pyrexia	5 (1.1)	3 (0.9)	1 (0.4)
Asthenia	3 (0.7)	3 (0.9)	3 (1.1)
Gait disturbance	3 (0.7)	3 (0.9)	3 (1.1)
Gastrointestinal disorders	21 (4.7)	17 (4.8)	9 (3.4)
Vomiting	6 (1.4)	5 (1.4)	3 (1.1)
Abdominal pain	3 (0.7)	3 (0.9)	3 (1.1)
Blood and lymphatic system disorders	14 (3.2)	13 (3.7)	8 (3.0)
Anaemia	12 (2.7)	11 (3.1)	6 (2.3)
Metabolism and nutrition disorders	8 (1.8)	8 (2.3)	4 (1.5)
Hyponatraemia	5 (1.1)	5 (1.4)	3 (1.1)
Psychiatric disorders	7 (2.4)	7 (2.0)	7 (2.7)
Confusional state	3 (0.7)	3 (0.9)	3 (1.1)

Abbreviations: NSCLC = non-small cell lung cancer; PT = preferred term, RP2D = recommended Phase 2 dose; SOC = system organ class; TEAE = Treatment-Emergent Adverse Event.
Notes: Percentages are based on the number of subjects 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.
Sources: Module 5.3.5.3, ISS Table 14.3.1.9.1, Table 14.3.1.9.2

Table 54. TEAEs Leading to Reduction of Study Drug in > 1% of Subjects by SOC and PT (Safety Analysis Set)

System Organ Class Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Subjects with TEAEs leading to reduction of study drug	151 (34.0)	134 (38.2)	93 (35.2)

System Organ Class Preferred Term	Overall Population (N = 444)	RP2D Subpopulations	
		RP2D Population (N = 351)	*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Grade 1	20 (4.5)	18 (5.1)	13 (4.9)
Grade 2	84 (18.9)	73 (20.8)	51 (19.3)
Grade 3	43 (9.7)	39 (11.1)	27 (10.2)
Grade 4	4 (0.9)	4 (1.1)	2 (0.8)
Nervous system disorders	89 (20.0)	78 (22.2)	50 (18.9)
Dizziness	47 (10.6)	41 (11.7)	23 (8.7)
Ataxia	24 (5.4)	22 (6.3)	13 (4.9)
Paraesthesia	10 (2.3)	9 (2.6)	6 (2.3)
Musculoskeletal and connective tissue disorders	20 (4.5)	18 (5.1)	12 (4.5)
Muscular weakness	16 (3.6)	15 (4.3)	12 (4.5)
Investigations	19 (4.3)	18 (5.1)	14 (5.3)
Blood creatine phosphokinase increased	7 (1.6)	7 (2.0)	6 (2.3)
Alanine aminotransferase increased	5 (1.1)	5 (1.4)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	17 (3.8)	15 (4.3)	13 (4.9)
Dyspnoea	6 (1.4)	5 (1.4)	5 (1.9)
Pleural effusion	3 (0.7)	3 (0.9)	3 (1.1)
General disorders and administration site conditions	10 (2.3)	8 (2.3)	6 (2.3)
Fatigue	5 (1.1)	4 (1.1)	2 (0.8)

Abbreviations: NSCLC = non-small cell lung cancer; PT = preferred term, RP2D = recommended Phase 2 dose; SOC = system organ class; TEAE = Treatment-Emergent Adverse Event.
Notes: Percentages are based on the number of subjects 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.
Sources: Module 5.3.5.3, ISS Table 14.3.1.8.1, Table 14.3.1.8.2

The Applicant's Position:

In the Overall population, TEAEs leading to interruption of study drug was reported for 45.0% of subjects and was consistent with the RP2D and *ROS1*-positive NSCLC Treated at RP2D Populations, respectively. Individual TEAE PTs in the Overall population were typically reported at low incidences (≤ 5% of subjects). Dose reductions were driven largely by on target TRK related CNS toxicities (20.0%) and muscular disorders (4.5%), allowing patients to continue on treatment and derive clinical benefit with optimally balancing the adverse events. Respiratory events were associated with 3.8% of dose reductions.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. In the RP2D safety population (N=351), dosage interruptions due to an adverse reaction occurred in 38% of patients who received repotrectinib. Adverse reactions requiring dosage interruption in ≥5% of patients included CNS toxicity (17%), dizziness (9%), ataxia (6%), and muscular weakness (5%).

In the RP2D safety population (N=351), dosage reductions due to an adverse reaction occurred in 38% of patients who received repotrectinib. Adverse reactions requiring dosage reduction in ≥5% of patients included CNS toxicity (21%), dizziness (12%), and ataxia (8%).

In the ROS1 positive safety population (N=264), dosage interruptions of repotrectinib due to an adverse reaction occurred in 48% of patients. Adverse reactions that required dosage interruption in ≥5% of patients included CNS toxicity (14%), dyspnea (8%), dizziness (6%), ataxia (6%), and muscular weakness (6%).

In the ROS1 positive safety population (N=264), dosage reductions of repotrectinib due to an adverse reaction occurred in 35% of patients. Adverse reactions that required dosage reductions in ≥5% of patients included CNS toxicity (17%), dizziness (9%), and ataxia (8%).

8.2.4.5. Significant Adverse Events

Adverse Events of Special Interest

Data:

Table 55. Treatment-Emergent Adverse Events of Special Interest in > 2 Subjects by Medical Concept (Safety Analysis Set)

	Overall Population	RP2D Subpopulation	
Adverse Event of Special Interest (AESI)[a]	**All Causality (N = 444)**	**All Causality RP2D Population (N = 351)**	**All Causality *ROS1*-positive NSCLC Treated at RP2D Population (N = 264)**
Subjects with at least one AESI	418 (94.1)	418 (94.1)	249 (94.3)
Medical Concept Term			
Ataxia	117 (26.4)	101 (28.8)	73 (27.7)
Cognitive disorders	90 (20.3)	79 (22.5)	60 (22.7)
Dizziness	282 (63.5)	224 (63.8)	167 (63.3)
Dysgeusia	239 (53.8)	192 (54.7)	139 (52.7)
Hepatic enzyme elevation	106 (23.9)	97 (27.6)	79 (29.9)
Mood disorders	26 (5.9)	20 (5.7)	16 (6.1)
Muscular weakness	83 (18.7)	67 (19.1)	55 (20.8)
Paraesthesia	165 (37.2)	135 (38.5)	103 (39.0)
Peripheral sensory neuropathy	75 (16.9)	60 (17.1)	44 (16.7)
Pneumonitis	12 (2.7)	10 (2.8)	7 (2.7)
QT prolongation	4 (0.9)	4 (1.1)	3 (1.1)

Adverse Event of Special Interest (AESI)[a]	Overall Population	RP2D Subpopulation	
	All Causality (N = 444)	All Causality RP2D Population (N = 351)	All Causality *ROS1*-positive NSCLC Treated at RP2D Population (N = 264)
Skeletal fractures	13 (2.9)	8 (2.3)	7 (2.7)
Sleep disorders	56 (12.6)	52 (14.8)	36 (13.6)
Vision disorders	57 (12.8)	44 (12.5)	31 (11.7)

Abbreviations: AESI = adverse event of special interest; EOSI = event of special interest; NSCLC = non-small cell lung cancer; RP2D = recommended Phase 2 dose; TEAE = treatment-emergent adverse event.
Notes: Percentages are based on the number of subjects 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. NS the SAP based on cross functional review of higher-level terms and preferred terms.
[a] Occurring in > 2 subjects, by preferred term, in any population. Sources: Module 5.3.5.3, 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 SAEs 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: ataxia, cognitive disorders, dizziness, dysgeusia, hepatic enzyme elevation, mood disorder, muscle weakness, paresthesia, pneumonitis, peripheral sensory neuropathy, QT prolongation, skeletal fractures, sleep disorders, 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 subjects) in the Overall population was typically within the first month of study treatment, irrespective of causality.

AESIs leading to discontinuation of study drug were infrequent (14 [3.2%] subjects), with pneumonitis (4 [0.9%] subjects) and cognitive disorders (4 [0.9%]) being the only Medical Concepts where any AESI PT was reported in > 1 subject. To mitigate against worst grade events, measures were implemented to allow for prophylactic management of toxicities, eg, 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 4.7% and 11.5% of subjects, respectively; in both event categories, the individual event PTs were typically reported at very low incidences (< 1% of subjects). There were no AESIs with fatal outcome. The most frequently reported serious AESIs (≥ 2 subjects) in the Overall population, summarized by Medical Concept, were

pneumonitis (5 [1.1%] subjects), skeletal fractures (4 [0.9%]), cognitive disorders (2 [0.5%]), and dizziness (2 [0.5%]). The most frequently reported grade ≥ 3 treatment-related AESIs (≥ 1% of subjects) in the Overall population), summarized by Medical Concept, were hepatic enzyme elevation (10 [2.3%]), dizziness (13 [2.9%]), and peripheral sensory neuropathy (5 [1.1%]).

There were no important differences in the incidence of Medical Concept terms across the RP2D subpopulations when compared to the Overall population.

In the Overall population (N = 444), 162 subjects were diagnosed with brain metastasis per Investigator assessment at baseline. Of these, 154 (95.1%) 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, including for comparison with the subpopulation comprising *ROS1*-positive NSCLC subjects (brain metastasis at baseline: N = 118 [Yes] vs N = 178 [No]).

The FDA's Assessment:

FDA agrees with the Applicant's summary of AESIs. AESIs 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. In addition, a grouped term was added for CNS toxicity; CNS toxicity is a broad group term encompassing several specific CNS effects (i.e., mood, sleep, dizziness, and ataxia) listed in Table 56. Refer to Section 8.2.4.7 for a discussion of a newly identified laboratory-based safety signal of hyperuricemia.

Table 56: FDA Definition of Group Term AESIs

Grouped Term	MedDRA Search Terms
Ataxia	ataxia, gait disturbances, balance disorder, cerebellar ataxia, and coordination abnormal
Cognitive Disorders	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
CNS Toxicity	somnolence, insomnia, hypersomnia, sleep disorder, narcolepsy, sleep apnea syndrome, snoring, 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, neurological decompensation, Affect lability, Affective disorder, Aggression, Agitated depression, Agitation, Anxiety, Anxiety disorder, Depressed mood, Depression, Euphoric mood, Irritability, Mania, Mood altered, Mood swings, Persistent depression disorder, Personality change, Personality disorder, Psychomotor retardation, Stress, Suicidal ideation, dizziness, vertigo, dizziness postural, dizziness exertional, vertigo positional, ataxia, gait disturbances, balance disorder, cerebellar ataxia, and coordination abnormal

Dizziness	Include terms: 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 swings, Persistent depression disorder, Personality change, Personality disorder, Psychomotor retardation, Stress, Suicidal ideation
Skeletal Fractures	Fractures: Acetabulum, Ankle, Foot, Rib, Spinal Compression, Sternal
Sleep Disorders	somnolence, insomnia, hypersomnia, sleep disorder, narcolepsy, sleep apnea syndrome, snoring
Myalgia	myalgia, musculoskeletal pain, myositis, musculoskeletal discomfort
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

The above grouped terms were used to assess these signals in the RP2D population (N=351).

Central nervous system adverse reactions were observed in patients receiving repotrectinib. Among the 351 patients who received repotrectinib in Study TRIDENT-1, and CNS toxicity, per the FDA grouped term above, occurred in 75% of patients of any grade. Dizziness occurred in 64% of patients of any grade; dose interruption was required in 9% and 12% required dose reduction. Ataxia occurred in 29% of patients of any grade; and dose interruption was required in 6% of patients, 8% required dose reduction, and one patient (0.3%) permanently discontinued repotrectinib due to ataxia. Cognitive disorders occurred in 23% of patients of any grade; dose interruption was required in 2% of patients, 1.7% required dose reduction, and 0.6% patients permanently discontinued repotrectinib due to cognitive adverse reactions. Mood disorders occurred in 6% of patients of any grade; dose interruption was required in 0.3% of patients and 0.3% of patients required a dose reduction due to mood disorders. Sleep disorders occurred in 15% of patients of any grade; dose interruption was required in 0.9% of patients and 0.3% of patients required a dose reduction due to sleep disorders. Based on review of this data, patient narratives and considering other findings such as the safety profile of other drugs in class, FDA considered these events likely to be related to repotrectinib, and it is appropriate to include them in the Warnings section of the product label.

Muscular weakness was identified by the Applicant as an AESI and an analysis was conducted across the RP2D population (N=351) utilizing the composite preferred terms of "muscle fatigue" and “muscular weakness.” Per the Applicant, it was reported that among 109 patients with muscular adverse reactions, most were low grade (Grade 1, n=65 [18.5%]; Grade 2, n=36 [10.3%]), with Grade 3 events reported in 8 (2.3%) patients. Muscular weakness was reported as an SAE in 4 [1.1%] patients, and lead to discontinuation of repotrectinib in (3 [0.9%] patients.

Of the 109 patients with muscular AEs, 47 patients had concurrent CPK elevation that was documented within 7 days of the onset of muscular adverse reaction. Given the concern for muscular adverse reactions with repotrectinib and to further characterize muscular AEs, FDA conducted an analysis using the grouped term myalgia which included terms such as muscular pain and myositis, defined in the table above. Myalgia with or without creatine phosphokinase (CPK) elevation was observed in patients receiving repotrectinib. Among the 351 patients in the RP2D safety population, myalgia occurred in 13% of patients of any grade. Concurrent increased CPK within a 7-day window was observed in 3.7% of patients. Three patients required dose interruption due to myalgia, one patient required a dose reduction and one patient required a dose interruption due to myalgia and concurrent CPK elevation. No events of rhabdomyolysis were observed in the RP2D safety population. Based on review of this data, patient narratives and considering other findings such as the safety profile of other drugs in class, FDA considered these events likely to be related to repotrectinib, and it is appropriate to include them as in the Warnings section of the product label.

Skeletal fractures were observed in some patients receiving repotrectinib. FDA conducted a grouped term analysis for any fracture occurring among patients in the RP2D safety population, n=351. Narrative summaries were reviewed for any potential confounding factors e.g., tumor involvement at site of fracture, prior radiation site.

Among 351 adult patients who received repotrectinib at the RP2D, fractures occurred in 2.3%. Fractures involved the ribs (0.6%), feet (0.6%), spine (0.3%), acetabulum (0.3%), sternum (0.3%), and ankles (0.3%). Some fractures occurred at sites of disease and prior radiation therapy. Repotrectinib was interrupted in 0.3% of patients. Skeletal fractures were also observed with another drug in the same class, entrectinib, although this safety signal was more pronounced in pediatric patients treated with entrectinib compared to adults (USPI Entrectinib). A selected patient narrative, which demonstrates a case confounded by prior radiation and skeletal metastases, is provided below:

> (b) (6): This patient is a 35-year-old Asian male with ROS1+ NSCLC received repotrectinib at 160 mg QD/BID. This patient had back pain and bone metastasis at enrollment. A serious adverse event of spinal compression fracture (verbatim: vertebral collapse), Grade 3 was reported on study day 85. Magnetic resonance imaging (MRI) showed known features of skeletal metastases, recognizable in the cervical, thoracic, and lumbar spinal column as well as post-radiation therapy changes from T10 to L3 vertebra, with some fatty degeneration of the vertebra in-situ, progressive collapse of corpus T11 with posterior osseous bending with features indicative of spinal cord compression. The study drug was interrupted from study day 89 to day 92. The event was resolved post-surgery by day 96. The patient continued repotrectinib at 160 mg BID with no further dose modifications.

Based on review of skeletal fracture and patient narratives and considering the safety profile of

other drugs in class, FDA considered these events likely to be related to repotrectinib, and it is appropriate to include them as in the Warnings section of the product label.

Interstitial lung disease (ILD) / pneumonitis was observed in patients treated with repotrectinib. FDA reviewed patient narratives and considered a broad search evaluating serious respiratory events in our analysis of pneumonitis and ILD. Among the 351 patients treated with repotrectinib, ILD/pneumonitis (pneumonitis [2.6%] and interstitial lung disease [0.3%]) occurred in 2.9% of patients; Grade 3 ILD/pneumonitis occurred in 1.1% of patients; dose interruption was required in 1.4% of patients, 0.6% of patients required dose reduction, and 1.1% patients permanently discontinued repotrectinib due to ILD/pneumonitis. Based on review of this data, patient narratives and considering other findings such as the safety profile of other drugs in class, FDA considered these events likely to be related to repotrectinib, and it is appropriate to include them as in the Warnings section of the product label.

Hepatotoxicity was observed in patients receiving repotrectinib. FDA reviewed patient narratives and searched the safety datasets for terms related to or possibly contributing to liver failure. Among the 351 patients treated with repotrectinib, increased alanine transaminase (ALT) occurred in 35%, increased aspartate aminotransferase (AST) occurred in 40% including Grade 3 or 4 increased ALT in 2% and increased AST 2.6%. 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 1.4% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.6%. During the course of the review a patient ((b) (6)) was identified with Grade 3 hepatic cytolysis.

> (b) (6) : This is a 31-year-old male with TKI-naïve ROS1+ NSCLC who was enrolled in EXP-1 and received repotrectinib at 160 mg QD. This patient had brain and liver metastases at baseline, and his medical history included dyspnea, visual impairment, hypothyroidism, and androgen deficiency. During his treatment with repotrectinib, he had an AE of “hepatic cytolysis” reported. Liver function labs were elevated at screening. Screening labs drawn on study day -17 showed high (grade 2) ALT of 219 U/L (range: 0, 55) and AST 68 U/L (range: 5, 34). Grade 3 hepatic cytolysis was reported on Cycle 1 Day 11 and was downgraded to Grade 2 hepatic cytolysis on Cycle 1 Day 15. The event resolved on Cycle 1 Day 21. Repotrectinib was interrupted due to hepatic cytolysis for 10 days, restarted at 160 mg QD escalated to 160 mg BID on Cycle 2 Day 1 (Day 27). The patient has stayed on the 160 mg BID dosing with no further dose modifications and continued treatment with no recurrence of hepatic cytolysis.

Based on review of this hepatotoxicity data, patient narratives and considering other findings such as the safety profile of other drugs in class, FDA considered these events likely to be related to repotrectinib, and it is appropriate to include them as in the Warnings section of the product label. The product label will advise providers to evaluate baseline liver function tests, and to evaluate every two weeks during the first month of treatment and monthly thereafter.

The AESIs are also tabulated in Table 57 below. Considering these AESIs, the risk:benefit ratio was favorable for repotrectinib to address an unmet clinical need in this patient population.

Table 57: FDA Group Term Analysis of Identified AESIs

Group Term	All Causality Any Grade	
	Overall RP2D Population (N=351)	ROS1 Positive Population (N=264)
Ataxia	29%	28%
Cognitive Disorders	23%	23%
CNS toxicity	75%	71%
Dizziness	64%	63%
Mood Disorders	6%	6%
Skeletal Fractures	2.30%	2.70%
Sleep Disorders	15%	14%
Myalgia	13%	12%
Vision Disorders	12%	11%

Vision disorders were observed in patients receiving repotrectinib. FDA analyzed the safety dataset and patient narratives to inform this review. Among the 351 patients treated with repotrectinib at the RP2D, vision disorders occurred in 12%, including Grade 3 to 4 in 0.3%. Vision disorders preferred terms observed in the safety dataset included blurred vision (3.7%), dry eye (1.4%), visual impairment (1.1%), and visual field defect (0.9%). There was 1 Grade 3 vision disorder of ophthalmic herpes zoster reported (0.3%). During the course of this review, we noted many of the vision disorder preferred terms included in the grouped term "vision disorders" were all reported as low grade. Some visual terms were not specifically listed in the Common Terminology Criteria for Adverse Events (CTCAE). For these ocular terms such as visual impairment and visual acuity decreased, that are not specifically listed in CTCAE v 4.03grading was done according to the Eye Disorders-Other grading scale. This may have caused some confounding in reporting AE grades. In depth review was done for patients with visual impairment (b) (6) visual field defect (b) (6) (b) (6) and visual acuity reduced (b) (6)

(b) (6): This is a 49-year-old White male with ROS1+ NSCLC was enrolled in EXP-2. The event "visual impairment" grade 1 was reported on study day 56. No description of the actual impairment was available. Ophthalmologic exam was not done per narrative. No treatment was provided for the event. No action was taken with the study drug. The event was ongoing and the patient ended therapy on study day 137 due to disease progression.

(b) (6) This is a 63-year-old White female with NTRK3 fusion positive cholangiocarcinoma who experienced "visual impairment" Grade 1on study day 8. No treatment was provided for the event. No action was taken with the study drug. No ophthalmologic or diagnostic testing was done. The event was ongoing and the patient died due to disease progression and pneumonia on study day 291.

(b) (6): This is a 64-year-old male (race not reported) with NTRK+ head and neck adenocarcinoma was enrolled in EXP-5. The event of "visual impairment" Grade 1 was reported on Day 390. No treatment was provided for the event. No action was taken with the study drug. No ophthalmic examinations have been performed for this event. The event was reported as ongoing at last study follow up.

(b) (6): This is a 60-year-old female with NTRK+ mammary ductal adenocarcinoma was enrolled in EXP-5. The event of "visual impairment" Grade 1 was reported on study day 388. No treatment was provided for the event. No action was taken with the study drug. No concomitant medications were given, and no ophthalmic evaluation was performed. The event was resolved. The patient ended treatment on study day 422 due to radiographic progression.

Most visual disorder AEs were reported as low grade as described by the Applicant. Dose interruptions occurred in 1 patient (0.3%) with "blurred vision." Ophthalmologic exams were not included in the TRIDENT-1 protocol. Due to the lack of ophthalmic evaluation and vision diagnostic testing, FDA considered that vision disorders were not adequately characterized in the safety dataset. Ocular toxicity is a known effect of drugs in this class, and ocular toxicity is not always predicted in humans based on general toxicology studies, including with drugs in this class. Given the lack of prospective ophthalmologic assessments, a signal of ocular findings in the clinical trial, and considering both the class effect observed in humans and inability to predict ocular toxicity based on nonclinical studies, FDA considered that the current safety database may underappreciate the severity of ocular toxicity associated with repotrectinib. Although the safety profile as currently characterized dose not support inclusion of a Warning in the product label, a PMR was issued for this application to further investigate the potential safety signal for vision disorders on study.

8.2.4.6. Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 58 summarizes the ADRs identified for repotrectinib that were reported in ≥ 10% of subjects in the Overall population.

