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)	218550
Priority or Standard	Priority
Submit Date(s)	April 28, 2023
Received Date(s)	April 28, 2023
PDUFA Goal Date	October 18, 2023
Division/Office	Division of Oncology 2/CDER
Review Completion Date	See Electronic Date
Established Name	Entrectinib
(Proposed) Trade Name	Rozlytrek
Pharmacologic Class	Kinase inhibitor
Code name	R071021222; formerly known as RXDX-101 and NMS-1191372
Applicant	Genentech, Inc.
Formulation(s)	Oral capsule, 100 mg and 200 mg Oral Pellets 50 mg per packet
Dosing Regimen	Adult:600 mg orally once daily Pediatric: Recommended dosage is based on age and body surface area (BSA)
Applicant Proposed Indication(s)/Population(s)	Adult and pediatric patients greater than 1 month of age with solid tumors that: have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult and pediatric patients older than 1 month of age with solid tumors that:

	have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.

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1 Reviewers of Multi-Disciplinary Review and Evaluation

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

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OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

3 Glossary

ADME	absorption, distribution, metabolism, excretion
AEs	adverse events
AESIs	adverse events of special interest
BICR	blinded Independent Central Review
BLA	biologics license application
BOR	best overall response
PBPK	physiologically-based pharmacokinetic
CBR	clinical benefit rate
CCOD	clinical cutoff date
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CRF	case report form
CR	complete response
CSR	clinical study report
CYP	cytochrome P450
ECG	electrocardiogram
eCTD	electronic common technical document
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	intent to treat
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NGS	next-generation sequencing
NME	new molecular entity
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
OPQ	Office of Pharmaceutical Quality
OR	objective response
ORR	Objective Response Rate
OS	Overall Survival

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCR	polymerase chain reaction
PD	pharmacodynamics
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	proton pump inhibitor
PR	partial response
PRO	patient reported outcome
QD	once daily
QTc	corredted QT interval
REMS	risk evaluation and mitigation strategy
RT	reverse transcriptase
SAEs	serious adverse events
SD	stable disease
SOC	system organ class
TTR	time to confirmed response
TEAEs	treatment emergent adverse events
WASI-II	Wechsler Abbreviated Scale of Intelligence - Second Edition

4 Executive Summary

4.1. Product Introduction

Entrectinib (RO7102112; also referred to as RXDX-101 and as NMS-1191372) is an oral inhibitor of tropomyosin receptor kinases (TRKA, TRKB and TRKC; encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively). Entrectinib also inhibits the kinase activities of ROS proto-oncogene 1 receptor tyrosine kinase (encoded by the ROS1 gene) and anaplastic lymphoma kinase (ALK; encoded by the ALK gene).

On August 15, 2019, entrectinib was granted traditional approval for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive and accelerated approval in for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:

have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion as detected by an FDA-approved test without a known acquired mutation,
are metastatic or where surgical resection is likely to result in severe morbidity, and
have progressed following treatment or have no satisfactory alternative treatment

On April 28, 2023, Genentech submitted a new NDA for a new entrectinib formulation and a supplemental NDA to expand the NTRK fusion indication to (b) (4) Entrectinib is approved as a capsule formulation with 100 and 200 mg strengths; the new formulation is a pellet packet (50 mg/packet). Additionally, the entrectinib prescribing information was updated with instructions to prepare an oral suspension derived from the capsule.

The recommended dose of entrectinib for the treatment of adult and pediatric patients older than 1 month of age with solid tumors that have an NTRK gene fusion is:

• **Age**	• **Recommended Daily Dosage**
• >6 months	• ≤0.50 m^2: 300 mg/m^2 • 0.51 to 0.80 m^2: 200 mg • 0.81 to 1.10 m^2: 300 mg • 1.11 to 1.50 m^2: 400 mg • BSA ≥1.51 m^2: 600 mg once daily
• >1 month to ≤6 months	• 250 mg/m^2 once daily

4.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support the expansion of the currently approved indication for patients 12 years of age and older with solid tumors with an NTRK gene fusion to pediatric patients older than 1 month of age and has provided data to support the two new formulations including a pellet packet (50 mg/packet) and an oral suspension that is derived from the capsule.

This marketing application is primarily based on pooled efficacy results from 33 pediatric patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of two multicenter, open-label, single arm clinical trials: STARTRK-NG (NCT02650401) and TAPISTRY (NCT04589845). The major efficacy outcome measure was overall response rate (ORR) as assessed by per Blinded Independent Review Committee (BICR) according to RECIST v1.1 for extracranial tumors and according to Response Assessment in Neuro-Oncology (RANO) for primary central nervous system (CNS) tumors. An additional efficacy outcome measure was duration of response (DOR) as evaluated by BICR. The ORR in pediatric patients with solid tumors harboring *NTRK* gene fusions (n=33) was 70% (95% CI 51, 84) with a median duration of response (DOR) of 25.4 months (95% CI 14.3, not estimable [NE]). The ORR observed in the primary efficacy population was consistent with the ORR observed in patients greater than 12 year of age that supported the original accelerated approval [ORR 57% (95% confidence interval: 43, 71)].

The most common tumor types included in the primary efficacy population were primary CNS tumors (52%), infantile fibrosarcoma(24%), and other extracranial tumors (24%). Overall, 85% of patients received prior anti-cancer therapy. Durable responses were obsevered in patients with both CNS tumors and extracranial solid tumors.

In addition, an adequate scientific bridge has been established between the coated granule (pellet packet) and oral capsule formulations, and between the oral capsule administered as suspension, either orally or via gastric/nasogastric tube, compared to the intact oral capsule formulation.

The submitted evidence meets the statutory evidentiary standard for accelerated approval. An ORR of sufficient magnitude and duration is an endpoint reasonably likely to predict clinical benefit in patients with solid tumors with an NTRK gene fusion. The observed results are considered to be clinically meaningful when considering the intended patient population and are supported by the durable responses observed in patients greater than 12 years of age with solid tumors harboring NTRK gene fusions.

4.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Solid tumors with an activating neurotrophic receptor tyrosine *NTRK* rearrangement are a heterogenous group of cancers. NTRK gene fusions occur in approximately 0.3% of all solid tumors with variability depending on age and cancer type. The annual incidence of *NTRK* fusion-driven tumors is estimated to be 1500-5000 cases in the United States (U.S.). NTRK fusions are pathognomonic or common in some very rare cancers such as mammary analogue secretory carcinoma (MASC), secretory breast carcinoma (SBC), and infantile fibrosarcoma (IFS); for common adult cancers such as lung, prostate, and colon cancer the incidence of *NTRK* fusions is less than 1%. There are limited data regarding prognostic implications of *NTRK* fusions in solid tumors; rather, NTRK fusions are thought to be predictive biomarkers for targeted inhibition.

Entrectinib (RO7102112; also referred to as RXDX-101 and as NMS-1191372) is an oral inhibitor of tropomyosin receptor kinases (TRKA, TRKB and TRKC; encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively). Entrectinib also inhibits the kinase activities of ROS proto-oncogene 1 receptor tyrosine kinase (encoded by the *ROS1* gene) and anaplastic lymphoma kinase (ALK; encoded by the *ALK* gene).

Entrectinib was granted accelerated approval in April 2019 for adult and pediatric patients 12 years of age and older with solid tumors that: are neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion-positive without a known acquired mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have either progressed following treatment or have no satisfactory alternative treatment

This indication was approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication is contingent upon verification and description of clinical benefit in the confirmatory trials. There is one FDA approved drug for the treatment of adult and pediatric patients with solid tumors harboring an *NTRK* fusion (larotrectinib). There are no approved treatments for tumors that frequently harbor *NTRK* fusions (e.g. mammary analogue secretory carcinoma, SBC, and IFS). In some cases where resection is a potentially curative approach, surgery can result in unacceptable morbidity such as limb amputation (e.g., in some patients with IFS).

On April 28,2023, Genentech submitted data to support expanding the current indication for entrectinib to pediatric patients ≥ 1 month old. In addition to expanding the indication, Genentech also proposed two new formuations: a pellet packet (50 mg/packet) and an oral suspension that is derived from the capsule.

The primary efficacy analysis population for this review includes results from 33 pediatric patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of two multicenter, open-label, single arm clinical trials: STARTRK-NG (NCT02650401) and TAPISTRY (NCT04589845). The ORR was 70% (95% CI 51, 84) with a median duration of response (DOR) of 25.4 months (95% CI 14.3, not estimable [NE]). A total of 43% of responders had a response duration of ≥12 months.

Entrectinib appears to have an acceptable safety profile when assessed in the context of a life-threatening disease. The primary safety population includes pediatric patients ages 1 month to 18 years with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label clinical trials: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2). The most common (≥20%) treatment-emergent adverse events (TEAEs) were pyrexia, constipation, increased weight, vomiting, diarrhea, nausea, cough, fatigue, pain in extremity, skeletal fractures, decreased appetite, headache, abdominal pain, urinary tract infection, upper respiratory tract infection, and nasal congestion.

The most common (≥20%) Grade 3 or 4 laboratory abnormalities were increased creatinine, increased aspartate aminotransferase (AST) decreased neutrophils, decreased hemoglobin, increased alanine aminotransferase (ALT), decreased leukocytes, increased sodium, increased lymphocytes, increased magnesium,increased glucose,increased potassium, increased alkaline phosphatase, decreased albumin, increased calcium, increased bilirubin.

Entrectinib increases the risk of skeletal fractures which is described in the Warnings and Precautions section of the U.S. prescribing information (USPI). A postmarketing requirement (PMR) was issued at the time of the original accelerated approval to further assess the risk of fractures with entrectinib. An updated analysis was includeded in this NDA submission which included data from an expanded safety population of 338 adult patients and 76 pediatric patient who received entrectinib across clinical trials. Section 5 has been updated to include these data which showed an increase in fractures in pediatric patients compared to the original approval (5% of adult patients and 25% of pediatric patients with fractures vs. 5% of adult patients and 23 % of pediatric patients with fractures).

Significant safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during the review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

According to FDA's review, an adequate scientific bridge has been established between the coated granule (pellet packet) and oral capsule formulations, and between the oral capsule administered as suspension, either orally or via gastric/nasogastric tube, compared to the intact oral capsule formulation.