Table 58. Adverse Drug Reactions in the Overall Population (in ≥ 10% of Subjects) and RP2D Subpopulations (Safety Analysis Set)

Adverse Reaction System Organ Class Grouped/Preferred Term	Overall Population (N = 444)		RP2D Subpopulations			
			RP2D Population (N = 351)		*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)	
	All Grades (%)	Grade ≥ 3* (%)	All Grades (%)	Grade ≥ 3* (%)	All Grades (%)	Grade ≥ 3* (%)
Nervous system disorders						
Dizziness[a]	63.5	2.9	63.8	2.8	63.3	1.9
Dysgeusia[b]	53.8	0	54.7	0	52.7	0
Paraesthesia[c]	37.2	0.7	38.5	0.9	39.0	0.8
Ataxia[d]	26.4	0.2	28.8	0.3	27.7	0.4
Cognitive disorders[e]	20.3	0.7	22.5	0.9	22.7	0.8
Headache	17.6	0.2	17.7	0	18.2	0
Peripheral sensory neuropathy[f]	16.9	1.1	17.1	1.1	16.7	1.1
Sleep disorders[g]	12.6	0.2	14.8	0	13.6	0
Gastrointestinal disorders						
Constipation	36.7	0.2	37.3	0.3	36.4	0
Nausea	20.7	0.7	20.2	0.3	18.6	0.4
Vomiting	13.3	0.9	12.0	1.1	10.2	0.8
Diarrhoea	12.2	0.5	12.8	0.6	12.5	0.4
Respiratory, thoracic and mediastinal disorders						
Dyspnoea*	28.8	7.7	27.1	7.1	27.7	7.2
Cough	13.7	0.2	12.0	0.3	11.0	0
General disorders and administration site conditions						
Fatigue	24.1	1.4	22.5	1.1	18.9	0.8
Pyrexia	11.3	0.7	8.8	0.9	8.0	0.8
Musculoskeletal and connective tissue disorders						
Muscular weakness	18.7	1.4	19.1	1.4	20.8	1.5

Adverse Reaction System Organ Class Grouped/Preferred Term	Overall Population (N = 444)		RP2D Subpopulations			
			RP2D Population (N = 351)		*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)	
	All Grades (%)	Grade ≥ 3* (%)	All Grades (%)	Grade ≥ 3* (%)	All Grades (%)	Grade ≥ 3* (%)
Arthralgia	13.1	0.5	13.1	0.3	14.0	0.4
Pain in extremity	10.4	0.2	9.7	0	11.0	0
Investigations						
Weight increased	12.2	1.8	13.4	1.7	13.6	1.9
Eye disorders						
Vision disorders[h]	12.8	0.5	12.5	0.6	11.7	0.4

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PT = preferred term; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TEAE = treatment-emergent adverse event

Notes:

** Includes one patient with Grade 5 dyspnea which was part of the pneumonia/disease progression that resulted in death.*

[g] Includes terms dizziness, vertigo, dizziness postural, dizziness exertional, and vertigo positional.

[b] Includes terms dysgeusia, taste disorder, ageusia, sensory disturbance, allodynia, hypogeusia, sensory loss.

[c] Includes terms paresthesia, hypoaesthesia, hyperaestheisa, dysaesthesia, burning sensation, formication.

[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 neuralgia, neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy.

[g] Includes terms somnolence, insomnia, hypersomnia, sleep disorder, narcolepsy, sleep apnoea syndrome, snoring.

[h] Includes terms vision blurred, dry eye, visual impairment, visual field defect, cataract, conjunctivitis, eye pain, photophobia, photosensitivity reaction, visual acuity reduced, vitreous floaters, blepharospasm, colour blindness, diplopia, eye haematoma, eye oedema, eye swelling, eyelid disorder, eyelid injury, eyelids pruritus, glaucoma, night blindness, ophthalmic herpes zoster, orbital oedema, periorbital oedema.

Sources: ADRs reported for All Grades as Grouped Terms, please refer to Module 5.3.5.3, ISS Table 14.3.1.31.1 and Table 14.3.1.51.1. For ADRs reported for All Grades as ungrouped PTs, Table 14.3.1.2.1 and Table 14.3.1.2.5. ADRs Grade ≥ 3, Table 14.3.1.38.1 (Grouped Terms in the Overall Population), Table 14.3.1.58.1 (Grouped Terms in the RP2D and ROS1-positive NSCLC Treated at RP2D Populations), for ungrouped PTs Table 14.3.1.17.1 (Overall Population), and Table 14.3.1.17.5 RP2D and ROS1-positive NSCLC Treated at RP2D Populations).

The Applicant's Position:

Adverse drug reactions were determined by evaluating TEAEs across the Overall population. For labeling purposes, ADRs are presented for the RP2D population. The following rules were used for determination of an ADR:

- TEAEs ≥ 10% in the Overall population, evaluated as having a possible causal drug-event relationship.
  - Events that met the 10% threshold assessed as related to alternative etiologies were excluded
  - Event terms and group terms representing medical concepts were used when applicable to better inform the prescriber with useful information about the drug
  - Events that were reported as abnormalities in clinical laboratory parameters were assessed to determine inclusion in the laboratory abnormality tables (parameters reported in ≥ 20% of subjects, inclusive) or listed as a clinically relevant if they did not meet the ≥ 20% threshold
- TEAEs < 10%, that were considered clinically relevant (ie, biologically plausible through a relationship to mechanism of action and/or class effect).

Table 58 summarizes the ADRs identified for repotrectinib that were reported in ≥ 10% of subjects in the Overall population.

TEAEs reported in < 10% of subjects in the Overall population that are considered clinically relevant, and an ADR include fall (3.8%) and skeletal fractures (2.9%).

The pattern of ADRs (Table 58) in the RP2D Population and the *ROS1*-positive NSCLC Treated at RP2D Population were similar to the Overall population.

The FDA's Assessment:

FDA agrees with the Applicant's summary of common adverse reactions in the overall population and safety population set.

Notably, the several grouped terms were revised in FDA's analysis of TEAEs: peripheral neuropathy, dizziness, ataxia, cognitive disorders, and vision disorders; refer to Table 59.

Table 59: FDA Adverse Reactions (≥10%) in Patients With ROS1-Positive NSCLC

Adverse Reaction[1]	Repotrectinib N=264	
	All Grades (%)	Grade 3 or 4 (%)
Nervous System Disorders		
Dizziness[a]	63	1.9
Dysgeusia[b]	48	0
Peripheral neuropathy[f]	47	1.9
Ataxia[c]	28	0.4
Cognitive disorders[d]	23	0.8
Headache[e]	19	0
Gastrointestinal Disorders		
Constipation	36	0
Nausea	19	0.4
Diarrhea	13	0.4
Vomiting	10	0.8
Metabolism and Nutritional		
Increased weight	14	1.9
General Disorders		
Fatigue[g]	24	1.1
Edema[h]	12	0.8
Musculoskeletal and Connective Tissue Disorders		
Myalgia[i]	12	0.4
Muscular weakness	21	1.5
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea[j]	30	7
Cough[k]	14	0
Eye Disorders		
Vision disorders[l]	11	0

[1] Table 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 ataxia, gait disturbance, balance disorder, cerebellar ataxia

d 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

e Includes terms headache, migraine, tension headache

f Includes terms neuralgia, neuropathy peripheral, peripheral sensory neuropathy, dysesthesia, peripheral motor neuropathy, polyneuropathy, paresthesia, hypoesthesia, hyperesthesia

g Includes terms fatigue and asthenia

h Includes terms generalized edema, periorbital edema, localized edema, face edema, edema peripheral, edema, eye edema, scrotal edema

i Includes terms myalgia, myositis, musculoskeletal discomfort, musculoskeletal pain

j Includes terms dyspnea and dyspnea exertional

k Includes terms productive cough, cough, and upper-airway cough syndrome

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

FDA agrees with the Applicant's summary of clinically relevant adverse reactions; an additional clinically relevant adverse reaction occurring in <10% of patients receiving repotrectinib was pyrexia (8%).

8.2.4.7. Laboratory Findings

Data:

Table 60. Laboratory Abnormalities (≥ 20%) of Subjects Worsening From Baseline (Safety Analysis Set)

Lab Abnormality (NCI CTCAE Grade) n (%)	Overall Population (N = 444)			RP2D Subpopulations					
				RP2D Population (N = 351)			*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)		
	Denominator[a]	All Grades	Grade 3 or 4	Denominator[a]	All Grades	Grade 3 or 4	Denominator[a]	All Grades	Grade 3 or 4
Hematology									
Hemoglobin (Low)	434	326 (75.1)	34 (7.8)	341	254 (74.5)	24 (7.0)	258	189 (73.3)	14 (5.4)
Lymphocytes (Low)	433	197 (45.5)	51 (11.8)	340	145 (42.7)	34 (10.0)	257	110 (42.8)	25 (9.7)
Leukocytes (Low)	434	150 (34.6)	13 (3.0)	341	124 (36.4)	13 (3.8)	258	94 (36.4)	12 (4.7)
Neutrophils (Low)	432	124 (28.7)	28 (6.5)	339	110 (32.5)	26 (7.7)	256	86 (33.6)	21 (8.2)
Coagulation									
Prothrombin Intl. Normalized Ratio (High)	424	104 (24.5)	0 (0.0)	334	74 (22.2)	0 (0.0)	249	51 (20.5)	0 (0.0)
Activated Partial Thromboplastin Time (High)	416	94 (22.6)	2 (0.5)	326	77 (23.6)	1 (0.3)	243	61 (25.1)	1 (0.4)
Chemistry									
Gamma glutamyl transferase (High)	223	109 (48.9)	30 (13.5)	214	104 (48.6)	28 (13.1)	163	79 (48.5)	20 (12.3)
Aspartate aminotransferase (High)	438	170 (38.8)	11 (2.5)	345	138 (40.0)	10 (2.9)	259	103 (39.8)	5 (1.9)
Alanine aminotransferase (High)	440	150 (34.1)	13 (3.0)	347	125 (36.0)	12 (3.5)	261	89 (34.1)	8 (3.1)

Lab Abnormality (NCI CTCAE Grade) n (%)	Overall Population (N = 444)			RP2D Subpopulations					
				RP2D Population (N = 351)			*ROS1*-positive NSCLC Treated at RP2D Population (N = 264)		
	Denominator[a]	All Grades	Grade 3 or 4	Denominator[a]	All Grades	Grade 3 or 4	Denominator[a]	All Grades	Grade 3 or 4
Sodium (High)	440	127 (28.9)	1 (0.2)	347	101 (29.1)	1 (0.3)	261	75 (28.7)	1 (0.4)
Alkaline phosphatase (High)	440	130 (29.6)	14 (3.2)	347	100 (28.8)	9 (2.6)	261	67 (25.7)	6 (2.3)
Glucose (High)	439	139 (31.7)	9 (2.1)	347	90 (25.9)	7 (2.0)	261	61 (23.4)	4 (1.5)
Creatinine (High)	440	113 (25.7)	3 (0.7)	-	-	-	-	-	-
Phosphate (Low)	436	100 (22.9)	26 (6.0)	-	-	-	-	-	-
Urate (High)	438	89 (20.3)	36 (8.2)	346	72 (20.8)	35 (10.1)	260	54 (20.8)	28 (10.8)

Abbreviations: NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC = non-small cell lung cancer; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; 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 subjects in the Safety Analysis Set.
[a] Denominator is the number of subjects who have both baseline and postbaseline results for each analyte.
Sources: Module 5.3.5.3, ISS Table 14.3.5.3, Table 14.3.5.4, Table 14.3.5.5

The Applicant's Position:

Abnormalities in clinical laboratory parameters reported in ≥ 20% of subjects in the Overall population for hematology and clinical chemistry are presented in Table 60. Clinically relevant lab abnormalities < 20% reported in subjects included blood creatine phosphokinase (CPK) increased (12.8%).

The abnormalities in clinical laboratory parameters (Table 60) in the RP2D Population and the *ROS1*-positive NSCLC Treated at RP2D Population were similar to the Overall population.

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 agrees with the Applicant's summary of common laboratory abnormalities in the overall RP2D population and that they are similar to those in the ROS1 positive NSCLC safety population.

In the ROS1 positive NSCLC population (N=264), the most common (≥2%) Grade 3 or 4

laboratory abnormalities were decreased hemoglobin, decreased lymphocytes, decreased leukocytes, increased alanine aminotransferase, decreased neutrophils, increased gamma glutamyl transferase, increased alkaline phosphatase, increased urate, increased magnesium, and decreased phosphate.

Table 61, 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 (N=351).

Hyperuricemia was observed in patients receiving repotrectinib. An analysis of hyperuricemia and blood uric acid increased in the adverse event and laboratory datasets was performed to identify patients with hyperuricemia and evaluate for any cases of potential tumor lysis syndrome (TLS). In the overall RP2D safety population (N=351) based on the adverse event dataset, 18/351 patients (5%) experienced hyperuricemia reported as an adverse reaction, and 0.9% of patients experienced Grade 3 or 4 hyperuricemia. The majority of these adverse reactions (23/26, or 88% 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 3/26 events. There was 1 Grade 4 event (not reported as an SAE); this patient did not require urate lowering medications. The Applicant performed an expanded search including an assessment of whether any patients met the Cairo-Bishop Diagnostic Criteria for TLS (Cairo & Bishop 2004); no patients met criteria for TLS.

The majority of patients with events of hyperuricemia were reported to have underlying co-morbid conditions, as noted in medical history (e.g., gout, hypothyroidism, diabetes mellitus, chronic kidney disease, renal cysts), had used concomitant medications (e.g., aspirin, furosemide), that were potential contributors to the events of elevated uric acid levels. The median time to onset of hyperuricemia/blood uric acid increased was 99.5 days (range: 7 to 1374) and median duration of hyperuricemia events was 13.5 days (for events with a resolution date).

One patient (b) (6) developed Grade 1 hyperuricemia on Cycle 1 Day 22 and required use of a urate lowering medication, allopurinol (Day 29 to Day 43); the event resolved during Cycle 2. Two other patients had been on treatment with urate lowering medications for gout prior to the first dose of repotrectinib and received concomitant urate lowering medications during treatment with repotrectinib for gout (b) (6) Brief narratives for these patients are provided below:

(b) (6): This is a 62-year-old White male with NTRK+ salivary gland cancer, previously treated with TKI (entrectinib) who was treated with repotrectinib at a starting dose of RP2D 160 mg QD. No relevant SAEs or TEAEs were reported on treatment. The patient was reported with an event of Grade 1 hyperuricemia on Day 22 of cycle 1.

Allopurinol was administered from Day 29 to Day 43. Clinically significant laboratory values included increased uric acid on Day 22 (8.7 mg/dl, reference range 4.0-8.0), Day 29 (8.9 mg/dl), creatinine increased on Day 29 (130 µmol/L, reference range 62-106), and hypotension (Day 29). Repotrectinib was continued, and the event resolved without recurrence.

(b) (6): This is a 52-year-old White Female with ROS1+ non-small cell lung cancer (NSCLC), previously treated with chemotherapy (pemetrexed, carboplatin) and TKI (crizotinib), was treated with repotrectinib at a starting dose of 80 mg once daily (QD). An event of Grade 1 hyperuricemia was reported on Day 14. On Day 17 blood uric acid was 9.4 mg/dL (reference range 2.3-6.6), potassium 3.7 mEq/L, phosphorus 3.3 mg/dL, creatinine 1.5 mg/dL (reference range 0.5-1.3). No action was taken with the study drug due to the event. The outcome of the event was reported as resolved on Day 24.

(b) (6): This is a 65-year-old White Female with ROS1+ NSCLC, previously treated with chemotherapy (pemetrexed, cisplatin), immunotherapy (nivolumab), bevacizumab, and TKIs (crizotinib, cabozantinib), who was treated with repotrectinib at a starting dose of 160 mg QD. An event of Grade 4 hyperuricemia was reported on Day 43. On C1D1, the baseline uric acid level was 2.9 mg/dL. Relevant labs included uric acid 10.4 mg/dL (reference range 2.5-6.5), phosphorus 4.3 mg/dL (reference range 2.5-4.2). No action was taken with the study drug due to this event. The outcome of the event was reported as resolved on Day 561. Another event of Grade 4 hyperuricemia occurred on Day 589. Relevant labs included uric acid 10.1 mg/dL. No action was taken with the study drug and the patient continued repotrectinib until study Day 1008 at the time of disease progression.

A review of hyperuricemia was also performed based on the laboratory dataset. In the overall RP2D population, urate was increased in 72/346 (21%) of all grade events and 35/346 (10%) of grade 3 to 4 events. None of the patients with grade 3 to 4 events had a dose interruption, dose reduction or discontinuation due to their laboratory elevations of uric acid/urate. In the ROS1 positive NSCLC population urate was increased in 54/260 (21%) of all grade events and 28/260 (11%) of grade 3 to 4 events. No repotrectinib dose modifications or discontinuations were required for any hyperuricemia/blood uric acid increased events.

Table 61: FDA Laboratory Abnormalities (≥20%) That Worsened From Baseline in Patients With ROS1-Positive NSCLC

Laboratory Abnormality[1]	PROPRIETARY NAME[2] N=264	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased Hemoglobin	73	5
Decreased Lymphocytes	43	10
Decreased Leukocytes	36	4.7
Decreased Neutrophils	34	8
Increased aPTT	25	0.4
Increased INR	20	0
Chemistry		
Increased Creatine Phosphokinase	57	6
Increased GGT	48	12
Increased AST	40	1.9
Increased ALT	34	3.1
Increased Sodium	29	0.4
Increased Alkaline Phosphatase	26	2.3
Increased Glucose	23	1.5
Increased Urate	21	11
Decreased Glucose	21	0.4

Abbreviations: AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gamma Glutamyl Transferase; aPTT: Activated Partial Thromboplastin Time; Prothrombin Intl. Normalized Ratio: INR

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

1 Based on NCI CTCAE v4.03

2 The denominator used to calculate the rate varied from 163 to 261 based on the number of patients with a baseline value and at least one post-treatment value.

Overall laboratory abnormalities observed from TRIDENT-1 and analyzed during the review of this application are shared similar findings with other TKIs. The overall RP2D and ROS1 positive safety 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 17.1% and 13.1% of subjects, respectively, and for decreases, 5.6% and 8.8% of subjects, respectively. Decreases or increases in pulse (bpm) meeting outlier values were reported in 1.8% and 18.7% of subjects, respectively; outlier values for temperature (°C) were reported in < 4% of subjects.

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 based on the triplicate ECGs matched with repotrectinib concentration data in 398 subjects from Phase 1a, Phase 1c and Phase 2 of the TRIDENT-1 study (refer to Section 6.3.1, QT/QTc Prolongation).

Repotrectinib had no reported clinically significant effects on heart rate, PR interval, or QRS duration. Repotrectinib also had no reported clinically significant effects on QTc based on the results of the by-time point and categorical outlier analyses.

A concentration-QTc analysis revealed negative slopes for the relationship between repotrectinib concentration and QTcF, with model predicted QTc increase < 10 ms for the highest exposures reached in all cohorts.

The Applicant's Position:

Analysis of the ECG parameters did not suggest any cardiac safety concerns with the dosing of repotrectinib.

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

8.2.4.10. QT

Data:

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

The Applicant's Position:

Analysis of the QT parameters did not suggest any cardiac QTc safety concerns with dosing of repotrectinib.

The FDA's Assessment:
FDA agrees with the Applicant's position. See section 8.2.4.1 of this review for a discussion on QT interval analysis and TEAEs. FDA agrees with the Applicant that QT parameters did not

suggest any cardiac QTc safety concerns with dosing of repotrectinib.

8.2.4.11. Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:

No safety issues related to immunogenicity were identified for repotrectinib.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. CNS Effects

Data:

In the Overall population (N = 444), dizziness (including dizziness, vertigo, dizziness postural, dizziness exertional, and vertigo positional) was reported in 63.5% of patients; grade 3 dizziness was reported in 2.9% of subjects. The median (range) time to onset was 6 days (1 day to 1.4 years). Dose reduction was required in 11.0% of subjects and 9.0% required dose interruption of repotrectinib due to reported dizziness. No subjects discontinued repotrectinib due to reported dizziness.

Ataxia (including ataxia, gait disturbances, balance disorder, cerebellar ataxia, and coordination abnormal) was reported in 26.4% of subjects; grade 3 ataxia was reported in 0.2% of subjects. The median time to onset was 15 days (1 day to 1.4 years). Dose reduction was required in 7.0% of subjects, 5.0% required dose interruptions and one subject was required to discontinue repotrectinib due to ataxia.

Cognitive disorders were reported in 20.3% of subjects. Cognitive disorders included memory impairment (10.4%), disturbance in attention (8.6%), cognitive disorder (5.2%), confusional state (2.5%), amnesia, delirium (0.9% each), aphasia, attention deficit hyperactivity disorder, depressed level of consciousness (0.5% each), delusion, hallucinations, mental disorder, mental status change, altered state of consciousness, and neurological decompensation (0.2% each). Grade 3 cognitive adverse reactions were reported in 0.7% of patients. The median time to onset of cognitive disorders was 37.5 days (1 day to 1.4 years). Dose reduction was required in 1.4% subjects, 1.6% required dose interruption and 0.9% of subjects discontinued repotrectinib due to cognitive adverse reactions.

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

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 subjects) 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 can be typically managed through - the risk mitigation, monitoring and management strategies included in the study protocol (including dose interruption or reduction), as well as specific risk communication, and advice on the correct use provided in the prescribing information and patient counselling materials.

The FDA's Assessment:

Among the RP2D safety population (n=351) patients who received repotrectinib in the TRIDENT-1 study, CNS disorders of any grade occurred 75% of patients. Refer to section 8.2.4.5 for FDA's analysis of CNS toxicity.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable

The FDA's Assessment:

Not Applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Intrinsic factors

Table 62. Overview of Adverse Events by Demographic Subgroups

	Overall Population (N = 444)				
Demographic Parameter	**All Subjects 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 = 329)	328 (99.7)	23 (7.0)	109 (33.1)	158 (48.0)	12 (3.6)
≥ 65 to < 75 Yrs (N = 88)	87 (98.9)	15 (17.0)	32 (36.4)	52 (59.1)	10 (11.4)
≥ 75 Yrs (N = 27)	27 (100.0)	5 (18.5)	15 (55.6)	16 (59.3)	2 (7.4)
Sex					
Male (N = 186)	185 (99.5)	23 (12.4)	77 (41.4)	105 (56.5)	12 (6.5)
Female (N = 258)	257 (99.6)	20 (7.8)	79 (30.6)	121 (46.9)	12 (4.7)
Race					
White (N = 199)	199 (100.0)	22 (11.1)	76 (38.2)	112 (56.3)	14 (7.0)
Asian (N = 200)	198 (99.0)	17 (8.5)	59 (29.5)	90 (45.0)	8 (4.0)
Brain Metastasis					
Yes (N = 162)	160 (98.8)	13 (8.0)	46 (28.4)	77 (47.5)	10 (6.2)

	Overall Population (N = 444)				
Demographic Parameter	**All Subjects with TEAEs n (%)**	**Leading to Discontinuation of Study Drug n (%)**	**SAEs n (%)**	**Grade ≥ 3 TEAEs n (%)**	**Fatal TEAEs n (%)**
No (N = 282)	282 (100.0)	30 (10.6)	110 (39.0)	149 (52.8)	14 (5.0)

Abbreviations: SAE = Serious Adverse Event; TEAE = Treatment-Emergent Adverse Event.
Sources: Module 5.3.5.3, ISS Table 14.3.1.2.1, Table 14.3.1.2.2 and Table 14.3.1.2.3, Table 14.3.1.11.7, Table 14.3.1.1.7

Extrinsic factors

Table 63. Overall Summary of Treatment Emergent Adverse Events by Region (Safety Analysis Set)

	Overall Population (N = 444)		
TEAEs by Event Category	**US (N = 154)**	**Asia (N = 162)**	**Other (N = 128)**
Subjects with TEAEs, n (%)			
All subjects with TEAEs	154 (100.0)	160 (98.8)	128 (100.0)
Leading to discontinuation of study Drug	20 (13.0)	11 (6.8)	12 (9.4)
Leading to dose modifications	73 (47.4)	88 (54.3)	65 (50.8)
Leading to dose reduction	42 (27.3)	63 (38.9)	46 (35.9)
Leading to drug interruption	66 (42.9)	77 (47.5)	57 (44.5)
SAEs	74 (48.1)	43 (26.5)	39 (30.5)
Grade ≥ 3 TEAEs	88 (57.1)	68 (42.0)	70 (54.7)
Fatal TEAEs	13 (8.4)	8 (4.9)	3 (2.3)
Subjects with TRAEs, n (%)			
All subjects with TRAEs	140 (90.9)	156 (96.3)	120 (93.8)
Leading to discontinuation of study Drug	8 (5.2)	2 (1.2)	5 (3.9)
Leading to dose modifications	47 (30.5)	72 (44.4)	50 (39.1)
Leading to dose reduction	37 (24.0)	61 (37.7)	39 (30.5)
Leading to drug interruption	37 (24.0)	60 (37.0)	41 (32.0)
Treatment-related SAEs	11 (7.1)	9 (5.6)	8 (6.3)
Grade ≥ 3 TRAEs	24 (15.6)	45 (27.8)	32 (25.0)
Fatal TRAEs	0	0	0
Subjects with TEAEs by maximum CTCAE grade (n [%])			
Grade 1	16 (10.4)	19 (11.7)	17 (13.3)
Grade 2	50 (32.5)	73 (45.1)	41 (32.0)
Grade 3	62 (40.3)	54 (33.3)	57 (44.5)
Grade 4	13 (8.4)	6 (3.7)	10 (7.8)
Grade 5	13 (8.4)	8 (4.9)	3 (2.3)
Subjects with TRAEs by maximum CTCAE grade (n [%])			
Grade 1	57 (37.0)	40 (24.7)	30 (23.4)
Grade 2	59 (38.3)	71 (43.8)	58 (45.3)

TEAEs by Event Category	Overall Population (N = 444)		
	US (N = 154)	Asia (N = 162)	Other (N = 128)
Grade 3	23 (14.9)	42 (25.9)	30 (23.4)
Grade 4	1 (0.6)	3 (1.9)	2 (1.6)
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 subjects 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 subject is counted once for each type of event reported. For maximum grade, a subject 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: Module 5.3.5.3, 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 subjects) in the Overall population in age groups ≥ 18 to < 65 and ≥ 65 to < 75 years. Differences were noted in the ≥ 75 age group (eg, for dizziness, dyspnea, ALT increased and fatigue), however, these should be treated with caution due to the small number of subjects in the cohort (N = 27) 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 (17.0% of subjects) and ≥ 75 year age group (18.5%) versus the ≥ 18 to < 65 year age group (7.0%), and for TEAEs leading to dose reduction, ≥ 65 to < 75 year age group (46.6%), ≥ 75 year age group (59.3%) versus the ≥ 18 to < 65 year age group (28.6%); a similar pattern was noted for dose interruptions, albeit differences were less marked.

The incidence of SAEs was highest ≥ 75 age group (55.6% of subjects) versus the ≥ 18 to < 65 age and ≥ 65 to < 75 years age groups (33.1% and 36.4%, respectively). There was no apparent difference between ≥ 65 to < 75 years and ≥ 75 age groups for grade ≥ 3 TEAEs (59.1% and 59.3%, respectively), both of which were higher compared to the ≥ 18 to < 65 age group (48.0% of subjects). These findings should be treated with caution due to the smaller number of subjects in the older age cohorts.

The incidence of SAEs was higher in males versus females with 41.4% vs. 30.6% of subjects, respectively. For other event categories, there were no marked differences by sex.

In the safety population of TRIDENT-1, there were no marked differences for reported TEAE event categories by the racial subgroups White and Asian. Meaningful comparisons for the subgroups Black or African American (N = 12), Native Hawaiian or Other Pacific Islander (N = 3) and American Indian or Alaskan Native (N = 1) were not practicable due to the size of each cohort. Of those TEAEs reported with the highest incidences (≥ 20% of subjects in the Overall population), differences by race (White versus Asian) were noted for anemia, dyspnea, and fatigue. Anemia was reported more frequently in Asian subjects versus White subjects (43.5% vs 29.1%). Dyspnea and fatigue were reported more frequently in White subjects versus Asian subjects: 37.2% vs 20.0% and 35.2% vs 13.0%, respectively. Otherwise, no marked differences were noted.

In the Overall population (N = 444), 162 subjects were diagnosed with brain metastasis per Investigator assessment at baseline. There was no marked difference in the incidence of TEAEs in subjects with brain metastasis per Investigator assessment (YES vs. NO).

Extrinsic

In the Overall population, there was a ≥ 10% difference for the incidence of subjects who required a dose reduction in the Asian and Other regions (38.9% and 35.9%, respectively) versus the US population (27.3%). Fewer subjects were reported with SAEs from the Asian and Other regions (26.5% and 30.5%, respectively) versus the US (48.1%). For grade ≥ 3 TEAEs, fewer events were reported for subjects from the Asian region (42.0%) versus the US and Other regions (57.1% and 54.7%, respectively).

The FDA's Assessment:

FDA agrees with the Applicant's position.

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:

The effect of repotrectinib on a pregnant woman is unknown. 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

The Applicant's Position:

The safety and effectiveness of repotrectinib in pediatric patients with *ROS1*-positive NSCLC has not been established. An ongoing Phase 1/2 clinical trial (TPX-0005-07; NCT04094610) is being conducted to evaluate the 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.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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 or information regarding the investigation of the dependence potential of repotrectinib.

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:

Repotrectinib has not been approved and marketed in any region.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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. Although the TKI class effect of ILD/pneumonitis and TRK-related targeted CNS toxicities are safety concerns for repotrectinib, they have been adequately characterized and can typically be managed through the risk mitigation, including monitoring and management strategies specified in the study protocol, as well as specific risk communication and advice on the correct use provided in the prescribing information and patient counseling materials. Based on the safety profile understood to date, routine risk minimization measures have demonstrated effectiveness in optimizing the safe use of repotrectinib.

The combination of the teratogenic findings in animals and the potential for neurological risks suggested by the mechanism of action and literature reports, support adding a warning in the label for the risk of embryo-fetal toxicity. Regular pregnancy testing is required per protocol as the effects of repotrectinib in pregnancy and breastfeeding are not yet known. In routine clinical practice, cancer patients will be thoroughly counselled against pregnancy by their HCPs before commencing repotrectinib. In addition, consistent with current recommendations for genotoxic compounds with embryo-fetal risk, the label also includes recommendations for female and male contraception.

Repotrectinib will be prescribed by oncologists who are experienced in monitoring and managing serious adverse reactions, and counselling patients on potential side effects prior to administration. CNS effects, ILD/pneumonitis and embryo-fetal toxicity will be monitored through routine pharmacovigilance activities. 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). The review of the safety profile of repotrectinib will also 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, respectively, to characterize potential serious risks of long-term adverse effects of repotrectinib. In TRIDENT-1, repotrectinib has been administered to patients with mild hepatic impairment and no dose modification for repotrectinib was indicated. The ongoing pharmacokinetic (TPX-0005-15) clinical trial will collect further data to evaluate the safety profile of repotrectinib in the treatment of patients with moderate or severe hepatic impairment.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The overall safety profile assessed in the pivotal TRIDENT-1 study in the Overall population (N = 444), the subpopulation receiving at least 1 dose of repotrectinib at the RP2D (N = 351), and subpopulation of *ROS1*-positive NSCLC subjects receiving at least 1 dose of repotrectinib at the RP2D (N = 264) 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. Long-term treatment with repotrectinib (> 12 months) showed no evidence of increased/cumulative toxicity. There were no clinically meaningful differences in the safety profile observed 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%) include dizziness, dysgeusia, constipation, ataxia, dyspnea, cognitive disorders, fatigue, and nausea. TEAEs leading to discontinuation of study drug were reported for < 10% of subjects in the Overall population; TEAEs were typically reported at very low incidences (≤ 2 subjects). The most frequently reported TEAEs leading to discontinuation of study drug (> 2 subjects) were dyspnea, pneumonitis, muscular weakness, and pneumonia. The most frequently reported TEAEs leading to dose reduction (> 2% subjects) were dizziness, ataxia, muscular weakness, and paresthesia.

The most frequently reported SAEs (≥ 2% of subjects) in the Overall population were pneumonia (5.6%), dyspnea (3.8%), pleural effusion (2.9%) and hypoxia (2.3%). The most frequently reported TEAEs with a fatal outcome at the SOC level were in Cardiac disorders and Infections and infestations, each with 6 (1.4%) subjects, followed by General disorders and administration site conditions and Respiratory, thoracic, and mediastinal disorders, each with 5 (1.1%) subjects. Overall, the pattern and frequency of SAEs and TEAEs with fatal outcome reported in the overall population are 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 (including no QTc prolongation) 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 subjects in the repotrectinib clinical development program have been treated for more than 12 cycles (i.e., 115 of the 444 subjects). 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 effect of ILD/pneumonitis and TRK-related targeted CNS toxicities have been adequately characterized and can typically be managed through the risk mitigation, including

monitoring and management strategies specified in the study protocol as well as specific risk communication and advice on the correct use provided in the prescribing information and patient counseling materials. Based on the safety profile understood to date, routine risk minimization measures have demonstrated effectiveness in optimizing safe use. The combination of the teratogenic findings in animals and the potential for neurological risks suggested by the mechanism of action support adding a warning in the label for embryo-fetal risk. In addition, consistent with current recommendations for compounds with aneugenic toxicity, the prescribing information will include recommendations for contraception use.

Preliminary PRO data from validated instruments (EORTC-QLQ-C30 and EORTC QLQ-LC13) showed that most subjects, both TKI-naïve and TKI-pretreated, demonstrated stable or improved GHS/QOL as well as stable or improved coughing and chest pain core lung cancer symptoms while on treatment with repotrectinib. Dyspnea also showed improvement in EORTC-QLQ-C30 for TKI-naïve subjects.

Overall, the evaluation of safety across the clinical program demonstrated a favorable safety profile for repotrectinib in adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.

The FDA's Assessment:

The overall RP2D safety population included 351 patients treated with repotrectinib in the TRIDENT-1 study. Overall, an analysis of the adverse reactions observed in TRIDENT-1 indicated some findings consistent other drug products in the same class.

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 adequately addressed in the Warnings and Precautions and Dose Modifications sections of the repotrectinib product labeling.

In the TRIDENT-1, among patients in the RP2D safety population (n=351), the most common (> 20%) adverse reactions were dizziness (64%), dysgeusia (50%), peripheral neuropathy (47%), constipation (37%), dyspnea (30%), ataxia (29%), fatigue (29%), cognitive disorders (23%), and nausea (20%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased gamma glutamyl transferase (13%), decreased lymphocytes (10%), increased urate (10%), decreased neutrophils (8%), decreased hemoglobin (7%), increased creatine phosphokinase (5.8%), decreased phosphate (4.9%), decreased leukocytes (3.8%), increased ALT (3.5%), decreased sodium (3.5%), increased AST (2.9%), increased magnesium (2.9%), increased alkaline phosphatase (2.6%), and increased glucose (2%).

In the ROS1 positive safety population (n=264), the most common adverse reactions (≥20%) were dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, ataxia, fatigue, cognitive disorders, and muscular weakness. The most common (≥2%) Grade 3 or 4 laboratory

abnormalities were decreased hemoglobin, decreased lymphocytes, decreased leukocytes, increased alanine aminotransferase, decreased neutrophils, increased gamma glutamyl transferase, increased alkaline phosphatase, increased urate, increased magnesium, and decreased phosphate. See Sections 8.2.4.6 and 8.2.4.7 for discussions of adverse reactions and abnormal lab values.

The review team considered the safety profile of repotrectinib to be acceptable when assessed in the context of a life-threatening disease. In addition, although repotrectinib can cause serious and severe toxicities, the safety concerns are described in product labeling; repotrectinib will be prescribed by oncologists who are trained to monitor and treat serious treatment-related toxicities. There were no 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:

The primary efficacy evaluation was based on results from the prespecified efficacy analysis set (EAS) in Pooled EXP-1 (TKI-naïve) and Pooled EXP-4 (TKI-pretreated) cohorts in TRIDENT-1. The EAS included patients who had centrally confirmed ROS1 mutations and had at least 8 months of follow-up from the start of treatment as of the original DCO date of June 20, 2022. In the 90-day update report (DCO date of December 19, 2022), an updated DOR was provided with additional 6 months of follow-up in the same responding patients.

Due to the single-arm design of TRIDENT-1 study, time-to-event endpoints such as PFS and OS are considered not interpretable as there is no comparator arm. The reported results are considered descriptive only. In addition, results from subgroup analyses are considered descriptive and should be interpreted with caution, particularly those with small sample sizes.

FDA identified a potential statistical issue in the estimation of duration of response due to informative censoring. In Pooled EXP-1 (N=71), 6 patients received subsequent anti-cancer therapy (ACT) in the absence of disease progression per BICR before the updated DCO and were censored at the last evaluable tumor assessment per BICR prior to the start of new ACT. In Pooled EXP-4 (N=56), 2 patients received subsequent ACT in the absence of disease progression per BICR before the updated DCO and were censored at the last evaluable tumor assessment per BICR prior to the start of new ACT.

The most common reasons for end of study treatment for these patients were radiographic disease progression per investigator, followed by adverse event, physician decision and withdrawal of consent. As these are non-randomized cohorts, a large percentage of censoring

of DOR due to new ACT could be concerning as if this censoring is related to potential outcome, informative censoring may lead to overestimation of DOR.

To assess the concern of overestimation of DOR, the Applicant conducted sensitivity analyses by treating those patients who were censored prior to new ACT as events per FDA's request. Median DOR in Pooled EXP1 changed from 34.1 months (95% CI 25.6, NE) to 27.4 months (95% CI 23.1, NE), while it remained similar in Pooled EXP-4. Although the results from sensitivity analyses indicate that the median DOR may be shorter than the estimate using the Kaplan-Meier method (which assumes non-informative censoring) in Pooled EXP-1, a relatively conservative estimate of DOR of 27.4 months remains substantial and clinically meaningful.

8.4. Conclusions and Recommendations

The FDA's Assessment:

FDA recommends traditional approval of repotrectinib for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC. This recommendation is based on ORR and DOR results in patients with ROS1-positive NSCLC (both previously treated with a ROS1-TKI and those naïve to a ROS1-TKI) from TRIDENT-1, an international, single-arm, first-in-human, dose-escalation and expansion study of repotrectinib.

Current standard of care for patients with ROS1 positive NSCLC includes treatment with an approved ROS1 inhibitor (crizotinib or entrectinib). Response rates in patients who received these therapies in clinical trials ranged from 66% to 78%. Neither of the approved product labels includes data describing the treatment effect on patients with ROS1-positive NSCLC previously treated with a ROS1-TKI.

The primary evidence of effectiveness for this application is derived from pooled cohorts EXP-1 and EXP-4 from TRIDENT-1. Patients with ROS1-positive NSCLC from the Phase 1 and Phase 2 portions of TRIDENT-1 who had either received a prior ROS1 TKI and no prior chemotherapy, or were ROS1 TKI-naïve, and received at least one dose of repotrectinib on or before October 15, 2021 were included in the primary efficacy populations. Patients received repotrectinib administered daily at the recommended phase 2 dose (RP2D) or for some patients, the dose administered in Phase 1. Patients enrolled on TRIDENT-1 were required to have a ROS1 fusion detected by CLIA lab or equivalent and at least 1 measurable target lesion per RECIST 1.1.

Among the 71 ROS1 TKI-naïve patients, the ORR was 79% (95% CI 68, 88) per RECIST v1.1 by BICR. The estimated median duration of response was 34.1 months (95% CI 25.6, NE). In addition, 8 patients had measurable CNS metastases at baseline as assessed by BICR. Responses in intracranial lesions were observed in 7 of 8 patients.

Among the 56 patients who had received 1 prior ROS1 TKI the ORR was 38% (95% CI 25, 52) per RECIST v1.1 by BICR. The median duration of response was 14.8 months (95% CI 7.6, NE). In

addition, 56 patients who had received 1 prior ROS1 inhibitor 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. Eight patients who had received 1 prior ROS1 TKI had resistance mutations following TKI therapy. Responses were observed in 6 of these 8 patients; responders included patients with solvent front (G2032R), gatekeeper (L2026M), and other mutations (S1986F/Y).

A companion diagnostic for repotrectinib was not available at the time of approval, but it is under development. Given the availability of local tests to identify *ROS1* 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 develop such a test. The final product labeling will reflect the lack of an approved companion diagnostic for the selection of patients for treatment with repotrectinib.

This submitted data for this NDA meets the statutory standard for demonstration of substantial evidence of effectiveness for traditional approval. The durable responses observed in the TRIDENT-1 study, in the setting of a genetically based biologic rationale, provide evidence of a clinically meaningful benefit of repotrectinib in the rare, genetically defined subgroup of patients with locally advanced or metastatic ROS1 positive NSCLC. Subgroup analyses support repotrectinib's antitumor activity in patients with CNS metastases and in patients with resistance mutations following prior ROS1 TKI therapy. Overall, this evidence suggests repotrectinib may address an unmet clinical need as first-line therapy for patients with ROS1 positive NSCLC and in patients with resistance mutations to other ROS1 TKIs, as well as in patients with CNS metastasis. 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 confirmatory evidence provided by the evidence of effectiveness of products in the same drug class which are approved in the same disease setting and strong mechanistic evidence of ROS1 alterations as molecular drivers in NSCLC. Based on the favorable risk-benefit assessment for this population with a serious, life-threatening disease, traditional approval is recommended for the following indication:

> 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).

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 Statistical Team Leader

X	X
Primary Clinical Reviewer	Clinical Team Leader

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 issues 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. (b) (4) The agreed iPSP also consisted of a request for a deferral for the report for the molecularly targeted pediatric investigation, which is also included in the NDA as the CARE study (TPX-0005-07; NCT04094610) in pediatric patients is currently ongoing.

The FDA's Assessment:

As agreed upon in the iPSP, FDA concluded that a molecularly targeted investigation in pediatric patients was required under the revised provisions of FDARA under PREA. Given that the CARE study is ongoing, FDA agreed that a deferral was reasonable. A PMR for the submission of the report of the molecularly targeted investigation in pediatric patients will be included in the approval letter.

11 Labeling Recommendations

Data:
Not applicable.

The FDA's Assessment:

The proposed labeling submitted by the Applicant required revision by FDA.

The safety population used to inform the Warnings and Precautions section (Section 5) and Adverse Reactions section (Section 6) of the product labeling comprises 351 patients with

advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements who received at least one dose of repotrectinib at the RP2D in the TRIDENT-1 study. The safety profile from the population of patients with ROS1 positive NSCLC treated with at least 1 dose of repotrectinib was also used to inform the Adverse Reactions (section 6) of the product label.

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidance and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

Table 64. Summary of Significant Labeling Changes (High Level Changes and Not Direct Quotations)

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
1 INDICATIONS AND USAGE	Indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC)	FDA reviewed and accepted the proposed indication.
2.2 Important Information Prior to Initiating AUGTYRO	N/A	New section added for consistency with the draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*
2.3 Recommended Evaluation and Testing Before Initiating AUGTYRO	N/A	New section added for consistency with the draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*
Table 2: Recommended Dosage Modifications for PROPRIETARY NAME Adverse Reactions	Refer to initial proposed product labeling; modifications included for CNS effects, ILD/pneumonitis, and other clinically relevant adverse reactions	New section added to provide dosage modification recommendations for hepatotoxicity, creatine phosphokinase (CPK) elevation and hyperuricemia.
2.6 Administration	(b) (4)	Minor revisions for consistency with current labeling practice.
3 DOSAGE FORMS AND STRENGTHS	(b) (4)	Minor revisions for consistency with current labeling practice.

	40 mg: Size 0, (b) (4) hard shell capsules, filled with a white to off-white powder which may appear as a plug. "REP 40" (b) (4) in blue text on the cap.	
5 WARNINGS AND PRECAUTIONS	Warnings for CNS Effects, ILD/pneumonitis, and embryo-fetal toxicity were proposed.	-FDA revised Section 5 for clarity, brevity and consistency with current labeling practices. FDA adjudicated all incidence percentages. -Added new subsections: hepatotoxicity, myalgia with creatine phosphokinase elevation, hyperuricemia, and skeletal fractures.
6 ADVERSE REACTIONS	The safety results from clinical trial TRIDENT-1 were described.	FDA revised Section 6 for clarity, brevity and consistency with current labeling practices. -FDA adjudicated all incidence percentages.
7 DRUG INTERACTIONS	Proposed instructions for strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers	FDA added new subsection: P-gp inhibitors, avoid concomitant use. FDA combined strong and moderate CYP3A inducers for brevity. FDA removed (b) (4) as not clinically relevant.
8.1 Pregnancy	Described relevant information based on mechanism of action and findings from animal studies.	FDA revised animal data text for clarity.
8.3 Females and Males of Reproductive Potential	Provided instructions for pregnancy testing and contraception.	FDA clarified that contraception should be non-hormonal due to drug interaction.
8.4 Pediatric Use	Included standard language communicating that safety and effectiveness of repotrectinib have not been established in pediatric patients.	FDA included information from the Juvenile Animal Study to highlight skeletal effects not specifically demonstrated in the clinical study.
8.6 Renal Impairment 8.7 Hepatic Impairment	Described limitations of available data with respect to severe renal impairment and moderate or severe hepatic impairment.	FDA revised Sections 8.6 and 8.7 for clarity, brevity and consistency with current labeling practices.
11 DESCRIPTION		Minor editorial revisions.
12.1 Mechanism of Action	Refer to originally submitted labeling.	Text revised to remove (b) (4) for consistency with 21 CFR 201.57(c)(2)(iv).