Based on the favorable risk-benefit assessment for this population with a serious, life-threatening disease, and in the context of the durable reponses observed in patients 12 years of age and older with NRTK gene fusions, the review team recommends extending the current indication under accelerated approval to pediatric patients ages ≥ 1 month to < 12 years. The review teams also recommend approval of the pellet formulation.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Solid tumors with NTRK fusions are a heterogenous group of tumors and the incidence of NTRK fusions is not fully characterized, but rare (<1 % for common solid tumors); however, NTRK fusions are pathonomonic for some very rare cancers such as mammary analogue secretory carcinoma (MASC), secretory breast carcinoma (SBC), or infantile fibrosarcoma (IFS). • *NTRK* fusion-positive tumors prevalence varies by age and cancer type; 0.28% in adults (aged ≥18 years) and 1.34% in pediatric patients (aged <18 years). Prevalence increases with decreasing age, with children <5 years demonstrating the highest incidence of 2.28% • When metastatic or unresectable, solid tumors are rarely curable and generally convey a poor prognosis.	NTRK fusion-positive solid tumors that are refractory to available therapy or that have no satisfactory treatment options are life threatening.
Current Treatment Options	• Treatment options are limited for adult and pediatric patients with unresectable locally advanced or metastatic solid tumors who have no satisfactory alternative treatment options or whose cancer has progressed following treatment.	Although standard treatment regimens exist for most patients with locally advanced or metastatic solid tumor malignancies, such treatment generally is not curative and additional treatment options are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Larotrectinib was granted accelerated approval in 2018 for the treatment of adult and pediatric patients with solid tumors with an NTRK fusion; this approval includes patients < 12 years of age.	There is an unmet medical need for pediatric patients with metastatic or unresectable NTRK-fusion solid tumors that have no satisfactory treatment options or progressed following treatment.
Benefit	• The efficacy of entrectinib for patients ≥ 1 month to < 12 years of age is primarily based on pooled efficacy results from 33 pediatric patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of two multicenter, open-label, single arm clinical trials: STARTRK-NG (NCT02650401) and TAPISTRY (NCT04589845). • The ORR observed in the primary efficacy population (n=33) was 70% (95% CI 51,84) with a median duration of response (DOR) of 25.4 months (95% CI 14.3, NE). • Durable response were observed across several tumor types where the majority progressed after prior therpay (e.g. CNS tumors, infantile fibrosarcoma, etc.)	The magnitude and duration of responses observed in pediatric patients enrolled in STARTRK-NG (NCT02650401) and TAPISTRY (NCT04589845), in the context of durable reponses in patients 12 years of age and older, provide evidence of a clinically meaningful benefit of entrectinib in pediatric patients older than one month of age to less than 12 years of age with NTRK solid tumors. A postmarketing requirement will be issued for additional clinical studies or data to verify the clinical benefit for this pediatric patient population.
Risk and Risk Management	• The primary safety population included pediatric patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label clinical trials: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2). • Serious adverse reactions occurred in 45% of patients who received ROZLYTREK. Serious adverse reactions in > 2% of patients included skeletal	Although entrectinb 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	fractures (12%), pneumonia (5%), pyrexia (5%), hydrocephalus (5%), device related infection (4%), hypoxia (4%), dyspnea (3%), headache (3%), gait disturbance (3%), pain (3%), upper respiratory infection (3%), and sepsis (3%). • The most common (≥20%) treatment-emergent adverse events (TEAEs) were pyrexia, constipation, increased weight, vomiting, diarrhea, nausea, cough, fatigue, pain in extremity, skeletal fractures, decreased appetite, headache, abdominal pain, urinary tract infection, upper respiratory tract infection, and nasal congestion. • The most common (≥20%) Grade 3 or 4 laboratory abnormalities were increased creatinine, increased aspartate aminotransferase (AST) decreased neutrophils, decreased hemoglobin, increased alanine aminotransferase (ALT), decreased leukocytes, increased sodium, increased lymphocytes, increased magnesium,increased glucose,increased potassium, increased alkaline phosphatase, decreased albumin, increased calcium, increased bilirubin. • Entrectinib also increases the risk of skeletal fractures. In an expanded safety population of 338 adult patients and 76 pediatric patients who received entrectinib across clinical trials, 5% of adult patients and 25% of pediatric patients experienced fractures.	A postmarketing requirement was issued at the time of the original accelerated approval for the NTRK indication to further assess the risk of fractures with entrectinib. Entrectinib will be prescribed by oncologists who are comfortable monitoring, identifying, and managing the toxicities described in the USPI. There were no significant safety concerns identified during this review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitgation Strategy (REMS).

4.4. Patient Experience Data

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

X	The patient experience data that was submitted as part of the application, include:							Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as						[e.g., Section 6.1 Study endpoints]
			X	Patient reported outcome (PRO)				Section 8.2.6, Neurocognitive assessments. This information was not included in labeling.
			□	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						[e.g., Section 2.1 Analysis of Condition]
	□	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

Amy Barone, MD
Cross-Disciplinary Team Leader

5 Therapeutic Context

5.1. Analysis of Condition

The Applicant's Position:

The neurotrophic tyrosine receptor kinase (NTRK) family of genes *NTRK1*, *NTRK2* and *NTRK3* encode TRKA, TRKB and TRKC, respectively. TRK family members are transmembrane proteins serving as high affinity signal transducing receptors for neurotrophins. Binding of neurotrophins to their cognate TRK receptors results in homodimerization, receptor autophosphorylation and activation of downstream signal transduction pathways involved in cell proliferation, apoptosis, and survival of neurons and other cell types.

NTRK gene alterations have been implicated in the pathogenesis of many cancer types. Chromosomal rearrangements resulting in oncogenic gene fusions were the first and the best-characterized *NTRK* gene aberrations to be described (Khotskaya et al. 2017). *NTRK* gene fusions arise from intra- or inter-chromosomal rearrangements that juxtapose 3' *NTRK* gene sequences encoding the catalytic tyrosine kinase domain in-frame with various 5' partner gene sequences. The transcribed chimeric TRK proteins have been shown to be oncogenic, promoting tumorigenesis by constitutive ligand-independent kinase activation leading to tumor cell proliferation, differentiation, and/or apoptosis.

NTRK fusions have been found in at least 45 different cancers (Westphalen et al. 2021). Studies conducted by the Applicant (entrectinib Investigator Brochure v11.0) and preclinical data published in the literature (Lee et al. 2015; Ardini et al. 2016) demonstrate that, regardless of the fusion partner or the tissue of origin, rearranged *NTRK* genes with an intact kinase domain result in a constitutively active kinase and are oncogenic drivers, providing the driving force for transformation and tumor progression. In addition, *NTRK* fusions tend to be mutually exclusive from other actionable targets, such as *ALK, ROS1, HER2, BRAF* or growth factor receptor (*EGFR)*.

In children, the prevalence of *NTRK* fusions is high (>90%) in certain tumors such as infantile fibrosarcoma, congenital mesoblastic nephroma, and secretory carcinoma, and lower (5%–26%) in pediatric papillary thyroid carcinomas and in a subset of pediatric gliomas. *NTRK* fusions are rarely identified in gastrointestinal stromal tumors, melanoma, lung adenocarcinoma, acute leukemia, and soft tissue sarcomas with a range of histologic morphologies (Zhao et al. 2021).

At the time of the initial entrectinib marketing authorization application in 2019, based on next-generation sequencing (NGS) profiling of 116,398 adult and pediatric tumor samples using the [redacted](b) (4) NGS platform, *NTRK* fusions were estimated to be prevalent in 0.32% solid tumors (FoundationCORE database, Q1 2019 data cut). The prevalence remains consistent

in recently published data from the same but now larger FoundationCORE database, wherein NGS profiling of 295,676 patient samples identified *NTRK* gene fusions in 889 of those samples (prevalence of 0.30%) (Westphalen et al. 2021). These data are comparable with estimates of the prevalence of *NTRK* fusions by genomic profiling reported in the literature using high-throughput NGS on tumors from a large and broad cohort of cancer patients (0.25% [MSK-IMPACT assay], Zehir et al. 2017) and also specifically for pediatric/adolescent patients (0.44%, Pavlick et al. 2017; 0.49%, Chmielecki et al. 2017).

The FDA's Assessment:
FDA agrees with the Applicants statement above. NTRK gene fusions occur in approximately 0.3% of all solid tumors, however this varies based on age and cancer type. There is a slightly higher prevalence in certain pediatric cancers where NTRK fusions are pathognomonic (e.g. infantile fibrosarcoma).

5.2. Analysis of Current Treatment Options

The Applicant's Position:
At the time that the entrectinib development program was initiated, there were no approved therapies specifically targeting NTRK fusion-positive tumors. Since that time, the TRK inhibitor, VITRAKVI, was approved under accelerated approval by the FDA for treatment of NTRK fusion-positive tumors in adult and pediatric patients. Entrectinib has also been approved under accelerated approval by the FDA for treatment of NTRK fusion-positive tumors in adult and pediatric patients ≥12 years of age.

While adult and pediatric patients with relapsed or refractory NTRK fusion-positive solid tumors are rare, the pediatric population represents one with targetable disease for which there are limited approved targeted therapies currently available for patients <12 years. It is evident that molecular targeted anti-neoplastic therapies offer the possibility of greater efficacy with less toxicity relative to traditional cytotoxic chemotherapy, particularly when administered in the context of a genomic alteration predicting sensitivity to such an agent. In addition, central nervous system (CNS) tumors, either metastatic or primary, are often ineffectively treated by traditional treatment options, whereas molecularly targeted CNS active treatment options would be able to address this unmet need. Furthermore, treatment options that are currently used beyond first line treatment for patients with NTRK fusion-positive solid tumors are generally not effective for the majority of patients and can be associated with notable toxicity. Thus, there is a clear unmet medical need for patients with these rare cancers harboring NTRK gene fusions.

The FDA's Assessment:

FDA agrees with the Applicant's position and that larotrectinib is the only targeted therapy FDA with accelerated approval for patients <12 years with NTRK fusion positive solid tumors.

6 Regulatory Background

6.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Rozlytrek was granted marketing approval in the US on 15 August 2019 for the treatment of adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test. In addition, Rozlytrek was approved for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that:
have a NTRK gene fusion, as detected by an FDA-approved test, without a known acquired resistance mutation,
are metastatic or where surgical resection is likely to result in severe morbidity, and
have either progressed following treatment or have no satisfactory alternative therapy.

The FDA's Assessment:

FDA agrees.

6.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

An overview of the key regulatory milestones and FDA interactions relevant are provided in Table 1 below.

Table 1 Key FDA Interactions relevant to Entrectinib

Date	Type of Correspondence	Key Outcomes	Reference
12 May 2017	Breakthrough Therapy Designation	Granted for NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies.	IND 120500 Ref ID: 4097609
5 July 2017	Orphan Drug Designation	Granted for NTRK fusion-positive solid tumors.	ODD 17-5871
12 June 2018	IND transfer from Ignyta to GNE	Initial IND submitted by Ignyta, Inc. on 26 Feb 2014.	IND 120500
15 Aug 2019	Accelerated Approval	ROZLYTREK granted FDA approval	NDA 212726 Serial No. 0001 Ref ID: 4492065
			(b) (4)

Date	Type of Correspondence	Key Outcomes	Reference
2 May 2022	Type B Pre-NDA Meeting (DO3)	Meeting to discuss the proposed sNDA for the treatment of NTRK pediatric solid tumors and the acceptability of the pediatric formulation. Key feedback: FDA agreed that the proposed pediatric sample size and associated follow-up that would be available at the August 2022 CCOD could be sufficient to characterize patients with NTRK fusion-positive tumors enrolled in STARTRK-NG and TAPISTRY. FDA encouraged the Sponsor to schedule a pre-submission meeting when topline data become available. FDA agreed the revised sample size is adequate to support a claim for (b) (4) provided the risk/benefit is favorable. FDA agreed that the Artificial Intelligence systems biology and in vitro study results could be supportive along with available data on bone fractures provided at the time of filing the sNDA. FDA requested updated PopPK and PBPK modeling and exposure-response analysis with all available data to support the proposed dose recommendations for patients ⩾12 years, 6 months to <12 years, and 1 month to <6 months. FDA requested a tabular display summarizing patient age, BSA, planned dose, actual dose, formulations used, formulation switch time, PK exposures (observed and predicted), efficacy results, tumor types, and whether or not the patient was efficacy evaluable (responders versus non-responders) from all 3 studies to be included in the dossier. FDA recommended evaluating all potential mechanisms that could explain the low exposure observed in patients <6 months old. FDA acknowledged the in vitro bridging strategy between the available capsules and age-appropriate formulation is acceptable, provided that the in vitro dissolution data comparing coated granules (b) (4) and coated granules (b) (4) are considered adequate and acceptable.	IND 120500 PMP Serial No. 0311 Minutes Ref ID: 4990533

The FDA's Assessment:

FDA agrees with the summary of regulatory interactions provided by the Applicant.

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

7.1. Office of Scientific Investigations (OSI)

Clinical data from Study CO40778 (STARTRK-NG) and Study BO41932 (TAPISTRY) were submitted to the Agency in support of New Drug Application (NDA 218550) for entrectinib for the treatment of adults (b) (4) with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have a progressed following treatment or have no satisfactory alternative therapy. One clinical investigator, Dr. Amar Gajjar (site # 19045), and the imaging Contract Research Organization (CRO) (b) (4) were inspected.

Inspections of Dr. Gajjar and (b) (4) revealed no discrepancies, regulatory violations or GCP non-compliance. Based on these inspections, Study CO40778 (STARTRK-NG) appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO for both Studies CO40778 and BO41932 appear acceptable in support of the proposed indication.

7.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) did not identify any product quality issues that would preclude approval of entrectinib pellets under NDA 218550.
The drug product is coated entrectinib granules of 50 mg strength. The coated entrectinib pellet drug product consists of brownish orange or greyish orange, approximately 2 mm round (b) (4) granules filled into a stickpack1 for oral administration.
The Applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. The applicant adequately justified performing most release testing (b) (4) All associated manufacturing, testing, packaging facilities were deemed acceptable. However, the Applicant's prediction of fasted bioequivalence (BE) between the oral pellets and oral capsules could not be verified via a modeling approach. Overall, based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends approval of NDA 218550 for Rozlytrek (Entrectinib) Oral Pellets 50 mg. See Integrated Quality Review for full detail.

7.3. Clinical Microbiology

Not applicable for this application.

7.4. Devices and Companion Diagnostic Issues

Not applicable for this application.

8 Nonclinical Pharmacology/Toxicology

8.1. Executive Summary

Entrectinib is a small molecule inhibitor of the tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC (encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes NTRK1, NTRK2, and NTRK3, respectively), proto-oncogene tyrosine-protein kinase ROS1 (ROS1), and anaplastic lymphoma kinase (ALK). The established pharmacological class for entrectinib is kinase inhibitor. Entrectinib was approved under NDA 212725 for ROS1-positive nonsmall cell lung cancer (NSCLC) and NTRK-gene fusion positive solid tumors. Toxicology data for entrectinib can be found under the review for NDA 212726.

The Applicant provided 2 pharmacology studies evaluating entrectinib and its major metabolite (i.e. comprised ≥10% of parental AUC), M5, in an enzymatic kinase assay and an antiproliferative cellular assay. Entrectinib and M5 inhibited a TRK receptors and ROS1 with IC_{50} values ranging from 0.02 to 1.4 nM. In Ba/F3 cells expressing 29 novel fusion events that were idetnfied in patients from the pivotal entrectinib clinical trials ALKA-372-001, STRTRK-1, STARTRK-2, and STARTRK-NG (Study 1114447), entrectinib and M5 showed antiproliferative activity in the nanomolar range (IC_{50}s of 2-207 nM). In vivo, treatment of mice bearing subcutaneous tumors with entrectinib at 5 mg/kg twice daily showed the highest exposure to both entrectinib and M5 in tumor tissue, followed by plasma, and then brain.
In a GLP-compliant bacterial reverse mutation assay, the impurity (b) (4) was considered negative for genotoxicity in this assay.

The Applicant is attempting to determine the mechanism of action of entrectinib-induced skeletal fractures observed in treated patients. In an in vitro bone metabolism assay using juvenile and adult bone models, physiologically relevant concentrations of entrectinib and M5 (10-1000 nM) dose-dependently decreased osteoblast function and stimulated osteoclastogenesis in both models. Alkaline phosphatase (ALP) activity, a marker for early osteogenesis, and formation of mineralized matrix, decreased with entrectininb or M5 treatment; however, additional osteoblastic markers (osteocalcin, procollagen type I N-propeptide [PINP]) were not significantly changed.

There were no proposed labeling changes to nonclinical sections of the label. The nonclinical team recommends approval.

8.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

The Applicant refers to the original entrectinib NDA 212726.

The FDA's Assessment:

FDA agrees.

8.3. Pharmacology

The Applicant's Position:

Primary pharmacology

The key results of studies 1107096 and 1114447 are presented below. For details on study 1096000 (entrectinib binding site analysis in TRK1–3, ALK, and ROS1), refer to Module 2.4 Nonclinical Overview Addendum and Module 4.2.1.1.

Table 2 Summary of IC_{50} Values for Kinase Activity Inhibition by Entrectinib and M5

	Compound IC_{50} (nM)	
Kinase	**Entrectinib**	**M5**
TRKA	3.6	7.0
TRKB	0.008	0.05
TRKC	0.007	0.007
ROS/ROS1	0.05	0.25
TXK	0.51	0.7
MUSK	4.3	8.9
JAK2	5.4	14.2
FMS	6.5	18.3
TYK1/LTK	10.3	16.7
ACK1	22	39.5
ITK	104	170

IC_{50}=50% inhibitory concentration.

Notes: The kinase inhibition potency of entrectinib and M5 was tested in biochemical assays in 10-dose IC_{50} duplicate mode with a 3-fold serial dilution starting at 10 μM. Reactions were carried out at Km ATP according to the Reaction Biology Corporation Km binning structure.

Source: 1107096, Module 4.2.1.1 Primary Pharmacodynamics

Table 3 Response of Ba/F3-NTRK Fusions Cell Lines to Entrectinib and the Entrectinib M5 Metabolite

Cell Line	Growth without mIL-3	Entrectinib		M5	
		qIC_{50} (μM)	Mean Viability	qIC_{50} (μM)	Mean Viability
LMNA-NTRK1 (Ignyta)	+	0.044	0.632	0.05	0.646
LMNA-NTRK1 G595R (Ignyta)	+	1	0.962	1	0.95
LMNA-NTRK1 G667A (Ignyta)	+	0.017	0.546	0.024	0.577
LMNA-NTRK1 G667S (Ignyta)	+	0.158	0.785	0.201	0.777
AKAP13ex36-NTRK3ex11	+	0.002	0.373	0.006	0.443
CD74ex4-NTRK1ex11	+	0.005	0.432	0.012	0.504
CGNex14-NTRK1ex11	+	0.032	0.597	0.106	0.715
EPS15Lex16-NTRK1ex11	+	0.033	0.591	0.075	0.697
EPS15Lex16-NTRK1ex11	+	0.025	0.586	0.058	0.674
ERC1ex16-NTRK1ex11	+	0.026	0.581	0.094	0.709
ETV6ex4-NTRK3-204ex14	+	0.005	0.404	0.01	0.471
ETV6ex4-NTRK3ex14	+	0.082	0.703	0.188	0.777
ETV6ex5-NTRK3ex15	+	0.065	0.645	0.147	0.746
FAM19A2ex2-NTRK3ex15	failed	ND	ND	ND	ND
KIF5Bex24_NTRK1ex10	+	0.016	0.542	0.025	0.571
KIF7ex19-NTRK3ex14	+	0.022	0.566	0.024	0.583
PDIA3ex11-NTRK1ex2	poor	1.408	0.850	1.172	0.825
Pear1Ex15-NTRK1ex10	poor	0.509	0.826	0.662	0.849
Pear1ex20-NTRK1ex10	+	0.023	0.579	0.065	0.638
RBPMSex5-NTRK3-204ex15	poor	0.365	0.877	0.576	0.893
SCAPERex7_NTRK3ex15	failed	ND	ND	ND	ND
SCAPERex7_NTRK3ex15	+	0.022	0.608	0.027	0.597
SPECC1Lex6-NTRK3ex12	+	0.057	0.684	0.207	0.783
SQSTM1ex4-NTRK2ex16	+	0.032	0.573	0.084	0.687
SQSTM1ex5_NTRK1ex10	+	0.017	0.566	0.029	0.593
SQSTM1ex5_NTRK2ex15	poor	1.000	0.964	1.000	0.975
SQSTM1ex6_NTRK1ex10	+	0.006	0.433	0.012	0.486
TPM3ex8-NTRK1ex10	+	0.018	0.574	0.058	0.679
TPRex12-NTRK1ex12	failed	ND	ND	ND	ND
TPRex21_NTRK1ex14	poor	1.000	0.947	1.000	0.960

Cell Line	Growth without mIL-3	Entrectinib		M5	
		qIC_{50} (μM)	Mean Viability	qIC_{50} (μM)	Mean Viability
TPRex21_NTRK1ex9	+	0.009	0.49	0.023	0.574
TPRex21-NTRK1ex10	+	0.035	0.628	0.058	0.714
TRIM33ex12-NTRK1ex12	poor	0.477	0.715	0.616	0.728

mIL-3=murine interleukin 3; ND=not determined; qIC_{50}=50% inhibitory concentration.

Notes: Ba/F3 stable mouse pro-B cell lines expressing novel *NTRK* gene fusions identified in patients from the pivotal entrectinib clinical trials (ALKA-372-001, STARTRK-1, STARTRK-2, and STARTRK-NG) were generated. The Ba/F3 cell-screening platform relies on the dependence of cells on exogenous mIL-3 in the media. If novel gene fusions are capable of driving growth in the absence of mIL-3, this is consistent with oncogenic potential and enables testing of therapeutics for response. Ba/F3 cell lines harboring the *LMNA-NTRK1* or *LMNA-NTRK1 G667A* gene fusions were used as positive control and Ba/F3 cell lines harboring the *LMNA-NTRK1 G595R* or *LMNA-NTRK1 G667S* gene fusions were used as negative control.