12.2 Pharmacodynamics	Refer to originally submitted labeling.	Minor editorial revisions.
12.3 Pharmacokinetics	Refer to originally submitted labeling.	FDA clarified the geometric mean of repotrectinib at steady state concentration, absolute bioavailability and apparent volume of distribution. FDA clarified the repotrectinib mean terminal half-life.
14 CLINICAL STUDIES	Described ORR and DOR results in pooled cohorts EXP1 and EXP4.	FDA revised text for clarity and brevity.
16 HOW SUPPLIED/STORAGE AND HANDLING	Refer to originally submitted labeling.	FDA revised text for clarity and brevity.
17 PATIENT COUNSELING INFORMATION	Refer to originally submitted labeling.	FDA revised text for consistency with current labeling practice, clarity and brevity. NDA added new subsections: hepatotoxicity, myalgia with creatinine phosphokinase elevation, hyperuricemia, and skeletal fractures.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
The revised labeling has been agreed upon and conveys adequate information for the safe and effective use of AUGTYRO.

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:
The following post-marketing requirements and post-marketing commitments will be included in the approval letter:

Post-Marketing Requirements:
4547-1:

Conduct a clinical study to assess the appropriate dose of repotrectinib and to assess safety, tolerability, pharmacokinetics (PK), and efficacy of repotrectinib, in pediatric and young adult patients with advanced or metastatic solid tumors, primary central nervous system (CNS) tumors, or anaplastic large cell lymphoma (ALCL), with ALK, ROS1, or NTRK alterations. At least 3 patients 6 years of age or younger will be evaluated in the dose-finding phase.

4547-2:

Conduct a prospective study to evaluate risk factors, manifestations, and outcomes associated with the signal of serious ocular toxicity with repotrectinib in patients with ROS1 positive NSCLC or other solid tumors. The study will include collection, grading, classification, and analysis of data on ocular toxicity in patients exposed to repotrectinib. Evaluate a sufficient number of patients treated at the recommended phase 2 dose (160 mg daily for the first 14 days, then increase to 160 mg twice daily) who receive repotrectinib as a single agent. Include baseline ophthalmologic exam with vision test, scheduled follow-up, and symptom-driven ocular assessments to include visual acuity assessments, ophthalmologic evaluations including slit lamp examination, and elicitation for visual symptoms.

4547-3:

Conduct a clinical pharmacokinetic trial in non-cancer hepatically impaired subjects to evaluate the effect of moderate and severe hepatic impairment on the single dose pharmacokinetics and

safety of repotrectinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling." In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trial, to evaluate the effect of hepatic impairment on multiple dose pharmacokinetics of repotrectinib, to determine an appropriate dosage of repotrectinib, and to identify and assess the potential serious risk of increased drug toxicity, in patients with moderate and severe hepatic impairment. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled "Physiologically Based Pharmacokinetic Analyses - Format and Content."

4547-4:

Conduct a clinical pharmacokinetic trial to evaluate the effects of multiple doses of a specific strong CYP3A inhibitor and a specific P-gp inhibitor, respectively on the single-dose pharmacokinetics and safety of repotrectinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions." In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trial, to evaluate the effects of a specific strong CYP3A inhibitor, a specific moderate CYP3A inhibitor, a specific P-gp inhibitor, and a dual P-gp and moderate CYP3A inhibitor, respectively on the multiple-dose pharmacokinetics of repotrectinib to identify and assess the potential serious risk of increased drug toxicity and to identify appropriate dosage recommendations for repotrectinib when used concomitantly with these inhibitors. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."

4547- 5:

Conduct a clinical pharmacokinetic trial to evaluate the effect of multiple doses of repotrectinib on the single dose pharmacokinetics of a substrate of MATE2-K, P-gp, OATP1B1, and BCRP, respectively to identify and assess the potential serious risk of increased drug toxicity with repotrectinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions".

Post-Marketing Commitments:

PMC 4546-6:

Complete a clinical study to further characterize the clinical benefit of repotrectinib for the treatment of adult patients with ROS1 fusion-positive metastatic NSCLC by providing a more precise estimation of the BICR-assessed overall response rate (ORR) and duration of response (DOR) in the 71 ROS1 TKI-naive patients with ROS1-positive NSCLC and 56 ROS1 TKI-pretreated patients with measurable disease enrolled on TRIDENT-1. Provide updated DOR results for the

56 responders in the efficacy evaluable population of 71 ROS1 TKI-naïve patients (primary analysis population) and for the 21 responders in the efficacy evaluable population of 56 ROS1 TKI-pretreated patients, after all responders have been followed for at least 18 months from the date of initial response.

4656-7:

Conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trials with specific CYP3A and P-gp inhibitors, to evaluate the effect of multiple doses of a moderate CYP3A inducer on the multiple-dose pharmacokinetics of repotrectinib to assess the magnitude of decreased drug exposure with appropriate dosage recommendations of repotrectinib when concomitantly used with moderate CYP3A inducers. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."

4656-8:

Conduct a clinical pharmacokinetic trial with repeat doses of repotrectinib on the single dose pharmacokinetics of a substrate of CYP2B6, CYP2C8, CYP2C9, and CYP2C19, respectively to assess the magnitude of decreased drug exposure. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions". In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study to predict impact of repotrectinib on the magnitude of decreased drug exposure of CYP2C8 substrates. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."

4546-9:

Commitment to support the availability of an in vitro diagnostic device, through an appropriate analytical and clinical validation study using clinical trial data that demonstrates the device is essential to the safe and effective use of repotrectinib for the treatment of adult patients with locally advanced or metastatic ROS1 positive non-small cell lung cancer.

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?
□	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.	__ Yes _x_ No

☐	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: Not applicable	__ Yes _x_ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or Designated Signatory Authority)

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.

X _____

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

A list of all Investigators in the TRIDENT-1 study was 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: Phase 1: 223 Phase 2: 1405		
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 (Participated in both Phase 1 and Phase 2)		
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: Turning Point Therapeutics, Inc.		
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) 19		
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:

FDA agrees with the Applicant's position. The financial disclosure forms were reviewed and summarized. As of the data cutoff date of June 20, 2022, financial disclosure information was submitted for 1628 investigators for Phase 1 and Phase 2 of Study TPX-0005-01 (TRIDENT-1). Financial Disclosure Forms for 6 sub-PIs in Phase 1 and 13 sub-PIs in Phase 2 were not submitted with the application. Further, there was one principal investigator (b) (6) as defined in 21 CFR 54.2(b) in the sponsor of TRIDENT-1, (Turning Point Therapeutic, Inc.).

(b) (6) disclosed financial information. (b) (6) was a PI at Site (b) (6) forTRIDENT-1 from (b) (6) due to Turning Point Therapeutic, Inc. (Sponsor) granting (b) (6) In addition, (b) (6) disclosed that (b) (6) at the time of the disclosure. (b) (6) reported the financial interest information to the (b) (6)

[redacted] considered this an acceptable relationship but determined that the interests must be disclosed in the text of any related publications and in presentations. In assessing the impact of this potential conflict, FDA considered that the number of enrolled patients at [redacted] site were limited to [redacted] of the overall study population, and that, since the ORR endpoint of the TRIDENT-1 study was determined by a BICR, any potential bias related to the conflict would be mitigated.

Overall, FDA finds that any possible bias due to financial interests as disclosed by investigators was minimal and unlikely to affect the interpretation of the study.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
Not applicable.
The FDA's Assessment:
Not applicable.

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

The FDA's Assessment:

In support of PK assessments of repotrectinib clinical studies, high-performance liquid chromatography-tandem mass spectrometry (LC/MS/MS) methods for the analysis of repotrectinib in human plasma were validated in accordance with the applicable regulatory guidelines and met all acceptance criteria as specified in the standard operating procedures of [redacted]

Tables below list the bioanalytical reports describing the individual method performance of repotrectinib in clinical studies using the capsule formulation (to-be-marketed formulation). Overall, the method and performance are reasonable.

Table 65. Summary Method Performance-Method MN16112 by [redacted] for Repotrectinib in Human Plasma in Clinical Studies

Method validation	**Method MN16112** [redacted]
Method description	A validated LC/MS/MS method for the determination of repotrectinib in human plasma
Materials used for standard calibration	Repotrectinib in human K_2EDTA plasma at 1.00, 2.00, 4.00, 8.00, 20.0, 40.0, 100, 200, 500, and 1000 ng/mL

curve and concentration			
Validated assay range	1.00 ng/mL to 1000 ng/mL		
Material used for quality controls (QCs) and concentration	Repotrectinib in human K_2EDTA plasma at 1.00 ng/mL, 3.00 ng/mL, 50.0 ng/mL or 300 ng/mL (validated and reported in MC20B-0106 on 05/18/2020), 800 ng/mL		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	NA		
Regression model and weighting	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	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ Repotrectinib	-1.60% to 2.00%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ Repotrectinib	≤ 2.30%	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs for Repotrectinib	-7.00% to -3.80%	Yes
	Inter-batch precision (%CV) in 4 QCs QCs for Repotrectinib	≤ 7.66%	Yes
	Total Error (TE)	NA	NA
Selectivity & matrix effect	6 lots, all passed		Yes
Interference & specificity	All 6 lots have < 20.0% lowest LLOQ analyte response and <5.00% lowest IS response		Yes
Hemolysis effect	1 lot, bias -4.33% (3.0 ng/mL) and -6.63% (800 ng/mL)		Yes
Lipemic effect	1 lot, bias -4.33% (3.0 ng/mL) and -4.38% (800 ng/mL)		Yes
Dilution linearity &	2500 ng/mL 10X dilution, bias -14.4%		Yes

hook effect	2510 ng/mL 50X dilution, bias -0.398%	
Bench-top/process stability	5 days at room temperature, bias: -8.67% (3.0 ng/mL) and -0.125% (800 ng/mL)	Yes
Freeze-Thaw stability	4 cycles (-70°C/RT), bias: 0.667% (3.0 ng/mL) and -2.00% (800 ng/mL)	Yes
Long-term storage	383 days at -20°C, bias: 3.00% (3.0 ng/mL) and 2.38% (800 ng/mL) 1203 days at -70°C, bias: -7.67% (3.0 ng/mL) and -10.6% (800 ng/mL)	Yes
Parallelism	NA	NA
Carry over	Carry over <20.0% lowest analyte response and <5.00% lowest internal standard response	Yes
Method performance in study TPX-0005-01 Phase 1 report MC22R-0010		
Assay passing rate	ISR passing rate	84.4%
Standard curve performance	• Cumulative bias range: -1.75% to 2.00% • Cumulative precision (%CV): ≤ 4.17%	Yes
QC performance	• Cumulative bias range: -2.67% to 5.00% with outlier excluded, -1.50% to 5.00% with outlier included • Cumulative precision (%CV): ≤ 6.94% with outlier excluded, ≤ 60.7% with outlier included	Yes
Method reproducibility	Incurred sample re-analysis was performed in 7.3% of study samples (calculated based on 154 ISR samples tested and total 2108 Phase 1 samples analyzed), and 84.4% of the samples met the pre-specified criteria.	Yes
Study sample analysis/ stability	The standard/QCs are stable at -70°C for 1,203 days; study samples were stored at -70°C for no more than 641 days	Yes
Method performance in study TPX-0005-01 Phase 2 interim report MC22R-0024		
Assay passing rate	ISR passing rate	79.8%
Standard curve performance	• Cumulative bias range: -1.50% to 1.80% • Cumulative precision (%CV): ≤ 4.94%	Yes
QC performance	• Cumulative bias range: -1.88% to 7.87% with outlier excluded or included • Cumulative precision (%CV): ≤ 7.43% with outlier excluded; ≤ 69.4%with outlier included	Yes

Method reproducibility	Incurred sample re-analysis was performed in 5.4% of study samples (calculated based on 114 ISR samples tested and total 2121 Phase 2 samples analyzed), and 79.8% of the samples met the pre-specified criteria.	Yes
Study sample analysis/ stability	All samples were analyzed within the established sample stability duration (1203 days frozen at -70°C)	Yes
Method performance in study TPX-0005-10 MC20B-0174		
Assay passing rate	ISR passing rate	97.4%
Standard curve performance	• Cumulative bias range: -2.10% to 2.00% • Cumulative precision (%CV): ≤ 3.09%	Yes
QC performance	• Cumulative bias range: -3.63% to -0.333% with outlier excluded, 2.67% with outlier included (3.00 ng/mL) • Cumulative precision (%CV): ≤ 9.01% with outlier excluded, 27.4% with outlier included (3.00 ng/mL)	Yes
Method reproducibility	Incurred sample re-analysis was performed in 9.7% of study samples (calculated based on 1200 samples analyzed and 116 ISR samples tested), and 97.4% of the samples met the pre- specified criteria.	Yes
Study sample analysis/ stability	The standard/QCs are stable at -70°C for 1,203 days. Study samples were analyzed within the established stability	Yes
Method performance in study TPX-0005-11 report MC20B-0243		
Assay passing rate	ISR passing rate	89.1%
Standard curve performance	• Cumulative bias range: -3.00% to 2.50% • Cumulative precision (%CV): ≤ 7.17%	Yes
QC performance	• Cumulative % bias range: -3.75% to 0.00% • Cumulative precision (%CV): ≤ 7.21%	Yes
Method reproducibility	Incurred sample re-analysis was performed in 10.3% of study samples (calculated based on 532 samples analyzed and 55 ISR samples tested), and 89.1% of the samples met the pre- specified criteria.	Yes
Study sample analysis/ stability	All samples were analyzed within 49 days of sample collection and within the 1,203 days of established sample stability at -70°C.	Yes

Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods Table 32.

Table 66. Summary Method Performance- Method ZRPNHPP by [redacted] (b) (4) for Analysis of Repotrectinib in Human Plasma

	Method ZRPNHPP [redacted] (b) (4)		
Method description	A validated LC/MS/MS method for the determination of repotrectinib in human plasma		
Materials used for standard calibration curve and concentration	Repotrectinib in human K_2EDTA plasma at 1.00, 2.00, 10.0, 30.0, 100, 300, 900, 1000 ng/mL		
Validated assay range	1.00 ng/mL to 1000 ng/mL		
Material used for quality controls (QCs) and concentration	Repotrectinib in human K_2EDTA plasma at 1.00 (LLOQ), 3.00 (LQC), 40.0 (LMQC), 400 (MQC), and 800 (HQC) ng/mL		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	NA		
Regression model and weighting	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	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ Repotrectinib	-3.4% to 2.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ Repotrectinib	≤3.3%	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QCs QCs for Repotrectinib	-5.6% to 0.3%	Yes
	Inter-batch precision (%CV) in 5 QCs QCs for Repotrectinib	≤6.7%	Yes

Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods Table 33.

Table 67. Summary Method Performance- Method [redacted]1788 by [redacted] for Analysis of Repotrectinib in Human Plasma

	Method [redacted]1788 [redacted]		
Method description	A validated LC/MS/MS method for the determination of repotrectinib in human plasma		
Materials used for standard calibration curve and concentration	Repotrectinib in human K_2EDTA plasma at 1.00, 2.00, 4.00, 16.0, 60.0, 240, 800, and 1000 ng/mL		
Validated assay range	1.00 ng/mL to 1000 ng/mL		
Material used for quality controls (QCs) and concentration	Repotrectinib in human K_2EDTA plasma at 1.00, 3.00, 400, and 750 ng/mL		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	NA		
Regression model and weighting	Linear with 1/concentration^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	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ Repotrectinib	-2.63% to 2.05%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ Repotrectinib	≤5.86%	Yes
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs QCs for Repotrectinib	-0.907% to 2.13%	Yes
	Inter-batch precision (%CV) in 4 QCs QCs for Repotrectinib	≤6.10%	Yes
	Total Error (TE)	NA	NA
Selectivity & matrix effect	8 lots, all passed		Yes

Interference & specificity	All 6 lots have 0.00% mean LLOQ analyte response and 0.00% mean IS response All 6 lots have no impact on LLOQ quantification	Yes
Hemolysis effect	1 lot, bias 4.03% (750 ng/mL) and 4.54% (3.0 ng/mL)	Yes
Lipemic effect	1 lot, bias 0.438% (750 ng/mL) and 4.08% (3.0 ng/mL)	Yes
Dilution linearity & hook effect	400 ng/mL 2.5X, bias 3.93% 2500 ng/mL, 10X, bias -1.28%	Yes
Bench-top/process stability	24.13 hours at room temperature, bias: -0.658% (750 ng/mL) and 3.45% (3.0 ng/mL)	Yes
Freeze-Thaw stability	5 cycles (-25°C/RT), bias 0.991% to 1.97% 5 cycles (-80°C/RT), bias 0.428% to 0.738%	Yes
Long-term storage	320 days at -25°C, bias 0.684% to 3.29% 320 days at -80°C, bias: -0.143% to 0.587%	Yes
Parallelism	NA	NA
Carry over	≤ 18.7% for analyte	Yes
Method performance in study TPX-0005-09 bioanalytical report AMAA		
Assay passing rate	ISR passing rate	100%
Standard curve performance	• Cumulative bias range: -2.24% to 1.90% • Cumulative precision (%CV): ≤ 3.51%	Yes
QC performance	• Cumulative bias range: -5.78 to -2.56% • Cumulative precision (%CV): ≤ 2.71%	Yes
Method reproducibility	Incurred sample re-analysis was performed in 10.9% of study samples, and 100% of the samples met the pre- specified criteria.	Yes
Study sample analysis/ stability	The standard/QCs are stable at -80°C for 320 days; study samples were stored at -80°C for no more than 44 days	Yes

Selectivity & matrix effect	6 lots, all passed	Yes
Interference & specificity	All 6 lots have 0.0% mean LLOQ analyte response and 0.0% IS response	Yes
Hemolysis effect	1 lot, bias -8.0% (3.00 ng/mL) and -4.1% (800 ng/mL)	Yes
Lipemic effect	1 lot, bias -3.3% (3.00 ng/mL) and -3.2% (800 ng/mL)	Yes
Dilution linearity & hook effect	2500 ng/mL 20X dilution, bias -3.2%	Yes
Bench-top/process stability	5 days at room temperature, bias: -7.7% to -5.0%	Yes
Freeze-Thaw stability	5 cycles (-30 to -10°C/RT), bias -9.4% to -2.7% 5 cycles (-80 to -60°C/RT), bias -9.4% to -3.3%	Yes
Long-term storage	359 days at -30 to -10°C, bias 9.9% to 14.7% 359 days at -80 to -60°C, bias: 6.1% to 14.3%	Yes
Parallelism	NA	NA
Carry over	≤ 10.1% for analyte ≤ 0.3% for internal standard	Yes
Method performance in study TPX-0005-01 Phase 2 interim report 8455-910		
Assay passing rate	ISR passing rate 97.1% when include 2 ISR samples that are tested out of validated stability and 97.0% when exclude these 2 ISR samples	Yes
Standard curve performance	• Cumulative bias range: -2.0% to 2.0% • Cumulative precision (%CV): ≤ 6.9%	Yes
QC performance	• Cumulative bias range: 1.0% to 3.1% • Cumulative precision (%CV): ≤ 7.2%	Yes
Method reproducibility	Incurred sample re-analysis was performed in 11.7% of study samples, and 97.1% of the samples met the pre- specified criteria. Two of the 68 ISR samples were tested out of validated stability, when exclude these 2 samples, ISR was performed in 11.4% of study samples and 97.0% of the samples met the pre-specified criteria.	Yes
Study sample analysis/ stability	The standard/QCs are stable at -80°C to -60°C for 359 days, study samples were stored at -80°C to -60°C for no more than 350 days	Yes

Source: Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods Table 34.

19.4.2. Population PK Analysis

19.4.2.1. PPK Executive Summary

The FDA's Assessment:

Population PK analysis was conducted by the Applicant in healthy volunteer and patients with advanced solid tumor harboring ALK, ROS1 or NTRK1-3 mutations from studies TPX-0005-01 (TRIDENT-1), TPX 0005 08, TPX-0005-09, TPX-0005-10, TPX 0005-11, TPX-0005-12, and TPX 0005-14. A 2-compartment model structure with first-order absorption with Tlag, non-linear elimination with autoinduction was developed to characterize the PK of repotrectinib in population PK analysis. Baseline body weight effect on CLs and volumes of distributions, food effects on KA and F1, dose on CLMAX were identified significant covariates in the analysis. Age, sex, race, ethnicity, renal impairment (mild/moderate impairment vs normal), hepatic impairment (mild impairment vs normal), formulation (capsules versus suspension), route of administration (oral versus IV), population (healthy subjects vs subjects with advanced solid tumors) and characteristics associate patients with advanced solid tumors including cancer histology, cancer type, genetic mutation, ECOG score, and TKI pretreatment did not show meaningful impact on PK parameters in the population PK analysis.

19.4.2.2. PPK Assessment Summary

The Applicant's Position: The population PK model of repotrectinib was adequately described with a 2-compartment model structure with first-order absorption with a T_{lag}, non-linear elimination with autoinduction modeled through a time-dependent E_{max} function, and an allometrically scaled baseline body weight effect on CLs and volumes of distribution parameters. Food effect on KA and F1 was identified as a significant covariate, while dose was a significant covariate on CLMAX. Rate of absorption increased under fed conditions.

Table 68. Applicant Table

General Information		
Objectives of PPK Analysis		• To characterize the PK of repotrectinib following oral administration in heathy subjects and in subjects with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 mutations • To identify the effects of intrinsic and extrinsic covariates that may be important predictors of repotrectinib PK variability • To generate exposures for model applications and exposure-response analysis
Study Included		TPX-0005-01 (TRIDENT-1), 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 subjects and subjects with advanced solid tumors
	General	Age 51.0 yr (18.0, 84.0), 20% subj ≥ 65 yr, 17% subj ≥ 75 yr) Weight 71.0 kg (39.5, 169)

Population Characteristics (Table 69)		288 (54.9%) male White: 285 (54.3%); Asian: 199 (37.9%); Other: 41 (7.8%)	
	Organ Impairment	Hepatic (Child-Pugh, NCI, etc.): Normal: 471 (89.7%); Mild impairment: 52 (9.9%); Missing: 2 (0.4%) Renal (eGFR): Normal: 350 (66.7%); Mild impairment: 123 (23.7%); Moderate impairment: 27 (5.1%); Missing: 25 (4.8%).	
	Pediatrics (if any)	Not included.	
No. of Patients, PK Samples, and BLQ		525 subjects, 8167 PK samples, BLQ 678 (6.1%)	
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	Baseline demographics, age, gender, race, ethnicity, body weight, height, BMI, body surface area, eGFR based on MDRD, aspartate aminotransferase, alanine aminotransferase, serum alkaline phosphatase, total bilirubin, creatinine, dose, hepatic and renal functions, subject classifications (healthy versus patient), formulations, food status, TKI pretreatment status, ECOG, cancer histology, genetic mutations, cancer type	
	Time-varying		
Final Model		**Summary**	**Acceptability [FDA's comments]**
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 4.2; R Foundation for Statistical Computing, Vienna, Austria); Rstudio (Version 1.2.5033; Rstudio, Boston, MA, USA)	Acceptable.
Model Structure		A 2-compartment model structure with first-order absorption with an absorption time lag, nonlinear elimination with autoinduction modeled through a time-dependent maximum effect function, and an allometrically scaled baseline body weight effect on clearances and volumes of distribution parameters	Acceptable.
Model Parameter Estimates		Table 70	Acceptable.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		All model parameters were reasonably well estimated, with the % RSE of most fixed-effects well below 20%, and the %RSE of all random-effects below 25%. The only fixed-effect parameter that had a RSE greater than 20% was	Acceptable.