Source: 1114447, Module 4.2.1.1 Primary Pharmacodynamics

The FDA's Assessment:

The FDA does not agree with the values in the Applicant's Table 2. With the exception of the IC_{50} values for entrectinib and M5 for 3 kinases (ACK1, TYK/LTK, MUSK) and the IC_{50} values for M5 for 2 additional kinases (TXK, ITK) different calculations were obtained based on the data provided in Study 1107096, IC_{50} Summary Table (pg 8 of study report). FDA calculated values are listed in FDA - Table 4.

FDA - Table 4: IC_{50} values for kinase activity inhibition by entrectinib and its metabolite M5

Kinase	Compound IC_{50} (nM)	
	Entrectinib	M5
TRKA	0.92	1.4
TRKB	0.019	0.2
TRKC	<0.508**	<0.508**
ROS/ROS1	<0.508**	<0.508**
TXK	<0.508**	**0.7**
MUSK	**4.3**	**8.9**
JAK2	9.15	1.95
FMS	7.2	15.4
TYK1/LTK	**10.3**	**16.7**
ACK1	**22**	**39.5**

Kinase	Compound IC_{50} (nM)	
	Entrectinib	M5
ITK	90.7	**170**

IC_{50}=50% inhibitory concentration.
Source: 1107096 IC_{50} Summary Table Pg 8. Data1 + Data2 /2 = average IC_{50}
Highlighted cells contain a different IC_{50} than that reported by the Applicant in Applicant Table 2.
Bolded values are the same IC_{50} values as those reported by the Applicant in Applicant Table 2.
**The study report states that an IC_{50} value less than 0.508 nM is estimated based on the best curve fitting available without elaboration.

In general FDA agrees with the Applicant's Table 3. Investigators generated Ba/F3 cells expressing 29 novel fusion events that were identified in patients from the pivotal entrectinib clinical trials ALKA-372-001, STRTRK-1, STARTRK-2, and STARTRK-NG (Study 1114447). Gene fusions in Ba/F3 cells capable of driving growth in the absence of murine interleukin-3 (mIL-3) are considered to have ongogenic potential. Twenty out of 29 of the gene fusions drove oncogenesis in the absence of mIL-3 and responded to entrectinib (IC_{50}s of 2-82 nM) and it's metabolite M5 (IC_{50}s of 6-207 nM). Six cell lines showed poor growth in the absence of mIL-3 with IC_{50} values that ranged from 365 to 1.4 µM. Three cells with NTRK gene fusions failed to grow in the absence of mIL-3 potentially due to unsuccessful expression in Ba/F3 cells. In general, entrectinib and its metabolite M5 had antiproliferative activity against NTRK gene fusions in the nanomolar range.

Secondary Pharmacology

No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees.

Safety Pharmacology

No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees.

8.4. ADME/PK

The Applicant's Position:

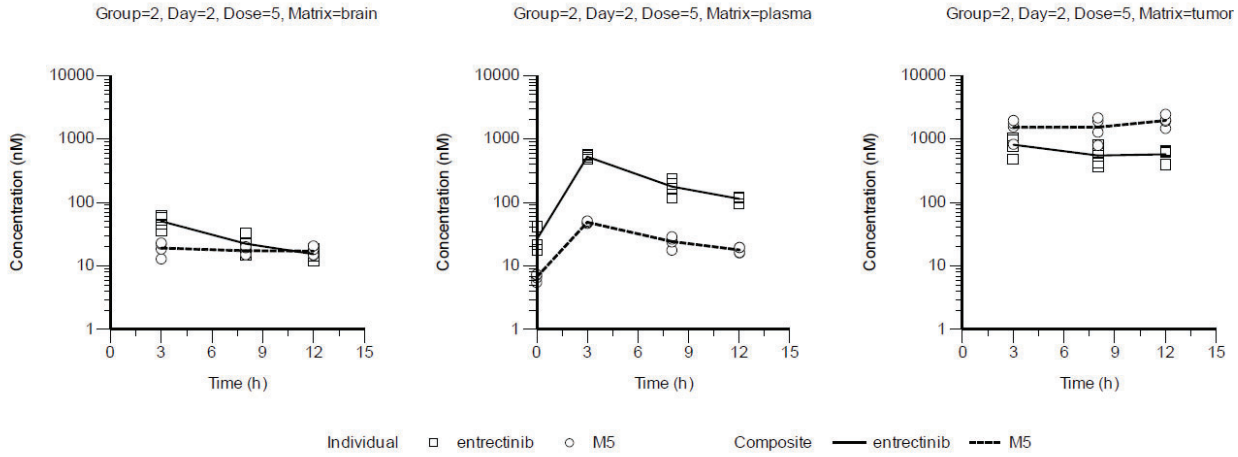
The ADME/PK studies included in this submission are presented below in tabular format.

Absorption
Pharmacokinetics of entrectinib and M5 in plasma, brain and tumor for a follow-up study on entrectinib in the treatment of KM12-luc subcutaneous tumor model on nude mice / 1098459 / Module 4.2.2.2 Study type / test system: PK in plasma, brain, and tumor / mouse (Nu/Nu), KM12-luc SC tumor model Dose / route of administration: 5 mg/kg twice daily / oral Key results: Highest exposure of entrectinib was observed in tumor, followed by plasma and brain.
Distribution
No new information is provided in the current submission.
Metabolism
Human cytochrome P450 (CYP) 3A reaction phenotyping for the metabolism of entrectinib and its M5 metabolite / 1116011 / Module 4.2.2.4 Study type / test system: CYP3A reaction phenotyping / HLM (including pediatric liver donor at 16 months old and CYP3A5 genotyped liver) and recombinant human CYP 3A4, 3A5, and 3A7 Dose: 0.1-0.3 μM Key results: CYP3A4 is the main CYP3A isoform involved in the metabolism of entrectinib and M5 in both adult and pediatric HLM.
Excretion
No new information is provided in the current submission.
Pharmacokinetic drug interactions
Effect of CYP-selective chemical inhibitors on metabolism of RO7102212 (entrectinib) by human liver microsomes / 1095945 / Module 4.2.2.6 Study type / test system: CYP inhibition / HLM for CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 Dose: 1, 10 μM Key results: Ketoconazole was the most effective inhibitor (50-80% inhibition), indicating an important role for CYP3A enzymes in the oxidative pathways, especially demethylation (to M5). Determination of the time-dependent inhibition of CYP3A4 by RO7102122 / 1092511 / Module 4.2.2.6 Study type / test system: time-dependent inhibition of CYP3A4 / HLM for CYP3A4 Dose: 0.156-10 μM Key results: Entrectinib showed weak time-dependent inhibition potential on CYP3A4 in HLM. Evaluation of the induction potential of cytochrome P450 2B6 isoform by RO7102122 in cultured human hepatocytes / 1095573 / Module 4.2.2.6 Study type / test system: CYP2B6 induction / cultured human hepatocytes Dose: 0.1-3 μM (enzyme activity), 0.1-5 μM (mRNA expression) Key results: Entrectinib did not show meaningful induction of CYP2B6.
Summary PK parameters from pharmacokinetic studies
Refer to Study 1098459, Module 4.2.2.2 Absorption
Integrative summary table of Cmax and AUC parameters across toxicology studies (general, reproductive, and carcinogenicity, if conducted).
No new information is provided in the current submission.
Tabulation of any exposure margins used in proposed labeling.
No new information is provided in the current submission.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment. In Study 1098459, the exposure of both entrectinib and its major metabolite, M5, was highest in tumor, then plasma, and then brain in mice bearing subcutaneous tumors and treated orally with 5 mg/kg twice daily.

FDA - Figure 1: Day 2 individual plasma, brain, and tumor concentrations of entrectinib and M5 after the 3rd dose of entrectinib at 5 mg/kg BID to subcutaneous tumor-bearing mice



(Excerpted from Applicant's Study 1098459)

8.5. Toxicology

8.5.1. General Toxicology

No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees.

8.5.2. Genetic Toxicology

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees.

8.5.3. Carcinogenicity

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees.

8.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees.

8.5.5. Other Toxicology Studies

The Applicant's Position:

Study Type (GLP Compliance)	Study Title	Study Number / eCTD Location	Test System (materials / methods / controls)	Key Findings
Bacterial reverse mutation (GLP)	(b) (4) Bacterial reverse mutation assay	1104576 / Module 4.2.3.7.6 Impurities	*Salmonella typhimurium*	Negative
Effect on bone metabolism in vitro (non-GLP)	Effect of entrectinib on bone metabolism in vitro	1121182 / Module 4.2.3.7.7 Other Toxicity Studies>Other	Juvenile model: Co-culture of THP-1 + SCP-1 cells Adult models: - Co-culture of THP-1 + SCP-1 cells + β-estradiol - Co-culture of THP-1 + SaOS-2 cells	Physiological concentrations of entrectinib and M5 dose-dependently decreased osteoblast function and stimulated osteoclastogenesis in co-cultures; the effect on osteoblast function was less pronounced than that on osteoclast function. ALP activity and formation of mineralized matrix tended to be decreased by entrectinib or M5 treatment in all three co-cultures; other osteoblastic markers such as osteocalcin or PINP were not significantly affected or were even slightly increased.

ALP=alkaline phosphatase; eCTD=electronic Common Technical Document; GLP=Good Laboratory Practice; PINP=procollagen type I N-propeptide.

The FDA's Assessment:

The Applicant conducted a GLP-compliant bacterial reverse mutation assay (Study 1104576) to evaluate the potential mutagenic activity of the impurity, (b) (4), using five histidine-requiring strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA102 and TA97) in the absence and in the presence of a rat liver metabolizing system (S9). Concentrations ranging from (b) (4) and appropriate positive and negative controls were used in the assay. Positive and negative controls performed as expected. Following (b) (4)

treatment, no biologically relevant increases in revertant numbers occurred, thus [redacted] (b) (4) was considered negative for genotoxicity in this assay.

The Applicant also evaluated the effect of entrectinib and its main metabolite M5 on bone metabolism in vitro (Study 1121182) to further investigate a possible mechanism of fracture with entrecinib administration to patients in the clinic. Investigators co-cultured myeloid cells/osteoclastic progenitor cells (THP-1) and immortalized human mesenchymal stem cells (SCP-1) to represent juvenile bone and THP-1 and SCP-1 cells cultured with 10 nM β-estradiol, or co-cultures of THP-1 and osteosarcoma-derived osteoblastic cells (SaOS-2) to represent adult bone. Cultures were treated with entrectinib and M5 at concentrations up to 10 µM. Physiologically relevant concentrations of entrectinib and M5 (10-1000 nM) dose-dependently decreased osteoblast function and stimulated osteoclastogenesis in co-cultures. Alkaline phosphatase (ALP) activity and formation of mineralized matrix decreased with entrectininb or M5 treatment; however, additional osteoblastic markers (osteocalcin, procollagen type I N-propeptide [PINP]) were not significantly changed.