	T50, which only impacts the time to reach steady-state. The final popPK model parameter estimates were contained within the 95% CI determined by a bootstrap analysis based on 500 replicates. Median values following bootstrapping were very similar to the parameter estimates of the final model, and the 95% CIs overlapped with those of the final model, indicating that the final popPK model had good precision for parameter estimates.	
BLQ for Parameter Accuracy	678 BLQ observations (6.7%) were excluded from analysis and had no impact on PK objectives	Acceptable.
GOF, VPC	Figure 8 and Figure 9.	Acceptable.
Significant Covariates and Clinical Relevance	Figure 10 Baseline BW was allometrically scaled on CLs and volumes of distributions. Food effect on KA and F1 was identified as a significant covariate, while dose was a significant covariate on CLMAX	Food effects in population PK should be interpreted with caution as the food status was unknown for the majority of subjects in popPK analysis
Analysis Based on Simulation (optional)	Table 71, Simulations of food effects after single dose and multiple doses	Acceptable.

Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	(b) (4)	Detailed recommendation of labeling language was provided in separated labeling document.

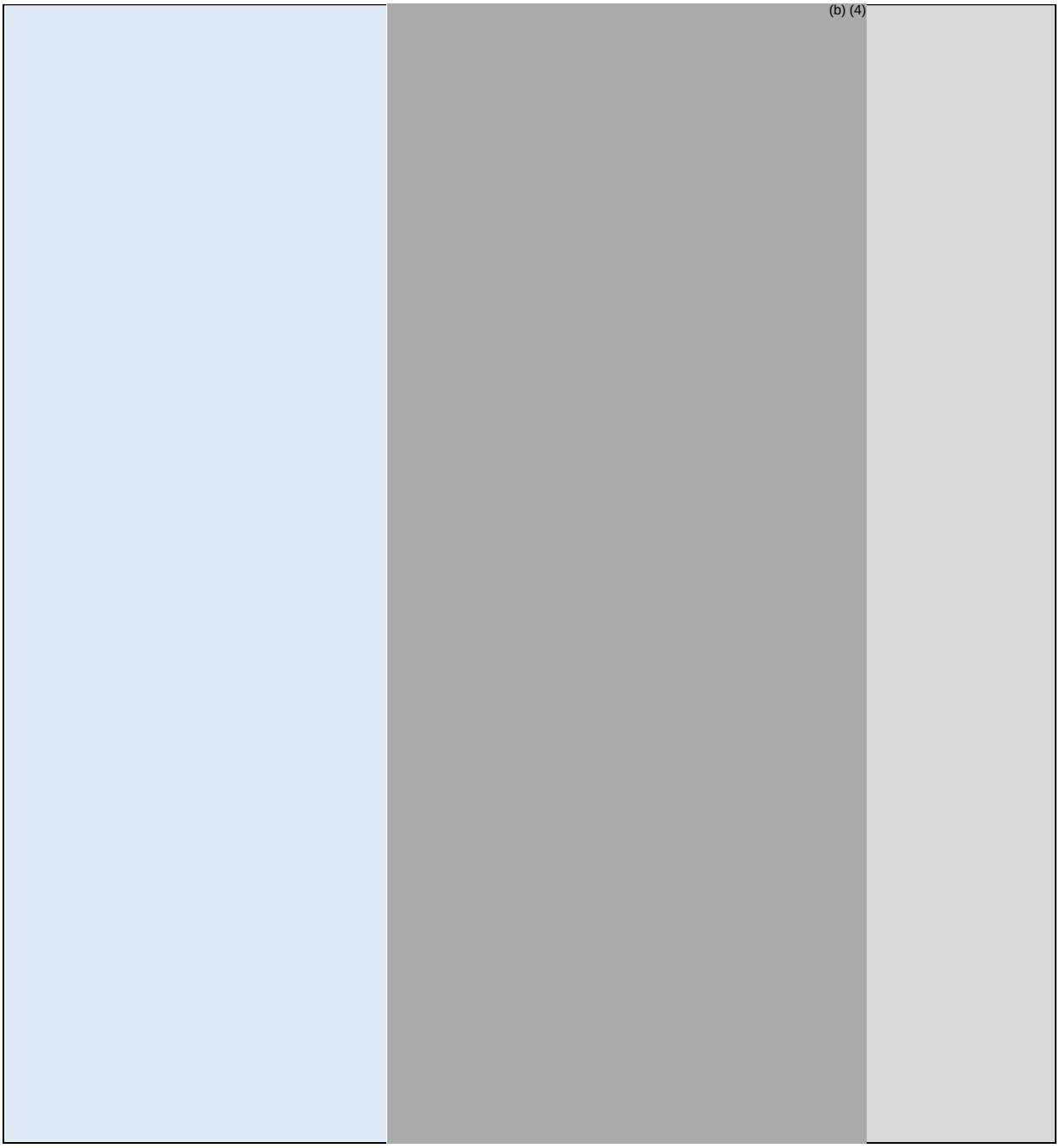


Table 69. Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study Continuous Covariates

	Study 501 (N = 407)	Study 508 (N = 14)	Study 509 (N = 7)	Study 510 (N = 30)	Study 511 (N = 14)	Study 512 (N = 17)	Study 514 (N = 36)	Overall (N = 525)
Age (years)								
Mean (SD)	55.0 (13.2)	33.6 (11.1)	37.6 (9.96)	39.9 (8.82)	36.1 (9.21)	40.5 (8.46)	33.9 (9.29)	50.9 (14.6)
Median [min, max]	56.0 [18.0, 84.0]	32.5 [21.0, 54.0]	38.0 [23.0, 55.0]	39.5 [22.0, 53.0]	34.5 [22.0, 55.0]	40.0 [29.0, 51.0]	33.0 [18.0, 53.0]	51.0 [18.0, 84.0]
Baseline body weight (kg)								
Mean (SD)	70.5 (17.5)	73.5 (7.65)	79.8 (15.0)	80.4 (9.47)	80.6 (14.6)	84.0 (13.2)	81.2 (10.5)	72.7 (16.8)
Median [min, max]	68.0 [39.5, 169]	72.7 [62.0, 86.1]	84.3 [50.8, 96.0]	79.0 [62.6, 99.3]	81.6 [59.3, 105]	84.2 [60.5, 113]	82.4 [57.6, 97.2]	71.0 [39.5, 169]
Baseline height (cm)								
Mean (SD)	166 (9.99)	180 (5.78)	173 (5.65)	174 (6.51)	175 (9.40)	177 (9.88)	176 (7.16)	169 (10.3)
Median [min, max]	166 [144, 196]	182 [169, 192]	175 [162, 179]	174 [159, 186]	173 [158, 189]	181 [157, 193]	176 [160, 192]	168 [144, 196]
Missing	4 (1.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.8%)
Baseline BMI (kg/m^2)								
Mean (SD)	25.3 (5.02)	22.7 (2.52)	26.5 (4.33)	26.5 (2.47)	26.1 (2.99)	26.6 (2.93)	26.2 (3.21)	25.5 (4.67)
Median [min, max]	24.2 [16.4, 45.8]	23.8 [18.6, 26.5]	26.2 [19.4, 31.5]	27.7 [21.8, 29.7]	26.6 [21.1, 29.9]	26.5 [22.5, 30.8]	26.9 [18.9, 30.2]	24.6 [16.4, 45.8]
Missing	4 (1.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.8%)
Baseline body surface area (m^2)								
Mean (SD)	1.78 (0.237)	1.93 (0.102)	1.93 (0.194)	1.95 (0.136)	1.96 (0.219)	2.01 (0.201)	1.97 (0.144)	1.82 (0.235)
Median [min, max]	1.76 [1.30, 2.92]	1.92 [1.79, 2.06]	2.00 [1.52, 2.11]	1.94 [1.66, 2.24]	1.94 [1.67, 2.31]	1.98 [1.61, 2.43]	2.01 [1.60, 2.27]	1.82 [1.30, 2.92]
Missing	4 (1.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0.8%)

	Study 501 (N = 407)	Study 508 (N = 14)	Study 509 (N = 7)	Study 510 (N = 30)	Study 511 (N = 14)	Study 512 (N = 17)	Study 514 (N = 36)	Overall (N = 525)
Baseline GFR-MDRD (mL/min/1.73 m^2)								
Mean (SD)	100 (30.2)	94.0 (17.6)	94.9 (19.5)	91.2 (11.8)	91.6 (20.5)	85.9 (13.3)	97.9 (13.3)	98.5 (27.7)
Median [min, max]	99.6 [29.5, 223]	90.0 [75.0, 132]	93.0 [69.3, 120]	91.9 [67.9, 114]	91.2 [62.0, 145]	88.2 [68.3, 117]	96.3 [74.5, 121]	96.4 [29.5, 223]
Baseline aspartate aminotransferase (U/L)								
Mean (SD)	25.6 (19.0)	18.0 (5.60)	20.9 (5.27)	23.2 (6.53)	21.1 (6.11)	19.9 (5.72)	19.9 (5.92)	24.5 (17.1)
Median [min, max]	21.0 [9.00, 221]	17.5 [12.0, 34.0]	20.0 [16.0, 30.0]	21.5 [13.0, 40.0]	19.0 [13.0, 32.0]	18.0 [12.0, 31.0]	18.0 [13.0, 39.0]	20.0 [9.00, 221]
Missing	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)
Baseline alanine aminotransferase (U/L)								
Mean (SD)	26.2 (28.1)	18.9 (9.14)	22.6 (5.41)	27.2 (13.9)	21.2 (7.40)	19.4 (8.74)	22.2 (12.1)	25.4 (25.4)
Median [min, max]	19.0 [5.00, 275]	16.0 [10.0, 39.0]	22.0 [16.0, 33.0]	20.0 [11.0, 60.0]	22.0 [9.00, 33.0]	16.0 [10.0, 42.0]	19.0 [9.00, 58.0]	19.0 [5.00, 275]
Baseline serum alkaline phosphatase (U/L)								
Mean (SD)	117 (98.2)	67.9 (18.8)	65.0 (12.5)	80.4 (21.7)	70.9 (17.7)	76.5 (21.4)	79.1 (16.4)	107 (88.6)
Median [min, max]	91.0 [24.0, 870]	62.5 [45.0, 97.0]	69.0 [43.0, 81.0]	81.0 [46.0, 128]	67.5 [52.0, 117]	72.0 [42.0, 122]	80.5 [51.0, 136]	86.0 [24.0, 870]
Baseline total bilirubin (mg/dL)								
Mean (SD)	0.472 (0.255)	0.686 (0.344)	0.614 (0.358)	0.543 (0.302)	0.486 (0.214)	0.476 (0.152)	0.630 (0.390)	0.495 (0.273)
Median [min, max]	0.420 [0.100, 1.53]	0.600 [0.300, 1.50]	0.500 [0.300, 1.30]	0.450 [0.200, 1.40]	0.400 [0.300, 1.10]	0.500 [0.200, 0.800]	0.500 [0.200, 1.90]	0.430 [0.100, 1.90]
Baseline creatinine (mg/dL)								
Mean (SD)	0.755 (0.223)	0.963 (0.124)	0.929 (0.160)	0.959 (0.124)	1.06 (0.190)	1.08 (0.129)	0.934 (0.0986)	0.805 (0.228)
Median [min, max]	0.700 [0.390, 1.80]	0.970 [0.740, 1.14]	0.900 [0.800, 1.20]	0.960 [0.740, 1.18]	1.08 [0.580, 1.44]	1.05 [0.760, 1.27]	0.945 [0.710, 1.11]	0.800 [0.390, 1.80]
Actual dose (mg)								
Mean (SD)	155 (29.0)	160 (0)	160 (0)	117 (40.6)	160 (0)	160 (0)	160 (0)	154 (28.8)
Median [min, max]	160 [40.0, 240]	160 [160, 160]	160 [160, 160]	80.0 [80.0, 160]	160 [160, 160]	160 [160, 160]	160 [160, 160]	160 [40.0, 240]

Source: Report 00516 Table 6

Categorical Covariates

Variables	Study 501 (N = 407)	Study 508 (N = 14)	Study 509 (N = 7)	Study 510 (N = 30)	Study 511 (N = 14)	Study 512 (N = 17)	Study 514 (N = 36)	Overall (N = 525)
Gender								
Male	170 (41.8%)	14 (100%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	288 (54.9%)
Female	237 (58.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	237 (45.1%)
Race								
White	198 (48.6%)	12 (85.7%)	5 (71.4%)	25 (83.3%)	8 (57.1%)	8 (47.1%)	29 (80.6%)	285 (54.3%)
Other	14 (3.4%)	1 (7.1%)	1 (14.3%)	4 (13.3%)	6 (42.9%)	9 (52.9%)	6 (16.7%)	41 (7.8%)
Asian	195 (47.9%)	1 (7.1%)	1 (14.3%)	1 (3.3%)	0 (0%)	0 (0%)	1 (2.8%)	199 (37.9%)
Ethnicity								
Hispanic or Latino	11 (2.7%)	1 (7.1%)	1 (14.3%)	20 (66.7%)	1 (7.1%)	3 (17.6%)	25 (69.4%)	62 (11.8%)
Not Hispanic or Latino	384 (94.3%)	13 (92.9%)	6 (85.7%)	10 (33.3%)	13 (92.9%)	14 (82.4%)	11 (30.6%)	451 (85.9%)
Missing	12 (2.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (2.3%)
Hepatic impairment								
Normal	355 (87.2%)	13 (92.9%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	35 (97.2%)	471 (89.7%)
Mild impairment	50 (12.3%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.8%)	52 (9.9%)
Missing	2 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)
Renal impairment (CrCL)								
Normal	247 (60.7%)	12 (85.7%)	7 (100%)	28 (93.3%)	12 (85.7%)	13 (76.5%)	35 (97.2%)	354 (67.4%)
Mild impairment	121 (29.7%)	2 (14.3%)	0 (0%)	2 (6.7%)	2 (14.3%)	4 (23.5%)	1 (2.8%)	132 (25.1%)
Moderate impairment	39 (9.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	39 (7.4%)

Variables	Study 501 (N = 407)	Study 508 (N = 14)	Study 509 (N = 7)	Study 510 (N = 30)	Study 511 (N = 14)	Study 512 (N = 17)	Study 514 (N = 36)	Overall (N = 525)
Renal impairment (eGFR)								
Normal	242 (59.5%)	12 (85.7%)	7 (100%)	27 (90.0%)	13 (92.9%)	16 (94.1%)	33 (91.7%)	350 (66.7%)
Mild impairment	113 (27.8%)	2 (14.3%)	0 (0%)	3 (10.0%)	1 (7.1%)	1 (5.9%)	3 (8.3%)	123 (23.4%)
Moderate impairment	27 (6.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	27 (5.1%)
Missing	25 (6.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	25 (4.8%)
Subject status								
Cancer subjects	407 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	407 (77.5%)
Healthy subjects	0 (0%)	14 (100%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	118 (22.5%)
Formulation								
Capsule	407 (100%)	7 (50.0%)	7 (50.0%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	518 (97.4%)
Suspension	0 (0%)	7 (50.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (1.3%)
IV solution	0 (0%)	0 (0%)	7 (50.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (1.3%)
Route of administration								
Oral	407 (100%)	14 (100%)	7 (50.0%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	525 (98.7%)
IV	0 (0%)	0 (0%)	7 (50.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (1.3%)
Food status								
Overnight fasted	0 (0%)	13 (92.9%)	7 (100%)	30 (100%)	14 (50.0%)	17 (100%)	34 (51.5%)	115 (19.4%)
Fed	46 (10.6%)	1 (7.1%)	0 (0%)	0 (0%)	14 (50.0%)	0 (0%)	32 (48.5%)	93 (15.7%)
Modified fasted	71 (16.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	71 (12.0%)
Unknown	315 (72.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	315 (53.0%)
Previous treatment								
TKI-naïve	137 (33.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	137 (26.1%)
TKI-pretreated	270 (66.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	270 (51.4%)
Missing	0 (0%)	14 (100%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	118 (22.5%)
ECOG								
Fully active	141 (34.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	141 (26.9%)
Restricted	265 (65.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	265 (50.5%)
Missing	1 (0.2%)	14 (100%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	119 (22.7%)

Variables	Study 501 (N = 407)	Study 508 (N = 14)	Study 509 (N = 7)	Study 510 (N = 30)	Study 511 (N = 14)	Study 512 (N = 17)	Study 514 (N = 36)	Overall (N = 525)
Cancer histology								
Adenocarcinoma	354 (87.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	354 (67.4%)
Sarcoma	10 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (1.9%)
Squamous	8 (2.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (1.5%)
Non-classified	35 (8.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (6.7%)
Healthy subjects	0 (0%)	14 (100%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	118 (22.5%)
Genetic mutations								
ALK	30 (7.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	30 (5.7%)
NTRK	87 (21.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	87 (16.6%)
ROS1	290 (71.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	290 (55.2%)
Healthy subjects	0 (0%)	14 (100%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	118 (22.5%)
Cancer type								
Other	58 (14.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	58 (11.0%)
Lung cancer non-small cell	349 (85.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	349 (66.5%)
Healthy subjects	0 (0%)	14 (100%)	7 (100%)	30 (100%)	14 (100%)	17 (100%)	36 (100%)	118 (22.5%)

Abbreviations: BMI = body mass index; GFR = glomerular filtration rate; max = maximum; MDRD = Modification of Diet in Renal Disease; min = minimum; N = number of subjects; popPK = population pharmacokinetic; SD = standard deviation.
Source: Report 00516 Table 7

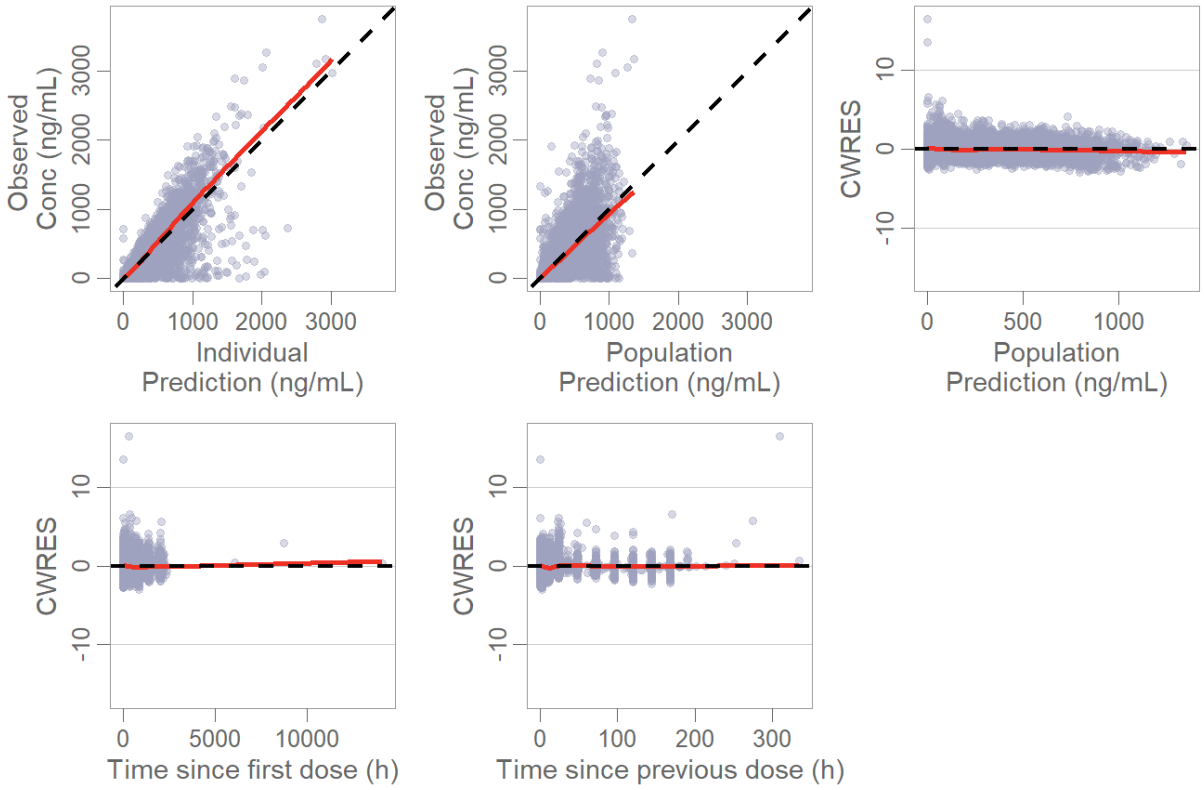
Table 70. Parameter Estimates and SE From Final Population PK Model

	Parameter	Estimate	SE	RSE (%)	Median [95% CI] From Bootstrap
Fixed effects					
CL(L/h)	θ1	7.06	0.574	8.13	7.07 [5.91, 8.73]
V2 (L)	θ2	21.0	2.40	11.4	22 [17, 30.2]
V3 (L)	θ3	224	16.7	7.43	224 [192, 277]
Q (L/h)	θ4	6.05	0.585	9.67	6.06 [4.83, 7.7]
KA – fasted (1/h)	θ5	0.0608	0.00447	7.35	0.0606 [0.0529, 0.0747]
KA – fed (1/h)	θ6	0.140	0.00787	5.61	0.14 [0.127, 0.163]
KA – modified fasted (1/h)	θ7	0.190	0.0249	13.1	0.19 [0.152, 0.281]
KA – unknown fed status (1/h)	θ8	0.267	0.0177	6.64	0.269 [0.234, 0.313]
F1 – fasted	θ9	0.492	0.0438	8.90	0.495 [0.405, 0.605]
F1 – fed	θ10	0.68	0.0586	8.62	0.682 [0.57, 0.847]
F1 – modified fasted	θ11	0.547	0.0601	11.0	0.55 [0.433, 0.703]
F1 – unknown fed status	θ12	0.471	0.0402	8.53	0.472 [0.395, 0.59]
Absorption time lag (h)	θ13	0.420	0.00871	2.07	0.42 [0.402, 0.437]
CLMAX(L/h)	θ18	12.0	1.39	11.6	12.2 [9.72, 15.8]
T50 (h)	θ19	143	30.7	21.5	144 [84.1, 212]
Allometry for clearances	θ20	0.75 FIX	-	-	0.75 [0.75, 0.75]
Allometry for volumes	θ21	1 FIX	-	-	1 [1, 1]
CLMAXDOSE	θ22	1.02	0.195	19.2	1.03 [0.543, 1.48]
V2POP	θ23	-0.844	0.0213	2.52	-0.851 [-0.896, -0.794]
IIV					
CL	ω.1.1.	0.0822	0.0198	24.1	0.0806 [0.0469, 0.141]
V2	ω.2.2.	0.792	0.0992	12.5	0.769 [0.585, 0.982]
Q	ω.4.4.	0.306	0.0373	12.2	0.297 [0.177, 0.429]
KA	ω.5.5.	0.0889	0.0181	20.4	0.087 [0.0565, 0.133]
F1	ω.6.6.	0.108	0.0148	13.8	0.107 [0.0809, 0.141]
CLMAX	ω.7.7.	0.217	0.0435	20.1	0.208 [0.13, 0.342]
Residual error					
Healthy subject proportional error	θ14	0.336	0.00943	2.81	0.334 [0.313, 0.353]
Healthy subject additive error	θ15	0.00001 FIX	-	-	1e-05 [1e-05, 1e-05]
Subject with advanced solid tumors proportional error	θ16	0.393	0.014	3.55	0.394 [0.365, 0.43]
Subject with advanced solid tumors additive error	θ17	43.7	9.46	21.7	43.1 [2.29, 61]

Abbreviations: ALAG1 = lag time; CI = confidence interval; CL = clearance; CL_{MAX} = Maximum Induced Clearance; $CL_{MAXDOSE}$ = dose effect on CL_{MAX}; CL_{QWT} = body weight effect on CL and Q; F1 = bioavailability; F1FASTED = F1 at fasted; F1FED = F1 at fed; F1MODIFIED = F1 at modified fasted; F1Unknown = F1 at unknown food status; IIV = interindividual variability; KA = first-order absorption rate constant; KAFASTED = KA at fasted; KAFED = KA at fed; KAMODIIFED = KA at modified fasted; KAUnknown = KA at unknown food status; Q = intercompartmental clearance; RSE% = relative SE percentage; SE = standard error; T50 = time to

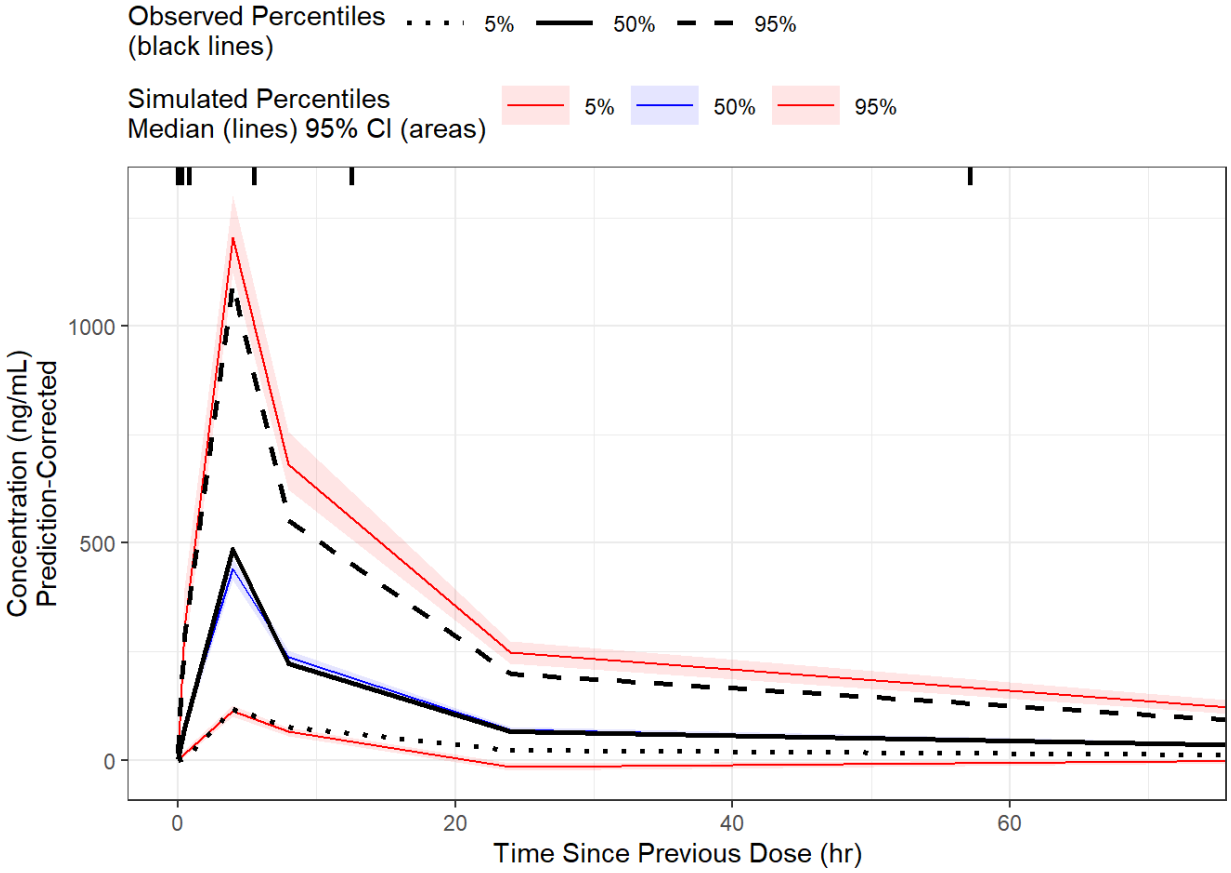
achieve half of CLMAX; V2 = central volume of distribution; V2POP = population effect on V2; V2V3WT = body weight effect on V2 and V3; V3 = peripheral volume of distribution.
Notes: Cis are from bootstrap with 85.4% successful runs.
Minimum value of the objective function = 77887.59. Condition number = 1451
Shrinkages: CL = 35.1%; V2 = 30.6%; Q = 36%; KA = 43.8%; F1 = 26.4%; CLMAX = 50.3%
Source: Report 00516 Table 12

Figure 8. Goodness-of-Fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)



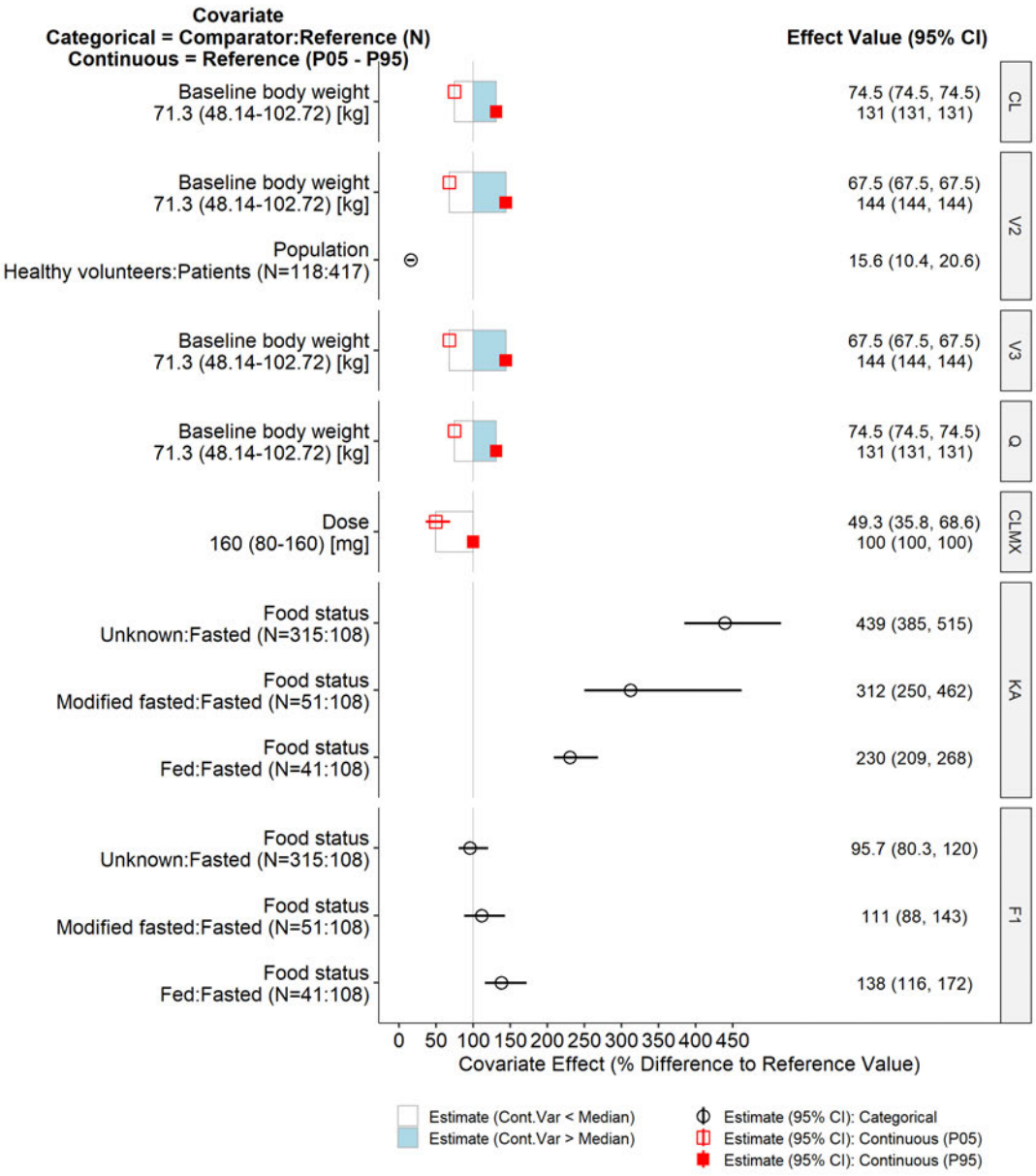
Abbreviations: Conc = concentration; CWRES = conditional weighted residuals; GOF = goodness-of-fit; LOESS = locally estimated scatterplot smoothing.
Note: The red line is the LOESS smooth curve.
Source: Report 00516, Figure 7

Figure 9. pcVPC of Final Population PK Model



Abbreviations: CI = confidence interval; DV = dependent variable (usually observation); pcVPC = prediction-corrected visual predictive check; popPK = population pharmacokinetic.
Note: The pcVPC plots show the median (solid black lines) and spread (5th to 95th percentiles; dashed black line) of the DV in all subjects. The red area is the 95% CI of the simulated median, and the blue area is the 95% CI of the simulated 5th and 95th percentiles.
Source: Report 00516 Figure 8

Figure 10. Impact of Significant Covariates on Exposure



Abbreviations: CI = confidence interval; CL = clearance; CLMAX = Maximum Induced Clearance; Cont.Var. = continuous variable; F1 = bioavailability; KA = first-order absorption rate constant; N = number of subjects; P05 = 5th percentile; P95 = 95th percentile; popPK = population pharmacokinetic; Q = intercompartmental CL; V2 = central volume of distribution. V3 = peripheral volume of distribution.
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: Report 00516 Figure 6

Table 71. Simulation of Food Effects Under Fasted, Modified Fasted, and Fed Conditions (Single Dose)

Exposure	Fasted (N = 407)	Fed (N = 407)	Modified Fast (N = 407)
AUC_{inf} (ng*h/mL)			
Median [Min, Max]	11100 [6890, 47400]	15300 [9540, 65600]	12100 [7530, 51800]
Geo. Mean (Geo. CV%)	11200 (19.5%)	15500 (19.5%)	12200 (19.5%)
5th Percentile	8560	11800	9350
10th Percentile	9090	12600	9930
90th Percentile	13700	18900	15000
95th Percentile	14700	20400	16100
C_{maxsd} (ng/mL)			
Median [Min, Max]	269 [92.0, 1130]	689 [215, 2690]	686 [188, 2560]
Geo. Mean (Geo. CV%)	271 (31.7%)	693 (32.8%)	682 (33.7%)
5th Percentile	161	409	393
10th Percentile	184	460	448
90th Percentile	401	1030	1020
95th Percentile	434	1140	1130
C_{minsd} (ng/mL)			
Median [Min, Max]	14.7 [1.36, 61.0]	46.8 [4.35, 160]	50.0 [4.78, 149]
Geo. Mean (Geo. CV%)	14.0 (56.2%)	44.4 (55.0%)	47.4 (52.6%)
5th Percentile	5.37	17.1	18.9
10th Percentile	7.34	23.4	25.2
90th Percentile	25.0	79.6	84.6
95th Percentile	31.4	98.9	96.8
C_{avgsd} (ng/mL)			
Median [Min, Max]	197 [69.4, 873]	364 [129, 1640]	301 [106, 1360]
Geo. Mean (Geo. CV%)	199 (32.4%)	367 (32.6%)	304 (32.7%)
5th Percentile	122	224	185
10th Percentile	136	250	206
90th Percentile	294	545	453
95th Percentile	318	591	489

Abbreviations: AUCinf = area under the plasma concentration-time curve after the first dose from 0 to infinity; C_{avgsd} = average plasma concentration after the first dose; C_{maxsd} = maximum plasma concentration after the first dose; C_{minsd} = minimum plasma concentration after the first dose; CV% = coefficient of variation percentage; Geo. = geometric; max = maximum; min = minimum; N = number of subjects; PK = pharmacokinetics.
Source: Report 00516 Table 17

Table 72. Simulation of Food Effects Under Fasted, Modified Fasted, and Fed Conditions (Steady State)

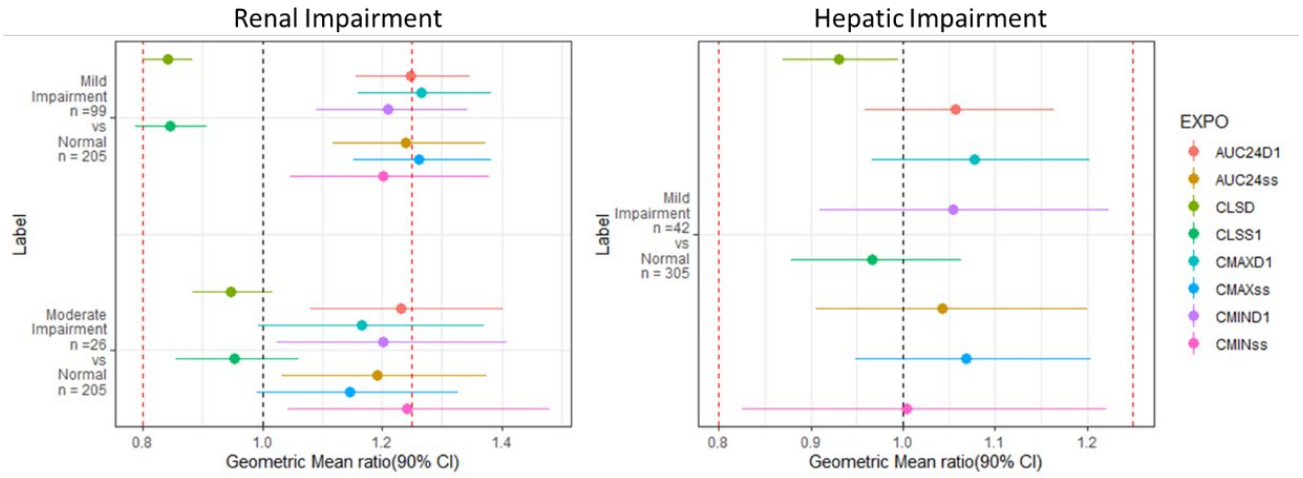
Exposure	Fasted (N = 407)	Fed (N = 407)	Modified Fast (N = 407)
$AUC_{ss}12$ (ng*h/mL)			
Median [Min, Max]	4840 [1350, 66400]	6700 [1870, 91900]	5290 [1470, 72600]
Geo. Mean (Geo. CV%)	4820 (45.5%)	6680 (45.5%)	5270 (45.5%)
5th Percentile	2490	3450	2720
10th Percentile	2930	4050	3200
90th Percentile	7780	10800	8500
95th Percentile	9340	12900	10200
AUC_{ss24} (ng*h/mL)			
Median [Min, Max]	9690 [2700, 133000]	13400 [3730, 184000]	10600 [2950, 145000]
Geo. Mean (Geo. CV%)	9650 (45.5%)	13400 (45.5%)	10500 (45.5%)
5th Percentile	4990	6900	5450
10th Percentile	5850	8100	6390
90th Percentile	15600	21500	17000
95th Percentile	18700	25900	20400
C_{maxss} (ng/mL)			
Median [Min, Max]	468 [137, 5580]	762 [241, 7820]	666 [219, 6220]
Geo. Mean (Geo. CV%)	462 (43.1%)	756 (40.9%)	664 (39.7%)
5th Percentile	245	415	372
10th Percentile	287	471	419
90th Percentile	733	1200	1050
95th Percentile	863	1350	1150
C_{minss} (ng/mL)			
Median [Min, Max]	332 [87.2, 5450]	353 [85.5, 7390]	237 [53.5, 5770]
Geo. Mean (Geo. CV%)	331 (48.6%)	353 (53.6%)	235 (57.4%)
5th Percentile	169	167	106
10th Percentile	195	200	131
90th Percentile	551	614	418
95th Percentile	668	757	533
C_{avgss} (ng/mL)			
Median [Min, Max]	404 [112, 5540]	558 [156, 7660]	441 [123, 6050]
Geo. Mean (Geo. CV%)	402 (45.5%)	556 (45.5%)	439 (45.5%)
5th Percentile	208	288	227
10th Percentile	244	337	266
90th Percentile	648	897	708
95th Percentile	779	1080	851

Abbreviations: AUC_{ss12} = area under the plasma concentration-time curve from 0 to 12 hours at steady state; AUC_{ss24} = area under the plasma concentration-time curve from 0 to 24 hours at steady state; BID = twice daily; C_{avgss} = average plasma concentration at steady state; C_{maxss} = maximum plasma concentration at steady state; C_{minss} = minimum plasma concentration at steady state; CV% = coefficient of variation percentage; Geo. = geometric; max = maximum; min = minimum; N = number of subjects; PK = pharmacokinetics.
Source: Report 00516 Table 18

The FDA's Assessment:

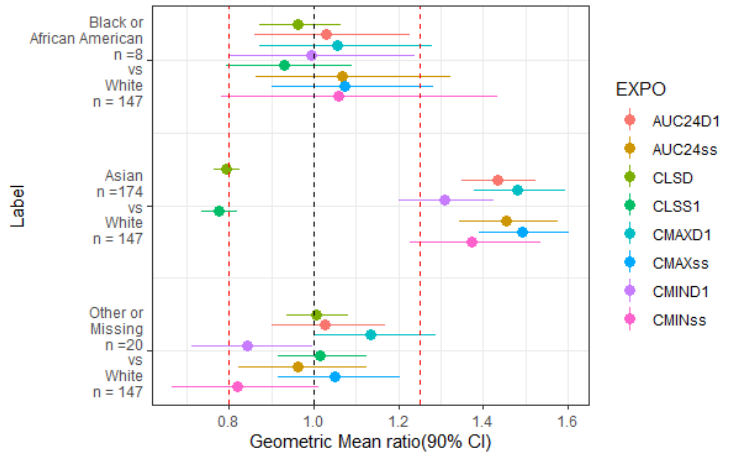
The result of population PK analysis for repotrectinib in healthy subjects and subjects with advanced solid tumors were checked by the reviewer. The results of the population PK analysis were generally acceptable due to the agreement of prediction and observation. Food effects were identified as significant covariates for KA and F1 in the final population PK model. While the food status was unknown for the majority of pooled subjects (59%), especially for patients with NSCLC (76%), in the population PK analysis. These results should be interpretated with caution and dose adjustment with regard to food should be based on the dedicated clinical pharmacology study. Comparisons among estimated PK parameters in different renal/hepatic impairment groups or races were shown in Figure 11 and Figure 12. No significant difference was observed, except Asian patients tend to have higher exposure comparing to White patients, which might be due to the relatively lower bodyweight for Asian patients.

Figure 11. Comparisons Among Empirical Bayes Estimate (EBE) of PK Parameters in Different Renal/Hepatic Impairment Groups to Normal Groups of Patients With NSCLC



Source: Reviewer's analysis based on dataset "ppk.xpt".

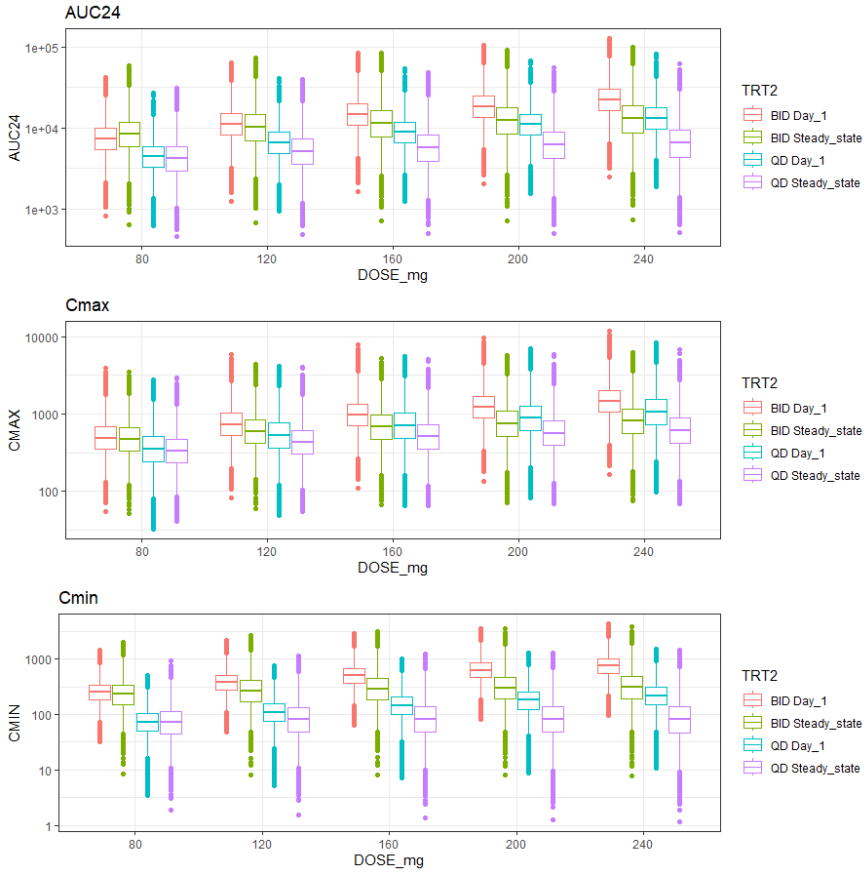
Figure 12. Comparisons Among EBEs of PK Parameters in Different Races of Patients With NSCLC



Source: Reviewer's analysis based on dataset "ppk.xpt".

Repotrectinib is predominantly metabolized via cytochrome P450 3A4 (CYP3A4) and exhibits time-dependent autoinduction in PK analysis. The non-linear elimination of repotrectinib with autoinduction was modeled through a time dependent E_{max} function in the population PK analysis. $C_{max,ss}$ of ROS1+ NSCLC patients treated with 160 mg BID is predicted to be comparable to $C_{max,Day1}$ with 160 mg QD, while AUC_{ss} and $C_{min,ss}$ with 160 mg BID are predicted to be slightly higher than AUC_{Day1} and $C_{min,\ Day1}$ with 160 mg QD. (Figure 13)

Figure 13. Model Predicted Repotrectinib Exposures Under Different Dose Levels



Source: Reviewer's analysis based on dataset "ppk.xpt".