X X

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

9 Clinical Pharmacology

9.1. Executive Summary

The FDA's Assessment:

- Entrectinib was approved in August 2019 for adult patients with *ROS1*-positive metastatic non-small cell lung cancer (NSCLC) and adult and pediatric patients 12 years or older with metastatic solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion. Entrectinib is currently available as capsules with a recommended dosage of 600 mg once daily (QD) for adults (*ROS1* NSCLC and *NTRK*$^{+}$ solid tumors) and a fixed dosage based on BSA categories in pediatric patients with *NTRK*$^{+}$ solid tumors (BSA > 1.50 m^2: 600 mg QD; BSA 1.11 to 1.50 m^2: 500 mg QD; BSA 0.91 to 1.10 m^2: 400 mg QD). The capsules are recommended to be administered with or without food.
- The current application seeks to extend the current indication for entrectinib in patients with solid tumors that have an NTRK gene fusion to include (b) (4) Table 5 lists the Applicant's proposed dosage recommendations for pediatric patients with NTRK positive solid tumors.

Table 5: Recommended Dosages (b) (4) with Solid Tumors that are positive for NTRK gene fusions

Age	BSA, m^2	Recommended Dosage
>6 months	≥1.51	600 mg QD
	1.11 to 1.50	400 mg QD
	0.81 to 1.10	300 mg QD
	0.51 to 0.80	200 mg QD
	(b) (4)	
>1 to 6 months	Not applicable	250 mg/m^2 QD*
(b) (4)		
* For dosage increments of 10 mg using capsules prepared as a suspension		

In addition, the current submissions seek approval of:

A new formulation of entrectinib, i.e., coated granules, for patients who are unable to swallow the currently approved capsules but are able to swallow soft food.

A new method of administration (oral suspension) of the currently approved capsule formulation for patients who cannot swallow capsules.

A new route of administration (via nasogastric/gastric tube) of the approved capsules for patients who require enteral administration.

The entrectinib capsules and coated granules are recommended to be administered with or without food. The primary efficacy and safety evidence supporting the proposed dosage for pediatric patients are derived from a dose escalation and expansion study STARTRK-NG

(CO40778) and the TAPISTRY (BO41392) and STARTRK-02 (GO40782) studies. The results demonstrate an overall objective response rate (ORR) of 70% and a complete response rate (CR) of 42% in pediatric patients, and an overall acceptable safety profile.

The key clinical pharmacology review issues focused on the evaluation of the proposed recommended dosages, dosage adjustments for patients taking strong and moderate CYP3A inhibitors, establishment of scientific bridges between coated granules and capsule formulations and between the new method and routes of administration of capsules and intact capsules, and the effect of food effect (b) (4) granules.

The proposed dosages for pediatric patients >1 month were found to be acceptable, with the exception of the dosages forpediatric patients >6 months with BSA ≤0.5 m^2.

The Applicant's proposed (b) (4) mg dosage for pediatric patients >6 months with BSA ≤0.5 m^2 is expected to be (b) (4) of adult exposures; these exposures are not adequately covered in the exposure-efficacy relationship and limited clinical data exist at the proposed dose for this patient subgroup. Therefore, FDA recommends a 300 mg/m^2 QD dosage for pediatric patients >6 months with BSA ≤0.5 m^2 which provides comparable exposures to those in other BSA categories of pediatric patients > 6 months and adult patients, and is not predicted to exacerbate toxicity.

FDA does not recommend (b) (4)

The Applicant's in silico demonstration of the lack of food effect for coated granules was found inadequate; however, the recommendation for administration without regard to food was supported based on clinical experience, as coated granules were administered without regard to food in the pediatric clinical studies.

Adequate scientific bridge was established between coated granules and capsules, and between capsules as suspension administered orally or via nasogastric tube and intact capsules.

The Applicant's proposed entrectinib dosage adjustments when coadministered with strong and moderate CYP3A inhibitors for pediatric patients ≥2 years were found to be acceptable.

Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 218550. This submission is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in Table 6.

Table 6: Key Clinical Pharmacology Review Issues and Recommendations by FDA

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td>Pivotal and supportive evidence of effectiveness</td><td>The primary evidence of effectiveness in pediatric patients ages ≥ 1 month to < 12 years is derived from STARTRK-NG (CO40778) and TAPISTRY (BO41392). The proposed dosages are supported by an ORR of 70% (95% CI 51,84) with a median duration of response (DOR) of 25.4 months (95% CI 14.3, not estimable [NE]) in pediatric patients with solid tumors that have NTRK positive gene fusions.</td></tr>
<tr><td>General dosing instructions</td><td>
<table>
<tr><th>Age</th><th>BSA, m^2</th><th>Recommended Dosage</th></tr>
<tr><td rowspan="5">>6 months</td><td>(b) (4)</td><td>600 mg QD</td></tr>
<tr><td>1.11 to 1.50</td><td>400 mg QD</td></tr>
<tr><td>0.81 to 1.10</td><td>300 mg QD</td></tr>
<tr><td>0.51 to 0.80</td><td>200 mg QD</td></tr>
<tr><td>≤0.50</td><td>300 mg/m^2 QD*</td></tr>
<tr><td>>1 to 6 months</td><td>N/A</td><td>250 mg/m^2 QD*</td></tr>
<tr><td colspan="3">* For dose increments of 10 mg using capsules prepared as a suspension</td></tr>
</table>
The recommended dosage mentioned above were selected based on the following rationale:
(b) (4) months provided exposures comparable to those in adults receiving 600 mg QD where efficacy was previously demonstrated.
The recommended 300 mg/m^2 QD dosage for pediatric patients >6 months with BSA ≤0.5 m^2 provides comparable exposures to those in pediatric patients > 6 months in other BSA categories and to adult patients. In contrast, the Applicant's proposed (b) (4) The recommended 300 mg/m^2 dosage for pediatric patients >6 months with BSA ≤0.5 m^2 is not predicted to pose any increased safety issues.
The recommended dosage of 250 mg/m^2 QD in pediatric patients >1 to 6 months old provides 60% of exposures observed in adults receiving 600 mg and has been demonstrated to be effective.
Low risk of bone fractures in the lowest BSA categories of patients >6 months and patients >1-6 months due to lower exposures in these patients compared to adults and pediatric patients in the other BSA categories.</td></tr>
</table>

<table>
<tr><th>Review Issue</th><th>Recommendations and Comments</th></tr>
<tr><td></td><td>(b) (4)</td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>No dosage adjustment is needed according to sex, race, mild to moderate renal impairment, or mild hepatic impairment. The effects of severe hepatic impairment (total bilirubin > 3x ULN, any AST) and severe renal impairment (creatinine clearance < 30 mL/min) are unknown.
Body weight was found to influence clearance and volume of distribution of entrectinb and M5.</td></tr>
<tr><td>Drug-drug interactions</td><td>Avoid coadministration of entrectinib with moderate or strong CYP3A inhibitors. If coadministration is unavoidable, reduce the dosage as proposed below with concomitant use of strong and moderate CYP3A inhibitors for pediatric patients 2 years and older.
<table>
<tr><th>Starting dose*</th><th>Moderate CYP3A</th><th>Strong CYP3A</th></tr>
<tr><td>200 mg</td><td>50 mg QD</td><td>50 mg on alternate days</td></tr>
<tr><td>300 mg</td><td>100 mg QD</td><td>50 mg QD</td></tr>
<tr><td>400 mg</td><td>200 mg QD</td><td>50 mg QD</td></tr>
<tr><td>600 mg</td><td>200 mg QD</td><td>100 mg QD</td></tr>
<tr><td colspan="3">* For pediatric patients with a starting dose <200 mg, avoid coadministration with moderate or strong CYP3A inhibitors</td></tr>
</table>
Avoid coadministration of entrectinib with moderate or strong CYP3A inhibitors for pediatric patients <2 years.
Avoid coadministration of strong and moderate CYP3A inducers with entrectinib.</td></tr>
<tr><td>Scientific Bridge</td><td>The results of relative bioavailability studies and exposures in clinical studies established an adequate scientific bridge between coated granules and capsules, and between capsules as suspension administered orally or via nasogastric tube and intact capsules.</td></tr>
<tr><td>Labeling</td><td>Overall, the proposed labeling recommendations are acceptable upon the Applicant’s agreement with the FDA recommended revisions to the labeling.</td></tr>
</table>

9.2. Summary of Clinical Pharmacology Assessment

9.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The key findings from the evaluation of the clinical pharmacology and PK of entrectinib in a pediatric population are as follows (Module 2.7.2):

Characterization of Pharmacokinetics
Non-compartmental analyses:

- Individual systemic exposure in patients dosed with 300 mg/m^2 using the commercial formulation capsules and coated granules is within the range of systemic exposure in patients dosed with F1 (containing no pH-modifier) at doses >300 mg/m^2 (400 mg/m^2 and 550 mg/m^2). This is consistent with previous reports showing the sensitivity of entrectinib to gastrointestinal conditions when administered with the formulation without a pH-modifier (F1; Report 1091111).
- Entrectinib systemic exposure was comparable in pediatric patients > 1-year-old following a 300 mg/m^2 regardless of the form of administration (capsule or coated granules).
- Overall, pediatric patients ≤ 1 year old showed lower systemic entrectinib exposure and higher metabolite-to-parent (M/P) ratios compared to older pediatric patients and adults regardless of the form of administration (nasogastric administration (F06) or coated granules).
- The available systemic exposure of entrectinib from patients receiving coated granules (F17 (b) (4) was comparable to patients receiving coated granules (F15 – (b) (4) and capsule (F06).
- No obvious trends or bias was observed in the distribution of exposures for entrectinib and sum (entrectinib + M5), across the age and body size ranges tested (2 months to 20 years, and 0.2 to 2 m^2). Although lower exposure of entrectinib and the sum (entrectinib + M5) was observed in the lower age range (< 1 year old).
- **Population pharmacokinetics**:
- Based on simulations from the popPK model, the entrectinib starting doses of 300, 400 and 600 mg once daily (QD) (based on the recommended dose of 300 mg/m^2), given in the pediatric body surface area (BSA) categories III, IV, and V, respectively, are expected to generate exposures (sum of entrectinib and M5 area under the plasma concentration-time curve [AUC] at steady state) within the adult range. Of note, adolescents > 12 years old mainly belong to categories IV and V.
- Based on simulations from the popPK model, the starting dose of 200 mg QD for BSA category II (0.51-0.80 m^2) (b) (4) (based on the recommended dose of 300 mg/m^2), are expected to generate a median sum (entrectinib + M5) exposures of about 58% (b) (4) of adult exposures, respectively. These lower exposures are mainly driven by the currently unexplained age effect on the bioavailability of entrectinib.

Effect of Intrinsic Factors on the Pharmacokinetics of Entrectinib

- Body weight was found to influence volume of distribution and clearance for both entrectinib and M5 in a popPK model.
- Based on the popPK model, pediatric cancer patients had lower bioavailability compared to adults. Entrectinib bioavailability in pediatric patients was estimated to be 29%, 62%, and 84% of the adult value, respectively at the age of 1, 6, or 12 years.
- Based on the popPK model, the apparent clearance of M5 increased with age in pediatric patients. M5 clearance was estimated to be 50% of adults at the age of 1 year, 86% at 6 years, and 92% of adults at 12 years.
- Race did not have a marked effect on entrectinib PK following administration of the F06 capsule or F15 coated granules to a pediatric population.

Effect of Extrinsic Factors on the Pharmacokinetics of Entrectinib

- Increasing gastric pH with a proton pump inhibitor (PPI) lansoprazole did not lower the bioavailability of entrectinib when given as an oral suspension in water indicating the effectiveness of the pH-modifier when entrectinib is given as an oral suspension in water. Increasing gastric pH by co-administration of the PPI (lansoprazole) increased entrectinib overall exposure (area under the plasma concentration-time curve from time zero to infinity [AUC_{inf}]) by 15% and reduced M5 overall exposure by 13% (Section 3.5.1; see details in 2.7.1 SBP, Section 2.3.2 [Study GP44192]).

Based upon PBPK simulations, co-administration of a range of cytochrome P450 (CYP) 3A4 inhibitors with entrectinib significantly increased entrectinib exposure across an age range of 2 to 18 years (Section3.5.2).

Based upon the simulated effects of co-administration of entrectinib with CYP3A4 inhibitors, dose adjustments are recommended for pediatric patients ≥ 2 years old depending on the starting dose defined in the corresponding BSA range and the availability of dose strengths (Section 3.5.2).

Effect of Entrectinib on the Pharmacokinetics of Other Medicinal Products

The effect of entrectinib on the pharmacokinetics of other medicinal products has previously been described in the initial 2.7.2 SCP.

Population Pharmacokinetics

The existing popPK model was updated based on data from five Phase I/II studies in 343 patients with solid malignancies, of which 73 were pediatric patients: Study GO40784 (also known as RXDX-101-01, and STARTRK-1; N = 57), Study GO40782 (also known as RXDX-101-02, and STARTRK-2; N = 203), Study CO40778 (also known as RXDX-101-03, and STARTRK-NG; N = 67), Study GO40785 (also known as RXDX-101-14; N = 12), and Study BO41932 (also known

as TAPISTRY; N = 4; popPK Report 1121816). These analyses were performed to quantitatively describe the PK of entrectinib and M5 in adult and pediatric patients.

- Evaluations of E-R relationships for clinical efficacy and selected clinical safety events were conducted for entrectinib and/or M5 in the pediatric population. Specific objectives of the exposure-efficacy and -safety analyses were:
- To investigate the exposure-efficacy relationships in the pediatric population for entrectinib and M5 using graphical analyses in:
- NTRK –fusion-positive tumors and
- ROS1 –fusion-positive tumors.
- To investigate whether the variability in responder status (as assessed by best overall response (BOR), with responders defined as complete response (CR) or partial response (PR), and non-responders as stable disease, progressive disease (PD), and non-CR/non-PD patients) could be attributed to the variability in the sum (entrectinib + M5) exposure in both NTRK and ROS1 fusion-positive tumors.
- To characterize:
- the relationship between exposure of entrectinib, M5, and the sum (entrectinib + M5) and treatment-emergent Grade $\geq$ 3 adverse events (AEs).
- the relationship between exposure of entrectinib, M5, and the sum (entrectinib + M5) and serious adverse events (SAEs; any Grade).
- the relationship between exposure of entrectinib, M5, and the sum (entrectinib + M5) and bone fractures.

Characterization of Pharmacodynamics

- Characterization of pharmacodynamics has previously been described in the initial 2.7.2 SCP.

Physiologically-Based Pharmacokinetic Simulations

Physiologically-based pharmacokinetic (PBPK) modelling has been utilized to integrate available in vitro nonclinical and clinical data and to support the development of entrectinib by assisting the interpretation of clinical studies (for full details refer to the PBPK GastroPlus Report 1113585 and PBPK Simcyp Report 1119857).

The two models developed using the GastroPlus and Simcyp software (previously described in the initial 2.7.2 SCP) have been updated to predict the outcomes of clinical pharmacology studies and have been used further to explore the impact of various intrinsic and extrinsic factors on entrectinib PK in pediatric patients.

The updated GastroPlus absorption model(s) integrate measured physicochemical and formulation-related data and has been employed:

- To support the absence of food effect with the coated granule formulation, by extrapolating the lack of food effect in capsules (GastroPlus Report 1113585).

The updated Simcyp model(s) integrate in vitro metabolism and drug interaction data and has been applied:

- To simulate drug-drug interaction arising from the co-administration of strong and moderate CYP3A4 inhibitors in pediatric populations (Simcyp Report 1119857).

Exposure Safety Relationship

- Exposure safety relationships have previously been described in the initial 2.7.2 SCP.
- For a pediatric population, no relationship between treatment-emergent adverse events (TEAEs) of grade 3 or higher or SAEs and entrectinib and M5 exposure was observed (Section 3.7.2.1 and popPK Report 1121816).
- • A positive association between entrectinib exposure (average concentration up to the time of first event) and the risk of bone fracture may exist (popPK Report 1121816, Section 6.4.3).

Exposure Efficacy Relationship

- Exposure efficacy relationships have previously been described in the initial 2.7.2 SCP for the adult population.
- Results indicate no relationship between clinical response based on BOR, and the sum (entrectinib + M5) exposure in pediatric patients with NTRK fusion or ROS1 fusion. Between patient variability in exposure levels could not explain, even partially, the variability in responder status, as assessed by BOR, in NTRK or in ROS1 fusion-positive patients.
- [redacted]

  The FDA's Assessment:

  FDA agrees with the Applicant's position, except for the following:
  While FDA agrees that the PK exposures for pediatric patients greater than 6 months with BSA at or below 0.5 m^2 are expected to be approximately 30% of adult exposures, FDA does not agree with the Applicant's proposed dosage [redacted] (b) (4) Instead, FDA recommends a dosage of 300 mg/m^2 QD for pediatric patients greater than 6 months with BSA at or below 0.5 m^2 (refer to Sections 6.2.2.1 and 6.3.2.1 for details).
  The updated Gastroplus model was found to be inadequate (see Biopharmaceutics review for details) to demonstrate a lack of food effect with coated granules. Nonetheless, coated granules were administered with or without food in the STARTRK-NG, TAPISTRY and STATTRK-02 studies (refer to Section 6.3.2.4 for details).]

9.2.2. General Dosing and Therapeutic Individualization

9.2.3. General Dosing

Data:

Table 7 Recommended dosing for Pediatric patients > 6 months

Category	Body Surface Area	Once Daily Dose
[redacted] (b) (4)		
II	0.51–0.80 m^2	200 mg
III	0.81–1.10 m^2	300 mg
IV	1.11–1.50 m^2	400 mg
V or adults	≥1.51 m^2	600 mg

Table 8 Recommended dosing for Pediatric patients [redacted] (b) (4)

Age	Once Daily Dose[a]
[redacted] (b) (4)	
> 1 month to ≤ 6 months[c]	250 mg/m^2

[a] Doses round to the nearest 10 mg for completeness.

[redacted] (b) (4)

[c] Supported by clinical safety, efficacy and exposure data.

The Applicant's Position:

Since bioequivalence has been shown between the approved capsule (F06) and coated granule formulations (Study GP41341 Report 1100283), the current dose recommendation is applicable for both capsules and coated granules. The comparable entrectinib systemic exposure in pediatric patients following capsule or coated granules further strengthens the recommendation (2.7.1 SBP, Section 3.5.1).

A recent relative bioavailability study conducted in healthy volunteers (GP44192 Data Memo) has shown comparable entrectinib systemic exposures among whole capsules, water and milk oral suspensions, and with nasogastric administration (2.7.1 SBP, Section 3.5.2). Hence, the dose recommendations shown in Table 4 are applicable for any of the tested routes of administration of entrectinib.

The updated popPK model (popPK Report 1121816) predicts comparable exposures between pediatric patients receiving 300 mg/m^2 in BSA categories III, IV and V and adults receiving 600 mg once daily. This is also consistent with the observed NCA results showing pediatric exposure within the range of the adult exposure (2.7.2 SCP. Section 3.1.3). These data together with the reported clinical efficacy and safety in the pediatric population confirm the appropriateness of the entrectinib 300 mg/m^2 QD dose in BSA categories III–V.

For younger children, from > 1 month to ≤ 6 months, the recommended dose is 250 mg/m^2 (b) (4)

For BSA categories I, II, and patients ≤ 6 months receiving 250 mg/m^2, lower exposures for entrectinib are predicted compared to adults and pediatric patients in the higher BSA categories. This is consistent with the NCA results, where patients ≤ 1 year old showed exposure levels that were at the lower end of the range of adult systemic levels (Section 3.1.3). Whilst in the popPK model these lower exposures are mainly driven by the currently unexplained age effect on the bioavailability of entrectinib, further dose adjustment in these two BSA categories to generate exposures closer to the adult range is not recommended, because the exposures generated within these two BSA categories (I and II), remain within the exposure range where similar efficacy was observed in adults. The current available clinical safety and efficacy data in the youngest pediatric population confirm the adequacy of the recommended dose(s) for BSA categories I, and II, and a 250 mg/m^2 dose for patients between 1 month to 6 months (Table 5; and 2.7.3 SCE). Additional evidence described below also supports the current dose recommendation in the pediatric population, including the youngest:

- The lack of relationship between responder status on BOR and entrectinib and M5 exposure in pediatric patients with NTRK fusion, or with ROS1 fusion, together with the flat relationship between exposure and clinical efficacy in adults (initial popPK Report 1091319).
- The positive trend between the probability of bone fracture and entrectinib exposure in pediatrics (popPK Report 1121816) together with the higher frequency of AEs of Grade ≥ 3 or SAEs observed at higher exposures in the adult population (initial popPK Report 1091319, and popPK Report 1121816) suggest that increasing the pediatric systemic exposure to match the adult systemic exposure may increase the risk of bone fractures, (popPK Report 1121816; 2.7.4 SCS, Section 2.1.8.1).
- Lower exposure in these BSA categories is also associated with a low risk of bone fracture (13% and 16% in the BSA category I and II, respectively). Similar conclusions can be drawn for children aged 1 to 6 months and for those receiving a starting dose of 250 mg/m^2 QD, for which simulated exposures were ~30% of the adults.