19.4.3. Exposure-Response Analysis

19.4.3.1. ER (Efficacy) Executive Summary

The FDA's Assessment:

E-R efficacy analysis for primary endpoint (ORR) and secondary endpoints (CBR, PFS, OS, SLD, and DOR) were conducted by the Applicant in *ROS1*+ NSCLC patients from study TRIDENT-1. Logistic regression analyses, Kaplan-Meier plots and Cox regression analysis were conducted to describe the relationships for efficacy endpoints (ORR, CBR, PFS, OS) with repotrectinib exposures in *ROS1*+ NSCLC patients.

Statistically significant relationship was observed between $C_{max,ss}$ of repotrectinib and the probability of ORR for ROS1+ NSCLC patients. TKI-naïve ROS1+ NSCLC patients tend to have better ORR than TKI-pretreated ROS1+ NSCLC patients. Statistically significant relationship was also observed between $C_{avg,ss}$ of repotrectinib and OS for ROS1+ NSCLC patients. TKI-pretreated ROS1+ NSCLC patients tend to have higher risk of than TKI- naïve ROS1+ NSCLC patients. The risk of death is predicted to be higher in subjects with an ECOG score of 1 (compared to a score of 0). There were no statistically significant relationships between repotrectinib exposures and

efficacy endpoints (CBR, PFS and DOR). The positive exposure-efficacy relationship should be interpreted with caution as more than 90% of the data was from a single dose level.

19.4.3.2. ER (Efficacy) Assessment Summary

The Applicant's Position:

There was a statistically significant relationship between repotrectinib exposure (C_{maxss}) and the probability of achieving an ORR for *ROS1*-positive NSCLC subjects. The median model predicted ORR is higher following 160 mg BID dose regimen than 160 mg QD dose regimen (86.5% (BID) and 81.9% (QD) for TKI-naïve *ROS1*-positive NSCLC, and 44.0% (BID) and 37.8% (QD) for TKI pretreated *ROS1*-positive NSCLC).

There was a statistically significant relationship between repotrectinib exposure (C_{avgss}) and OS with the risk of death predicted to decrease with increasing C_{avgss}. The risk of death is predicted to be higher in subjects with an ECOG score of 1 (compared to a score of 0) and with TKI-pretreated subjects (relative to TKI-naïve).

There was no statistically significant relationship between repotrectinib exposure (C_{maxss} and C_{avgss}) and the following efficacy endpoints, including CBR, PFS, DOR, or SLD.

Table 73. Applicant Table.

General Information		
Goal of ER analysis		Characterize the relationship between repotrectinib exposures and efficacy endpoints in subjects with advanced solid tumors harboring *ROS1* rearrangements in the TRIDENT-1 study
Study Included		2 pooled patient populations in the TRIDENT-1 study: • Pooled EXP-1 (TKI-naïve *ROS1*+ NSCLC): 71 subjects (8 from Phase 1 and 63 from Phase 2) • Pooled EXP-4 (TKI-pretreated *ROS1*+ NSCLC with 1 prior TKI and no prior platinum-based chemotherapy): 56 subjects (3 from Phase 1 and 53 from Phase 2)
Endpoint		*Primary:* ORR *Secondary:* CBR, PFS, OS, SLD, and DOR.
No. of Patients (total, and with individual PK)		*71 TKI-naïve patients and 56 TKI-pretreated patients*
Population Characteristics (Table 74)	General	*Age median (range): 57 (28.0, 80.0)* *Weight median (range): 63.7 (39.5, 119)* *male n (%): 46 (36.2%)* *race n (%): 75 (59.1)* Asian; *43 (33.9%) White; 2 (1.6%) Black or African American; 2 (1.6%)* Native Hawaiian or Other Pacific Islander, 5 (3.9%) Missing
	Pediatrics (if any)	*No.*
Dose(s) Included		*40 mg to 240 mg*
Exposure Metrics Explored (range)		*C_{maxss} and C_{avgss}*

Covariates Evaluated	Age, baseline body weight, race, sex, baseline ECOG performance status score, and TKI pretreatment status	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Logistic regression* $$\boldsymbol{Logit}P_i = log\left(\frac{P_i}{1-P_i}\right) = \beta_0 + \beta_{exp}X_{iexp} + \beta_1 X_{i1} + \cdots + \beta_p X_{ip}$$ where $\boldsymbol{Logit}$ is the logit transformation using the natural logarithm function *log*, P_i is the probability of occurrence of a specific event for the i^{th} subject, and β_0 is the intercept representing the logit probability of occurrence of the event in the absence of repotrectinib and added covariate(s). β_{exp} is the slope of the relationship between repotrectinib's exposure X_{iexp} and the logit probability of occurrence of the event. $\beta_1 \ldots \beta_p$ is the vector of parameters for covariate effects, and $X_{i1} \ldots X_{ip}$ is the vector of covariate variables for subject i. p-Values, where provided, were descriptive only (not adjusted for multiplicity).	Logistic regression for E-R efficacy analysis between ORR or CBR and repotrectinib exposures is acceptable. Kaplan-Meier plots and Cox regression analysis were conducted for PFS and OS in E-R analysis.
Model Parameter Estimates	Table 75 (for primary and major secondary endpoints)	Acceptable.
Model Evaluation	A VPC was performed for the logistic regression model using 1000 sets of model parameters randomly drawn based on the uncertainty of model estimation and applied to the subjects in the analysis dataset. The VPC graphs demonstrated good agreement between the observed and simulated proportions of subjects with objective response.	Acceptable.
Covariates and Clinical Relevance	TKI-pretreatment status	TKI-naïve patients tend to have better ORR and lower risk of OS in E-R efficacy analysis. The results are acceptable.
Simulation for Specific Population	Food effect on ORR was evaluated based on simulated PK exposures under fasted, modified fasted and fed conditions.	Acceptable.
Visualization of E-R relationships	Figure 12, Table 74	Acceptable. Visualization of E-R relationships for CBR,

		PFS and OS were shown in Figure 4, Figure 5, and Figure 6.
Overall Clinical Relevance for ER	Higher exposure is associated with higher ORR as well as OS.	Acceptable.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		NA

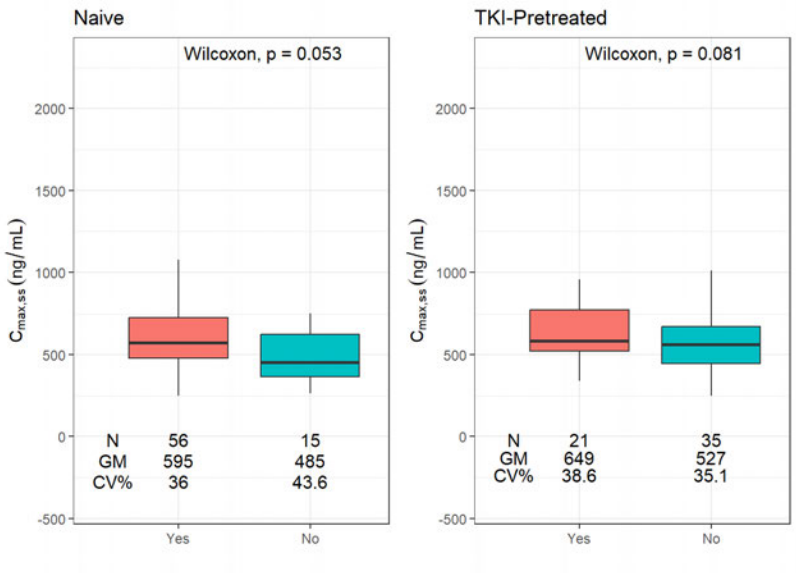
Table 74. Summary of Baseline Characteristics and Laboratory Values in the Dataset

	Responders (N = 77)	Nonresponders (N = 50)	Overall (N = 127)
Age			
Mean (CV%)	55.5 (23.1%)	56.0 (21.6%)	55.7 (22.4%)
Median [min, max]	57.0 [30.0, 80.0]	57.0 [28.0, 78.0]	57.0 [28.0, 80.0]
Gmean (CV%)	54.0 (25.2%)	54.6 (23.9%)	54.2 (24.6%)
Baseline body weight (kg)			
Mean (CV%)	63.7 (18.1%)	68.2 (24.7%)	65.5 (21.3%)
Median [min, max]	63.4 [40.5, 93.9]	66.2 [39.5, 119]	63.7 [39.5, 119]
Gmean (GCV%)	62.7 (18.4%)	66.3 (23.8%)	64.1 (20.8%)
Baseline height (cm)			
Mean (CV%)	164 (5.7%)	164 (5.7%)	164 (5.7%)
Median [min, max]	164 [150, 187]	163 [149, 187]	164 [149, 187]
Gmean (GCV%)	164 (5.7%)	164 (5.7%)	164 (5.7%)
Baseline body mass index (kg/m^2)			
Mean (CV%)	23.6 (15.7%)	25.1 (21.0%)	24.2 (18.4%)
Median [min, max]	23.1 [17.0, 35.2]	24.1 [17.3, 45.1]	23.4 [17.0, 45.1]
Gmean (GCV%)	23.3 (15.3%)	24.6 (19.5%)	23.8 (17.2%)
Baseline body surface area (m^2)			
Mean (CV%)	1.69 (10.5%)	1.74 (13.0%)	1.71 (11.6%)
Median [min, max]	1.69 [1.33, 2.08]	1.72 [1.30, 2.30]	1.70 [1.30, 2.30]
Gmean (GCV%)	1.68 (10.6%)	1.72 (12.9%)	1.70 (11.6%)
Sex			
Male	27 (35.1%)	19 (38.0%)	46 (36.2%)
Female	50 (64.9%)	31 (62.0%)	81 (63.8%)
Race			
White	24 (31.2%)	19 (38.0%)	43 (33.9%)
Black or African American	0 (0%)	2 (4.0%)	2 (1.6%)
Asian	48 (62.3%)	27 (54.0%)	75 (59.1%)
Native Hawaiian or Other Pacific Islander	2 (2.6%)	0 (0%)	2 (1.6%)

	Responders (N = 77)	Nonresponders (N = 50)	Overall (N = 127)
Missing	3 (3.9%)	2 (4.0%)	5 (3.9%)
Baseline ECOG			
Fully active	25 (32.5%)	17 (34.0%)	42 (33.1%)
Restricted	52 (67.5%)	33 (66.0%)	85 (66.9%)
Genetic mutations			
ROS1	77 (100%)	50 (100%)	127 (100%)
Previous treatment			
TKI naïve	56 (72.7%)	15 (30.0%)	71 (55.9%)
TKI pretreated	21 (27.3%)	35 (70.0%)	56 (44.1%)
Previous treatment 2			
Prior TKI without any prior chemotherapy or immunotherapy	21 (27.3%)	35 (70.0%)	56 (44.1%)
TKI-naïve with platinum-based chemotherapy	14 (18.2%)	6 (12.0%)	20 (15.7%)
TKI-naïve without platinum-based chemotherapy	42 (54.5%)	9 (18.0%)	51 (40.2%)
Cancer type			
Lung cancer, non-small cell	77 (100%)	50 (100%)	127 (100%)
Fasting status steady state			
Fed	2 (2.6%)	2 (4.0%)	4 (3.1%)
Modified fasted	6 (7.8%)	1 (2.0%)	7 (5.5%)
Unknown	69 (89.6%)	47 (94.0%)	116 (91.3%)

Abbreviations: CV% = coefficient of variation percentage; E-R = exposure-response; ECOG = Eastern Cooperative, Gmean = geometric mean, GCV% = CV% of Geomean, Oncology; max = maximum; min = minimum; N = number of subjects; n = number of subjects in the category; ORR = objective response rate; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.
Note: Continuous variables are summarized by median [min, max] and mean (standard deviation). Percentages are calculated based on the total per column based on pretreatment status.
Source: Report 00534 Table 2

Figure 14. Box Plots of Repotrectinib Cmaxss Stratified by Pretreatment Status of Objective Response



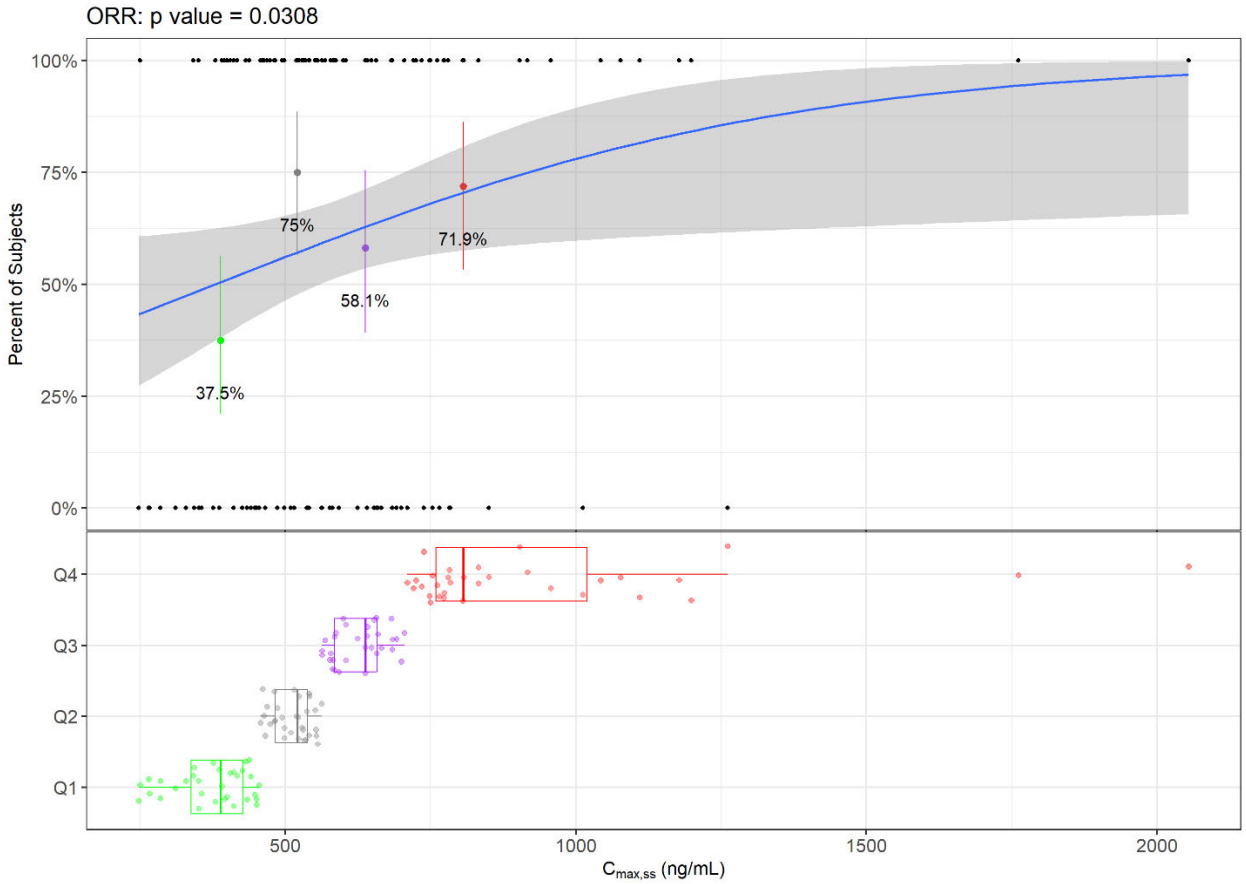
Abbreviations: C_{avgss}=steady-state average plasma concentration; C_{maxss}=steady-state maximum plasma concentration; CV% = coefficient of variation percentage; GM = geometric mean; N = number of subjects; TKI = tyrosine kinase inhibitor.
Source: Report 00534 Figure 1

Table 75. Parameter Estimates From Final ER Model of ORR (Endpoint)

Parameter	Estimate (Standard Error)	95% Confidence Interval for Estimate	Odds Ratio (Standard Error)	95% Confidence Interval for Odds Ratio	p-Value
(Intercept)	-0.133 (0.653)	-1.47, 1.10	-	-	0.838
C_{maxss}	0.00255 (0.00108)	0.000615, 0.00487	1.0026 (0.0010828)	1.0006, 1.0049	0.0188
Pretreatment status: TKI pretreated	-1.94 (0.421)	-2.80, -1.14	0.14370 (0.060499)	0.060810, 0.31982	0.00000377

Abbreviations: C_{maxss} = steady-state maximum plasma concentration; E-R = exposure-response; TKI = tyrosine kinase inhibitor.
Note: The p-value is based on the Wald statistics.
Source: Report 00534 Table 6

Figure 15. ER Curves of ORR vs Cmaxss in 127 Patients



Abbreviations: CI = confidence interval; C_{maxss} = steady-state maximum plasma concentration; N = number of subjects; ORR = objective response rate; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile.
Note: The independent variables were divided into 4 equally sized, rank-ordered groups. Colored points (green, gray, purple, and red) and error bars represent the observed proportions for each quartile and the 95% CIs for each exposure group (plotted at the mean exposure within each exposure group), respectively. The blue curve represents the prediction of the univariate logistic regression model, and the gray shaded region represents the 95% CI of the prediction.
Percentages in the upper part of the graph represent the proportion of subjects in each exposure group who experienced objective response.
The p-value is based on the Wald statistical test.
Source: Report 00534 Figure 2

19.4.3.3. ER (Safety) Executive Summary

The FDA's Assessment:

E-R safety analyses for dizziness, dysgeusia, constipation, anemia, paresthesia, dyspnea, fatigue, nausea, ALT increased, AST increased, ataxia, muscular weakness, headache, grade ≥ 3 TEAEs, and grade ≥ 2 dizziness were conducted by the Applicant in subjects with advanced solid tumors harboring *ALK*, *ROS1*, or *NTRK1-3* alterations from study TRIDENT-1. Univariate logistic regression analyses were conducted to describe the relationships for the safety endpoints with repotrectinib exposures.

Statistically significant relationships between repotrectinib exposures (either C_{max}, C_{avg}, or both) for the following 11 safety endpoints including dizziness, headache, muscular weakness, ataxia,

AST increased, ALT increased, paresthesia, anemia, constipation, dysgeusia, and dizziness, were observed. On the other hand, no statistically significant relationship was found between exposure and Grade ≥ 3 TEAEs, nausea, fatigue and dyspnea. In the full E-R model for grade ≥ 2 dizziness, increasing of C_{max} or age was found to be significantly associated with an increased probability of Grade ≥ 2 dizziness.

19.4.3.4. ER (Safety) Assessment Summary

The Applicant's Position:

There was a statistically significant relationship between repotrectinib exposure (either C_{max}, C_{avg}, or both) for 11 out of the 15 safety endpoints evaluated (grade ≥ 2 dizziness, headache, muscular weakness, ataxia, AST increased, ALT increased, paresthesia, anemia, constipation, dysgeusia, and dizziness).

Repotrectinib C_{max} was significantly associated with an increased probability of grade ≥ 2 dizziness. Increasing age also increased the probability of grade ≥ 2 dizziness. Simulations conducted at different doses and regimens indicated that the probability of experiencing grade ≥ 2 dizziness increases with the dose. However, the absolute risk of grade ≥ 2 dizziness was still relatively low.

Table 76. Applicant Table.

General Information		
Goal of ER analysis		Characterize the relationship between repotrectinib exposures and safety endpoints in subjects with advanced solid tumors harboring *ALK*, *ROS1*, or *NTRK1-3* rearrangements in the TRIDENT-1 study
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		Dizziness, dysgeusia, constipation, anemia, paresthesia, dyspnea, fatigue, nausea, ALT increased, AST increased, ataxia, muscular weakness, headache, Grade ≥ 3 TEAEs, and grade ≥ 2 dizziness
No. of Patients (total, and with individual PK)		*407 patients*
Population Characteristics (Table 77)	General	*-Age median (range): 56.0 yrs (18.0, 84.0)* *-Weight median (range): 68.0 kg (39.5, 169)* *male, n (%): 170 (41.8%)* *race, n (%): 177 (43.5%) White; 11 (2.7%) Black or African American; 191 (46.9%) Asian; 1 (0.2%); American Indian/Alaskan Native; 3 (0.7%) Native Hawaiian or Other Pacific Islander; 3 (0.7%) Other; 21 (5.2%) Missing*
	Organ impairment	*-Hepatic (NCI, Child-Pugh, etc.): NA* *-Renal (CrCL, etc.):NA*
	Pediatrics (if any)	*No*
	Geriatrics (if any)	*-Age* 56.0 yr (18.0, 84.0)-170 (41.8%) *male*
Dose(s) Included		*40 mg to 240 mg*

Exposure Metrics Explored (range)	C_{max}, C_{avg}, C_{maxss}, C_{avgss}	
Covariates Evaluated	Age, baseline body weight, race, sex, baseline ECOG performance status score, genetic mutation, and TKI pretreatment status	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Logistic regression* $$\boldsymbol{Logit}P_i = log\left(\frac{P_i}{1-P_i}\right) = \beta_0 + \beta_{exp}X_{iexp} + \beta_1 X_{i1} + \cdots + \beta_p X_{ip}$$ where ***Logit*** is the logit transformation using the natural logarithm function *log*, P_i is the probability of occurrence of a specific event for the i^{th} subject, and β_0 is the intercept representing the logit probability of occurrence of the event in the absence of repotrectinib and added covariate(s). β_{exp} is the slope of the relationship between repotrectinib's exposure X_{iexp} and the logit probability of occurrence of the event. $\beta_1 \ldots \beta_p$ is the vector of parameters for covariate effects, and $X_{i1} \ldots X_{ip}$ is the vector of covariate variables for subject i. p-Values, where provided, were descriptive only (not adjusted for multiplicity).	**Logistic regression analysis is acceptable for E-R safety analysis.**
Model Parameter Estimates	Table 78	Acceptable
Model Evaluation	A VPC was performed for the final logistic regression model using 1000 sets of model parameters randomly drawn based on the uncertainty of model estimation and applied to subjects in the analysis dataset. The VPC graphs demonstrated good agreement between the observed and simulated proportions of subjects with grade ≥ 2 dizziness.	Acceptable
Covariates and Clinical Relevance	A statistically significant age effect on grade ≥ 2 dizziness. As age increased, the probability of having grade ≥ 2 dizziness increased.	Acceptable.
Simulation for Specific Population	Food effect on grade ≥ 2 dizziness was evaluated based on simulated PK exposures under fasted, modified fasted and fed conditions.	Acceptable.
Visualization of E-R relationships	Figure 13	Acceptable.

Overall Clinical Relevance for ER	Higher exposure and older age are associated with higher incidence of grade ≥ 2 dizziness.	Acceptable.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		NA

Table 77. Summary of Baseline Characteristics and Laboratory Values in the Dataset

	TKI Naïve (N = 137)	TKI Pretreated (N = 270)	Overall (N = 407)
Age			
Mean (CV%)	55.7 (25.0%)	54.6 (23.4%)	55.0 (23.9%)
Median [min, max]	58.0 [24.0, 84.0]	56.0 [18.0, 81.0]	56.0 [18.0, 84.0]
Gmean (GCV%)	53.8 (28.5%)	52.9 (26.8%)	53.2 (27.3%)
Baseline body weight (kg)			
Mean (CV%)	66.9 (21.6%)	72.3 (25.7%)	70.5 (24.8%)
Median [min, max]	64.0 [40.5, 141]	70.0 [39.5, 169]	68.0 [39.5, 169]
Gmean (GCV%)	65.5 (20.3%)	70.2 (24.7%)	68.6 (23.5%)
Baseline height (cm)			
Mean (CV%)	165 (6.2%)	167 (5.9%)	166 (6.0%)
Median [min, max]	165 [144, 196]	166 [147, 196]	166 [144, 196]
Gmean (GCV%)	165 (6.1%)	167 (5.9%)	166 (6.0%)
Missing	0 (0%)	4 (1.5%)	4 (1.0%)
Baseline body mass index (kg/m^2)			
Mean (CV%)	24.4 (17.7%)	25.8 (20.5%)	25.3 (19.8%)
Median [min, max]	23.6 [17.3, 45.1]	24.7 [16.4, 45.8]	24.2 [16.4, 45.8]
Gmean (GCV%)	24.0 (16.6%)	25.3 (19.5%)	24.9 (18.7%)
Missing	0 (0%)	4 (1.5%)	4 (1.0%)
Baseline body surface area (m^2)			
Mean (CV%)	1.73 (12.0%)	1.80 (13.7%)	1.78 (13.3%)
Median [min, max]	1.71 [1.33, 2.70]	1.79 [1.30, 2.92]	1.76 [1.30, 2.92]
Gmean (GCV%)	1.72 (11.7%)	1.79 (13.5%)	1.77 (13.0%)
Missing	0 (0%)	4 (1.5%)	4 (1.0%)
Sex			
Male	60 (43.8%)	110 (40.7%)	170 (41.8%)
Female	77 (56.2%)	160 (59.3%)	237 (58.2%)
Race			
White	35 (25.5%)	142 (52.6%)	177 (43.5%)
Black or African American	4 (2.9%)	7 (2.6%)	11 (2.7%)
Asian	83 (60.6%)	108 (40.0%)	191 (46.9%)
American Indian/Alaskan Native	1 (0.7%)	0 (0%)	1 (0.2%)
Native Hawaiian or Other Pacific Islander	1 (0.7%)	2 (0.7%)	3 (0.7%)
Other	2 (1.5%)	1 (0.4%)	3 (0.7%)

	TKI Naïve (N = 137)	TKI Pretreated (N = 270)	Overall (N = 407)
Missing	11 (8.0%)	10 (3.7%)	21 (5.2%)
Baseline ECOG performance score			
Fully active (0)	51 (37.2%)	90 (33.3%)	141 (34.6%)
Restricted (1)	86 (62.8%)	179 (66.3%)	265 (65.1%)
Missing	0 (0%)	1 (0.4%)	1 (0.2%)
Genetic mutations			
ALK	3 (2.2%)	27 (10.0%)	30 (7.4%)
NTRK	41 (29.9%)	46 (17.0%)	87 (21.4%)
ROS1	93 (67.9%)	197 (73.0%)	290 (71.3%)
Cancer type			
Brain tumor	0 (0%)	1 (0.4%)	1 (0.2%)
Breast cancer	2 (1.5%)	1 (0.4%)	3 (0.7%)
Cholangiocarcinoma	1 (0.7%)	1 (0.4%)	2 (0.5%)
Colorectal cancer	1 (0.7%)	2 (0.7%)	3 (0.7%)
Esophageal cancer	1 (0.7%)	0 (0%)	1 (0.2%)
Gallbladder cancer	0 (0%)	1 (0.4%)	1 (0.2%)
Gastric cancer	1 (0.7%)	0 (0%)	1 (0.2%)
Glioblastoma	2 (1.5%)	2 (0.7%)	4 (1.0%)
Head and neck cancer	1 (0.7%)	0 (0%)	1 (0.2%)
Inflammatory myofibroblastic tumor	0 (0%)	1 (0.4%)	1 (0.2%)
Isolated fibrous tumors	0 (0%)	1 (0.4%)	1 (0.2%)
Liver cancer	0 (0%)	1 (0.4%)	1 (0.2%)
Lung cancer, non-small cell	115 (83.9%)	234 (86.7%)	349 (85.7%)
Malignant peripheral nerve sheath tumor	0 (0%)	2 (0.7%)	2 (0.5%)
Melanoma	0 (0%)	1 (0.4%)	1 (0.2%)
Neuroendocrine tumor	0 (0%)	2 (0.7%)	2 (0.5%)
Pancreatic cancer	0 (0%)	2 (0.7%)	2 (0.5%)
Peripheral nerve sheath tumor	1 (0.7%)	0 (0%)	1 (0.2%)
Renal cell cancer	1 (0.7%)	1 (0.4%)	2 (0.5%)
Salivary gland cancer	3 (2.2%)	7 (2.6%)	10 (2.5%)
Soft tissue sarcoma	3 (2.2%)	4 (1.5%)	7 (1.7%)
Thyroid cancer	5 (3.6%)	4 (1.5%)	9 (2.2%)
Unknown primary cancer	0 (0%)	1 (0.4%)	1 (0.2%)
Uterine cancer	0 (0%)	1 (0.4%)	1 (0.2%)
Fasting status steady state			
Fasted	0 (0%)	0 (0%)	0 (0%)
Fed	5 (3.6%)	16 (5.9%)	21 (5.2%)
Modified fasted	19 (13.9%)	52 (19.3%)	71 (17.4%)
Unknown	113 (82.5%)	202 (74.8%)	315 (77.4%)

Abbreviations: ALK = anaplastic lymphoma kinase; CV% = coefficient of variation percentage; E-R = exposure-response; ECOG = Eastern Cooperative Oncology Group; Gmean = geometric mean; GCV% = coefficient of variation percentage of Gmean;

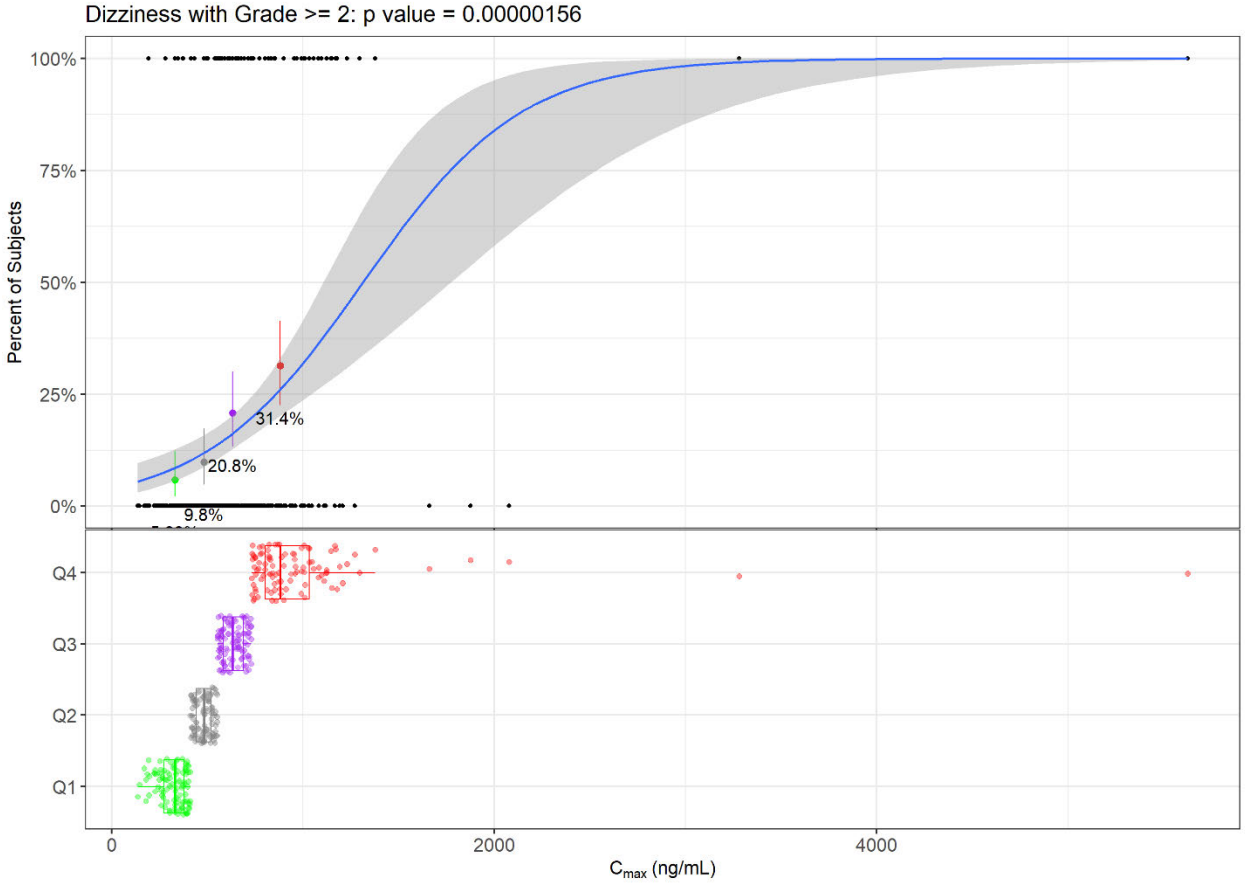
max = maximum; min = minimum; N = number of subjects; NTRK = neurotrophin receptor kinase; ROS1 = receptor tyrosine kinase encoded by the ROS1 gene; TKI = tyrosine kinase inhibitor.
Note: Percentages are calculated based on the total per column based on pretreatment status.
Source: Report 00534 Table 37

Table 78. Final E-R Model Parameter Estimates for Grade ≥ 2 Dizziness

Parameter	Estimate (Standard Error)	95% Confidence Interval	Odds Ratio (Standard Error)	95% Confidence Interval for Odds Ratio	p-Value
(Intercept)	-6.58 (0.870)	-8.38, -4.96	-	-	3.94E-14
C_{max}	0.00221 (0.000505)	0.00126, 0.00324	1.0022 (0.00050612)	1.0013, 1.0032	0.0000122
Age	0.0608 (0.0130)	0.0363, 0.0873	1.0627 (0.013815)	1.0370, 1.0912	0.00000278

Abbreviations: C_{max} = maximum plasma concentration-time; E-R = exposure-response.
Note: The p-value is based on the Wald statistics.
Source: Report 00534 Table 42

Figure 16. Univariate Logistic Regression Plots for the Probability of Grade ≥ 2 Dizziness Versus Repotrectinib C_{max}



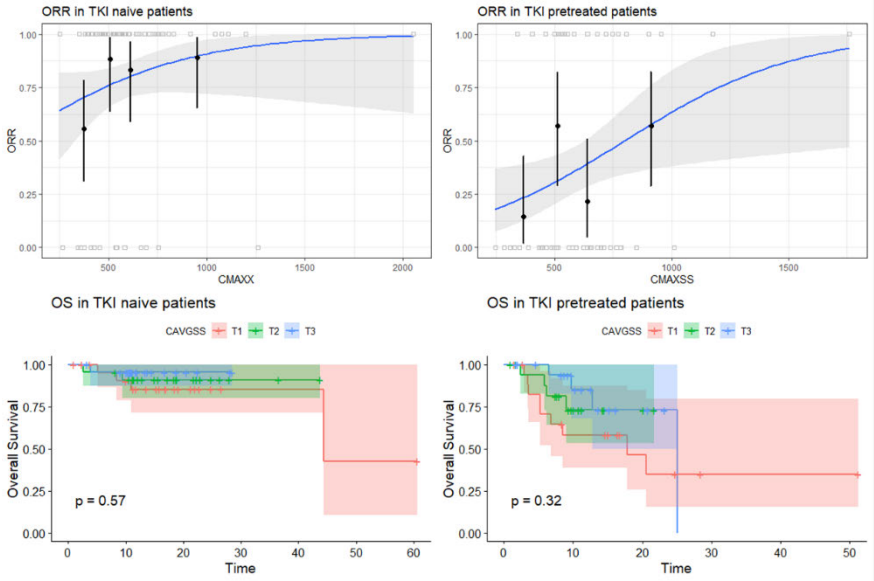
Abbreviations: AE = adverse event; CI = confidence interval; C_{max} = maximum plasma concentration; E-R = exposure-response.
Note: The independent variables were divided into 4 equally sized, rank-ordered groups. Colored points (green, gray, purple, and red) and error bars represent the observed proportions for each quartile and the 95% CIs for each exposure group (plotted at the

mean exposure within each exposure group), respectively. The blue curve represents the prediction of the univariate logistic regression model, and the gray shaded region represents the 95% CI of the prediction.
Percentages in the upper part of the graph represent the proportion of subjects in each exposure group who experienced the AE. The displayed p-value is the p-value for the E-R slope.
Source: Report 00534 Figure 30

The FDA's Assessment:

E-R efficacy analyses in *ROS1*+ NSCLC patients from study TRIDENT-1 were performed by the reviewer. Statistically positive relationships were found between ORR and OS with repotrectinib exposures in the pooled dataset of TKI-naïve and TKI pretreated ROS1+ NSCLC patients. Better responses and longer survival time were also observed in TKI-naïve patients comparing to TKI-pretreated patients. Positive relationships were still observed for efficacy endpoints (ORR and OS) with repotrectinib exposures in TKI-naïve patients or TKI-pretreated patients separately. However, the positive exposure-efficacy relationship should be interpreted with caution as more than 90% of the data was from a single dose level. As stated in Section 8.1, time-to-event endpoints are difficult to interpret in single arm trials, and therefore the results of E-R efficacy analyses with OS results should be interpreted with caution.

Figure 17. Plots of E-R Relationships Between ORR, OS With Repotrectinib Exposures in TKI-Naïve and TKI-Pretreated ROS1+ NSCLC Patients



Source: Reviewer's analysis based on dataset "eff.xpt".

E-R safety analysis in patients with advanced solid tumor were checked by the reviewer. The results were generally acceptable. Positive E-R relationships were observed for 11 safety endpoints including dizziness, headache, muscular weakness, ataxia, AST increased, ALT increased, paresthesia, anemia, constipation, dysgeusia, and dizziness. However, there was no statistically significant relationship between exposure and Grade ≥ 3 TEAEs, nausea, fatigue and dyspnea. E-R analysis for grade ≥ 2 dizziness showed that higher C_{max} or age is associated with

an increased probability of grade ≥ 2 dizziness. Model predicted probability of grade ≥ 2 dizziness by dose level were shown in Table 79 and Figure 18.

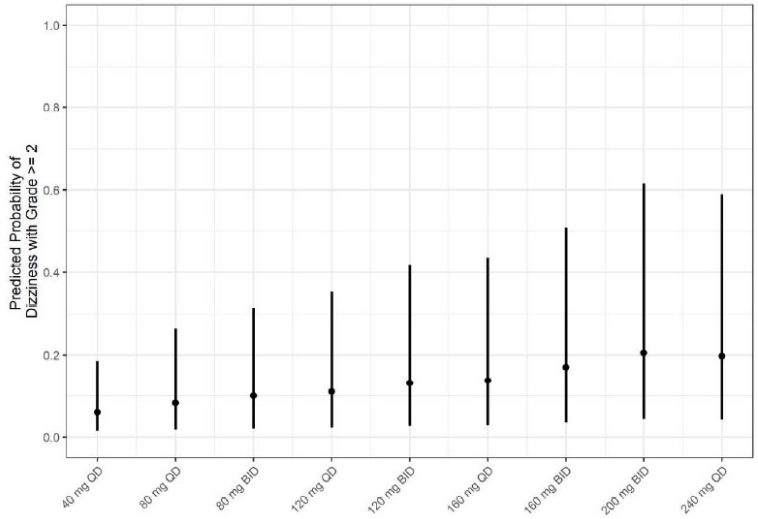
Table 79. Model-Predicted Probability of Grade ≥ 2 Dizziness by Dose Level Based on $C_{max,ss}$ Without Regard to Food

Model-Predicted Probability	40 mg QD (N = 407)	80 mg QD (N = 407)	80 mg BID (N = 407)	120 mg QD (N = 407)	120 mg BID (N = 407)	160 mg QD (N = 407)	160 mg BID (N = 407)	200 mg BID (N = 407)	240 mg QD (N = 407)
Mean (SD)	0.0756 (0.0590)	0.106 (0.0874)	0.126 (0.109)	0.138 (0.113)	0.169 (0.138)	0.172 (0.138)	0.213 (0.165)	0.257 (0.190)	0.243 (0.182)
Median [min, max]	0.0600 [0.00639, 0.554]	0.0825 [0.00825, 0.890]	0.100 [0.0103, 0.996]	0.110 [0.0103, 0.977]	0.132 [0.0136, 1.00]	0.138 [0.0127, 0.995]	0.171 [0.0167, 1.00]	0.206 [0.0198, 1.00]	0.198 [0.0183, 1.00]
[5th %tile, 95th %tile]	(0.0152, 0.186)	(0.0185, 0.264)	(0.0205, 0.314)	(0.0231, 0.354)	(0.0273, 0.417)	(0.0284, 0.434)	(0.0352, 0.509)	(0.0437, 0.616)	(0.0410, 0.590)
[25th %tile, 75th %tile]	(0.0344, 0.102)	(0.0460, 0.141)	(0.0534, 0.164)	(0.0578, 0.183)	(0.0703, 0.225)	(0.0715, 0.232)	(0.0903, 0.289)	(0.110, 0.356)	(0.105, 0.339)

Source: TPTI-PMX-TPX0005-3158-ER-Binary-Safety-Version-12.html
Abbreviations: %tile=percentile; BID=twice daily; C_{max}=maximum plasma concentration; max=maximum; min=minimum; N=number of subjects; QD=once daily; SD=standard deviation

Source: Applicant's E-R analysis report 00534, Page 94, Table 45.

Figure 18. Model-Predicted Probability of Grade ≥ 2 Dizziness by Dose Level Based on $C_{max,ss}$ Without Regard to Food



Source: Applicant's E-R analysis report 00534, Page 94, Figure 34.

19.4.3.5. Overall Benefit-Risk Evaluation Based on E-R Analyses

The Applicant's Position:

In summary, the E-R safety and efficacy simulations demonstrated that the proposed clinical dose regimen of 160 mg QD/BID achieved maximal ORR with low incidence rate of grade ≥ 2 dizziness. Taking into consideration the overall benefit/risk assessment, the

cumulative data support the dose regimen of repotrectinib 160 mg orally QD for 14 days, then increase to 160 mg BID as the optimal dose for adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.

The FDA's Assessment:

The proposed dose was supported by the efficacy and safety data from the pivotal trial. Positive trends were observed for efficacy endpoints (ORR and OS) in patients with ROS1+ NSCLC and 11 safety endpoints including dizziness, headache, muscular weakness, ataxia, AST increased, ALT increased, paresthesia, anemia, constipation, dysgeusia, and dizziness in patients with advanced solid tumors. However, the positive exposure-efficacy relationship should be interpreted with caution as more than 90% of the data was from a single dose level.

19.4.4. Physiologically Based Pharmacokinetic Modeling Analyses

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's following PBPK report to support the intended uses: "Development of a PBPK model for repotrectinib with the Simcyp population-based simulator and subsequent evaluation of DDI liability as a victim of CYP and P-gp-mediated interactions and as a perpetrator of CYP-mediated interactions".

The Division of Pharmacometrics has reviewed the PBPK report, supporting modeling files and the Applicant's responses to FDA's information requests (IR) submitted on Aug 21st, 2023, to conclude the followings:

- The repotrectinib PBPK model (b) (4)
- The repotrectinib PBPK model is inadequate to predict (b) (4)
- The repotrectinib PBPK model is inadequate (b) (4) .

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(b) (4)

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Please refer to Section 8.2 for FDA's safety analyses.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Stephanie Aungst, PhD	CDER/OOD/DHOT	Sections: 5	Select one: ___x Authored x Approved
	Signature: Stephanie L. Aungst -S Digitally signed by Stephanie L. Aungst -S Date: 2023.11.13 12:45:02 -05'00'			
Nonclinical Supervisor	Claudia P. Miller, PhD	CDER/OOD/DHOT	Sections: 5	Select one: x Authored x Approved
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Nonclinical Division Director (NME only)	John K. Leighton, PhD	CDER/OOD/DHOT	Sections: 5	Select one: ___ Authored X Approved
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Clinical Pharmacology Reviewer	Lili Pan, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: _X Authored ____Approved
	Signature: Lili Pan -S Digitally signed by Lili Pan -S Date: 2023.11.13 13:57:44 -05'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: X Authored X Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2023.11.13 14:03:33 -05'00'			
Division of Pharmacometrics (DPM) Reviewer	Yangbing Li, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4.2, 19.4.3	Select one: _X_ Authored Approved
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Division of Pharmacometrics (DPM) Team Leader	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4.2, 19.4.3	**Select one:** _X_ Authored _X_ Approved
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Division of Pharmacometrics (DPM) PBPK Reviewer	Jianghong Fan, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4.4	**Select one:** _X_ Authored ___ Approved
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Division of Pharmacometrics (DPM) PBPK Scientific Leader	Manuela Grimstein, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4.4	**Select one:** _X_ Authored X Approved
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Genomics Reviewer/Team Leader	Sarah Dorff, PhD	CDER/DTPM/Genomics	Sections: 6	**Select one:** _X_ Authored _X_ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S Date: 2023.11.13 13:02:57 -05'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** __Authored X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2023.11.13 13:00:04 -05'00'			
Clinical Reviewer	Michael Barbato, MD	CDER/OOD/DO2	Sections: 1 – 4, 7 – 13, 19.2	**Select one:** _X_ Authored ___ Approved
	Signature: Michael I. Barbato -S Digitally signed by Michael I. Barbato -S Date: 2023.11.13 13:51:13 -05'00'			
Clinical Team Leader	Diana Bradford, MD	CDER/OOD/DO2	Sections: see CTDL	**Select one:** ___ Authored _____ Approved
	Signature: see CDTL signature			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Yi Ren	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** x Authored ___ Approved
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Statistical Team Leader	Anup Amatya, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** ___ Authored x Approved
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Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OOD	Sections: 11	**Select one:** x Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2023.11.13 11:54:47 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Diana Bradford, MD	CDER/OOD/DO2	Sections: All	**Select one:** X Authored X Approved
	Signature: See DARRTS signature			
Deputy Director (Clinical)	Nicole Drezner, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored X Approved
	Signature: See DARRTS signature			

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/s/

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