(b) (4)

Cumulatively, the clinical safety, efficacy, pharmacokinetics, simulations, and the exposure-response relationships confirm the appropriateness of the entrectinib (b) (4) dosing regimen for (b) (4) 250 mg/m^2 dosing regimen from $>$ 1 month to $\leq$ 6 months (b) (4)

Dosing Recommendations

- A 600 mg flat dose is recommended for (b) (4) with $\geq$1.51 m^2 BSA.
- (b) (4)
- A 250 mg/m^2 dose is recommended for pediatric patients from $>$1 month to $\leq$6 months of age. (b) (4)
- Since bioequivalence has been met between coated granules and capsules and comparable exposure has been shown among capsule, nasogastric, and water and milk oral suspension administration; the recommended doses of 300 mg/m^2, 250 mg/m^2 and (b) (4) are applicable for any form of administration (e.g., intact F06 capsules, coated granules, water and milk suspension and nasogastric administration).
- Whilst in the popPK model these lower exposures are mainly driven by the currently unexplained age effect on the bioavailability of entrectinib, further dose adjustment in these two BSA categories to generate exposures closer to the adult range is not recommended, because the exposures generated within these two BSA categories (I and II), remain within the exposure range where similar efficacy was observed in adults.
- Cumulatively, the clinical safety, efficacy, pharmacokinetics, simulations, and the Exposure-Response relationships confirm the appropriateness of the entrectinib (b) (4) 250 mg/m^2 dosing regimen from $>$1 month to $\leq$ 6 months (b) (4)
- Based on the victim DDI PBPK simulations, and taking into account the availability of the dose strengths, dose reductions and/or a less frequent dosing for entrectinib are being proposed in pediatric subjects with BSA categories when entrectinib is co-administered with either strong CYP3A4 or a moderate CYP3A4 inhibitor (Table 15 in the SCP 2.7.2).
- No dose adjustment is recommended when entrectinib is administered with a weak CYP3A4 inhibitor.
- Concomitant use of entrectinib with CYP3A inducers should be avoided.
- No dose adjustment is required when entrectinib is co-administered with CYP3A substrates.
- Overall, based on the clinical efficacy and safety, the proposed dose regimen is considered appropriate in the pediatric population.

The FDA's Assessment:

FDA agrees with the Applicant's assessment regarding the dosage recommendations in pediatric patients greater than 1 month old (Table 7), except (b) (4) . Instead, FDA recommends a

dosage of 300 mg/m^2 for pediatric patients greater than 6 months with BSA at or below 0.5 m^2.

FDA does not agree with the [redacted]

Rationale for 300 mg/m^2 for pediatric patients greater than 6 months with BSA at or below 0.5 m^2 (refer to Section 6.3.2.1 and 19.4.1.3 for details)*:*

FDA recommends a dosage of 300 mg/m^2 instead of the [redacted] for pediatric patients greater than 6 months in BSA Category I and to revise the BSA Category I to at or below 0.5 m^2 instead [redacted] for the following reasons (refer to Section 6.3.2 for details):

[redacted]

A higher doseage of 300 mg/m^2 may provide better exposure matching in young pediatrics with low BSA.

A dosage of 300 mg/m^2 should be safe based on E-R for safety, with the risk of bone fracture is expected to be lower in low BSA and age group compared to older children.

The proposed [redacted] (refer to Sections 6.3.2.1 and 19.4.3 for details)*:*

FDA does not agree with the Applicant's proposed [redacted]

The recommended dosages shown in Table 7 are applicable for any of the tested routes of administration of entrectinib. Comparable exposures were demonstrated between the

approved capsule (F06) and coated granule formulations in healthy subjects with a light meal. Further, in the clinical studies the entrectinib systemic exposures were comparable in pediatric patients following administration of capsule or coated granules. Also, comparable entrectinib systemic exposures were demonstrated in healthy subjects between capsules contents administered as oral suspensions in water or milk and via nasogastric tube compared to intact capsules.

9.2.4. Therapeutic Individualization

The Applicant's Position:

Dose individualization is not applicable.

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

9.2.5. Outstanding Issues

The Applicant's Position:
There are no outstanding issues

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

9.3. Comprehensive Clinical Pharmacology Review

9.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
Not applicable.

9.3.2. Clinical Pharmacology Questions

9.3.3. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:
Yes, the data provides supportive evidence of effectivess of the proposed regimen.

The FDA's Assessment:
FDA agrees with the Applicant's position regarding effectiveness of the Applicant's proposed dosage in pediatric patients greater than 1 month (see Tables 7, 8 and 9), except for the proposed dosage of (b) (4) . FDA recommends a BSA-based dosage of 300 mg/m^2 for patients greater than 6 months with BSA at or below 0.5 m^2.

FDA does not agree with the Applicant's position regarding the effectiveness of the proposed dosage (b) (4)

Table 9: Efficacy Evaluable Pediatric Patients with NTRK fusions in Studies STARTRK-NG and TAPISTRY.

Age (months)	BSA Category (m^2)	Proposed Dose (mg)	Administered Dose QD (mg)	n	ORR (%)
> 6	≤0.5	100	100	1	0
	0.51-0.80	200	200	9	78
			300	4	50
			400	3	67
	0.81-1.10	300	200	1	100
			300	1	100
	1.11-1.50	400	300	1	100
			400	3	100
			600	1	0
			700	1	100
	≥1.51	600	600	3	33
>1 – 6	N/A	250 mg/m2	~250 mg/m^2	5	80
ORR=Overall response rate; Yellow highlights correspond to the proposed doses					

Exposure matching with adult exposures and exposure-response relationships for safety and efficacy in pediatric patients were used to determine the proposed dosages for pediatric patients greater than 1 month old. A BSA-based dosage of 300 mg/m^2 was

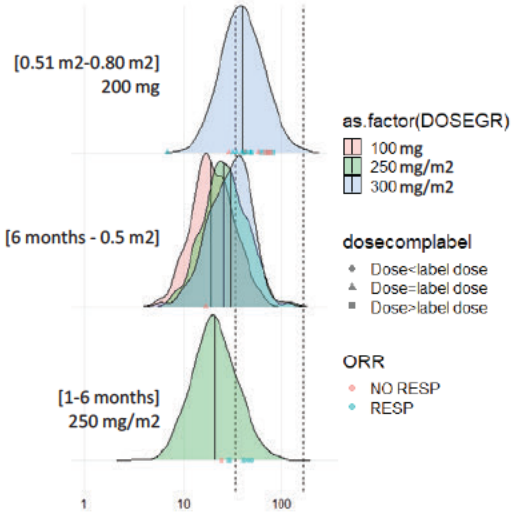
Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

found to be within the range of adult exposures for the pediatric patients greater than 6 months with BSA greater than 0.5 m^2. However, pediatric patients greater than 6 months with BSA at or below 0.5 m^2 were predicted to have lower exposures, i.e., ~30% of adult exposures.

BSA-based dosage of 300 mg/m^2 for patients greater than 6 months with BSA at or below 0.5 m^2:

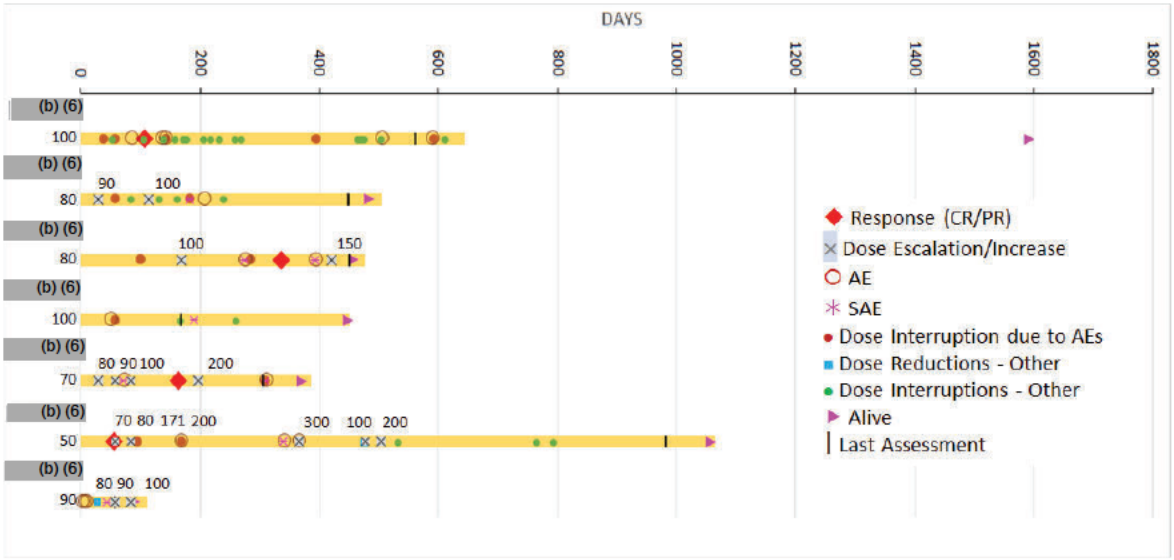
There was limited clinical data for patients greater than 6 months with BSA ≤0.5 m^2, with only one patient in this age/BSA group given (b) (4) dosage of 100 mg QD. (b) (4) ould be less than the proposed dosage for pediatric patients in the greater than 1 month to 6 month age group (250 mg/m^2). While the E-R analysis for efficacy was flat (see Section 19.4.2) in pediatric patients, there are limited E-R data to cover the exposures achieved with dosages under 250 mg/m^2 (i.e., 30% of adult exposures). Therefore, FDA recommends a BSA-based dosage of 300 mg/m^2 for patients > 6 months with BSA at or below 0.5 m^2 as this dosage will likely provide exposures comparable to those in pediatric patients > 6 months at higher BSA categories and adult patients. Since the exposure and efficacy data in pediatric patients greater than 6 months with BSA less than 0.5 m^2 is minimal, leveraging PK and efficacy data from other pediatric groups such as the pediatrics greater than 1 month to 6 months old and pediatrics greater than 6 months with BSA within 0.51 m^2 to 0.8 m^2 is a reasonable approach. From exposure matching perspective, the observed exposures pediatrics in greater than 1 month to 6 months with ~250 mg/m^2 dosage (227-333 mg/m^2) (who were mostly responders) are mostly in the adult range and overlap with observed and predicted exposures of pediatrics greater than 6 months and BSA within 0.51 m^2 to 0.8 m^2 receiving 200 mg dosage (Figure 2). Therefore, the recommended dosage of 300 mg/m^2 in pediatric patients greater than 6 months with BSA at or below 0.5 m^2 is expected to achieve exposures that match the reference more closely than with (b) (4) dosage (Refer to Section 19.4.1.3 for details).

Figure 2: Predicted Exposure Distributions based on Patient Age Group and Entrectinib Doses



Further, FDA's recommended dosage of 300 mg/m^2 is reasonable from a safety perspective. The potential risk for bone fractures increased only marginally from 13.1% to 14.4% when dosage is increased from 100 mg to 300 mg/m^2. The bone fracture risk is also expected to be lower in low BSA and age group compared to older pediatric patients. In addition, in patients greater than 1 month to 6 months old, although adverse reactions were observed there was no dose reductions due to adverse reactions in Study STARTRK-NG (Figure 3). Adverse reactionss were mostly managed by dosage interruptions.

Figure 3: Swimmer Plot of Adverse Reactions and Dose Adjustments in Pediatric Patients >1 month to 6 month in Study STARTRK-NG



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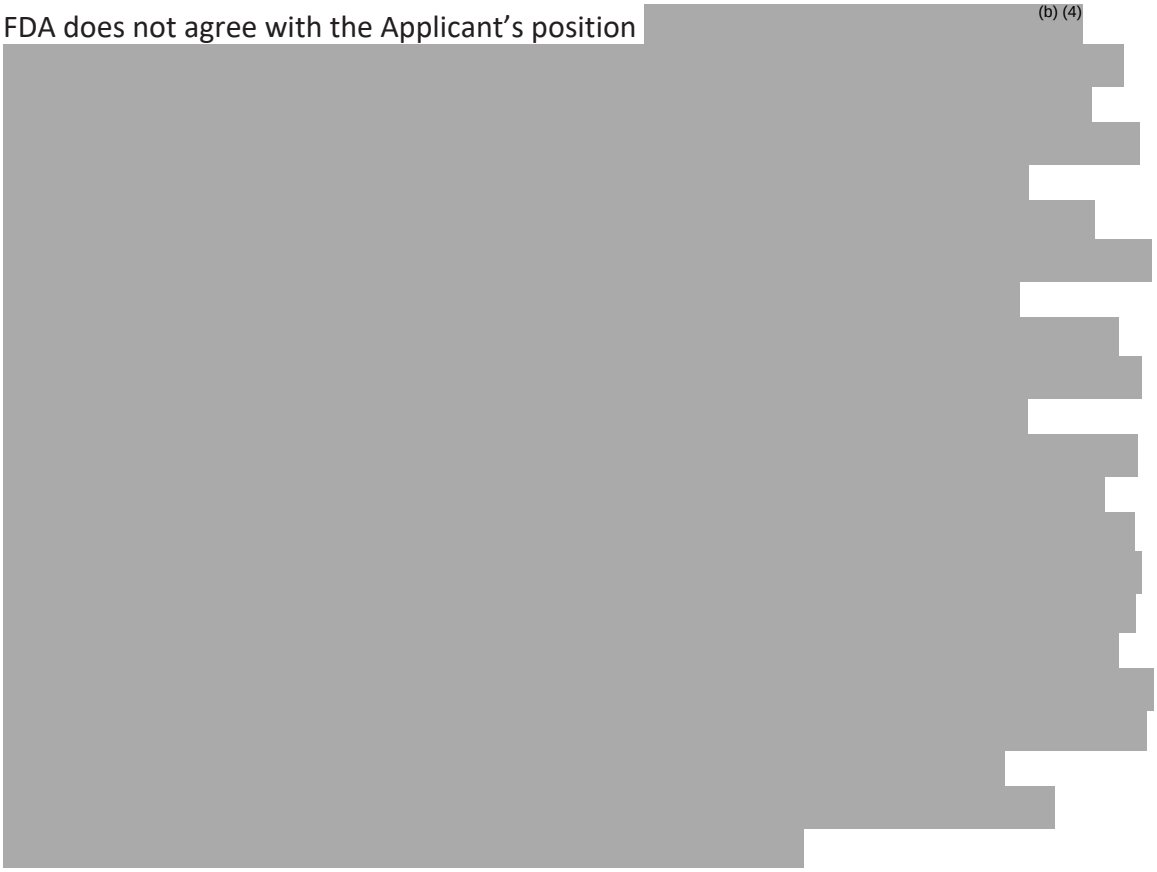
Applicant and do not necessarily reflect the positions of the FDA.

FDA does not agree with the Applicant's position (b) (4)



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

The Applicant's Position:
Yes, see Section 6.3.2.1.

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

9.3.5. 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.)?

The Applicant's Position:
Based on the popPK analysis, no clinically meaningful covariates were identified that warrant dose adjustment.

The FDA's Assessment:

FDA agrees with the Applicant's position.

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

The Applicant's Position:
There is no information on drug-food interaction.

The FDA's Assessment:
FDA agrees with the Applicant's position on no dosage adjustment with food for the capsule and coated granule formulations.
FDA agrees with the Applicant's position on the proposed dosage adjustments for strong and moderate CYP3A inhibitors for patients >2 years old (Table 10). FDA agrees with the recommendation to avoid moderate and strong CYP3A inhibitors in patients 2 years or younger.

Table 10: Recommended Dose Modifications of ROZYLTREK for Concomitant Use with Moderate or Strong CYP3A Inhibitors for Adults and Pediatric Patients 2 Years and Older

Starting dose*	Moderate CYP3A	Strong CYP3A
200 mg	50 mg QD	50 mg on alternate days
300 mg	100 mg QD	50 mg QD
400 mg	200 mg QD	50 mg QD
600 mg	200 mg QD	100 mg QD
* For pediatric patients with a starting dose <200 mg, avoid coadministration with moderate or strong CYP3A inhibitors		

Food Effect: In the original NDA, a high-fat meal was demonstrated to have no significant effect on entrectinib exposure withthe capsule formulation . No in vivo food effect study was conducted for the coated granule formulation. In addition to relative bioavailability study comparing coated granules and capsules following administration of a light meal (Section 6.3.2.5) , the Applicant provided a physiologically based biopharmaceutical model (PBBM) to assess the bioequivalence of coated granules and capsules under the fasted state. The PBBM model was found to be inadequate (refer to OPQ Biopharmaceutics Review). Nonetheless, the recommendation for administration without regards to food was supported based on clinical experience, as coated granules were administered without regards to food in the pediatric clinical studies.

Different soft foods were reportedly used to administer coated granules orally across STARTRK-NG and TAPISTRY studies. However, this information was not formally

collected. Nonetheless, the exposures for pediatric patients who received coated granules were within range of pediatric patients who received other entrectinib formulations and administration methods (see Section 19.4.4.1 for details).

Dose Adjustment for Strong and Moderate CYP3A inhibitors:
FDA agrees that the PBPK analyses are adequate to support the dosage adjustment scheme proposed by the Applicant shown in Table 10. The PBPK models of entrectinib and M5 could reasonably well simulate the effects of itraconazole and rifampin on entrectinib and M5 observed in adults and the exposure of entrectinib and M5 PK in patients older than 2 years. When the proposed dosing regimens were given following coadministration with strong or moderate CYP3A inhibitors, the combined exposure of entrectinib and M5 in pediatrics aged 2 to 12 years old was within the observed efficacious exposure in adults. For detailed assessment, see section 19.4.3.

9.3.7. Is a scientific bridge established between the proposed formulations and administration methods ?

The FDA's Assessment:

FDA finds that an adequate scientific bridge has been established between coated granule and F06 capsule formulation, and between F06 capsule administered as suspension, either orally or via gastric/nasogastric tube, compared to intact F06 capsule formulation.
Single dose entrectinib exposures were found to be comparable between coated granules and capsules in healthy subjects when administered with a light meal (refer to Section 19.4.4.2 for details). Further, entrectinib exposures between coated granules and capsules were comparable in pediatric patients in STARTRK-NG (refer to Section 19.4.4.1) and were within the range of adult exposures.
Single dose entrectinib exposures were shown to comparable when capsule contents were administered as suspension in milk or water either orally or via nasogastric tube compared to intact formulation in healthy subjects under fasted conditions (see Table 11) refer to Section 19.4.4.2 for details)

Table 11: Statistical Summary of Capsule Administered as Oral Suspension or as Suspension in Milk or Water via Nasogastric Tube compared to Intact Capsule in Healthy Subjects under Fasted Conditions in Study GP44192.

Comparisons (600 mg dose) (fasted conditions)	**n**	**PK parameters**	**GMR (90% CI)**	
			Entrectinib	**M5**
F06: NG vs. Capsules	13-16	Cmax	0.99 (85, 116)	0.98 (79, 122)

		AUCinf	1.04 (87, 125)	1.03 (89, 120)
F06: Oral Susp (20 mg/mL in milk) vs. Capsules	13-16	Cmax	1.24 (106, 145)	1.48 (119, 184)
		AUCinf	1.13 (94, 135)	1.32 (112, 154)
F06: Oral Susp (20 mg/mL in water) vs. Capsules	15	Cmax	0.81 (72, 93)	0.73 (55, 98)
		AUCinf	0.91 (82, 101)	0.88 (70, 110)
GMR: geometric mean ratio, CI: confidence interval Source: CSR GP44192				

The statistical comparisons in the table above indicate higher PK exposures for F06 capsule administered as oral suspension in milk compared to intact F06 capsules. Based on exploratory exposure-safety relationships in pediatric patients, a positive relationship was observed only between entrectinib exposure and the probability of bone fractures. Nonetheless, the predicted increase in the probability of bone fractures for the observed increase in entrectinib exposure following administration of F06 capsule as oral suspension in milk varied only between 0.4% to 1.6% in pediatric patients 1-6 month and pediatric patients >6 months with BSA between 0.5 to- 0.8 m^2.

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Primary Reviewer: Sriram Subramaniam Team Leader: Jeanne Fourie Zirkelbach

10 Sources of Clinical Data

10.1. Table of Clinical Studies

The Applicant's Position:

Table 12 Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of pediatric patients	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
STARTRK-NG (CO40778)	NCT02650401	Phase I/II open-label, dose escalation, and expansion	**Phase I:** Doses ranging from 250 to 750 mg/m^2/day orally **Phase II:** F06: Doses ranging from 100 to 600 mg PO or from 20 to 600 mg as aqueous suspension via NG/gastric tube or orally via a syringe daily F1: Doses ranging from 300 to 600 mg PO daily Coated granules: Doses ranging from 100 to 600 mg PO daily	BICR-assessed ORR	Until disease progression, unacceptable toxicity, withdrawal of consent or death	N=68	Pediatric patients with locally advanced or metastatic solid or primary CNS tumors	25 sites in 9 countries
TAPISTRY (BO41932)	NCT04589845	Phase II, global, multicenter, open-label	600 mg PO daily for patients with BSA ≥1.51 m^2 Doses ranging from 100 to 600 mg PO daily for patients with BSA<1.51 m^2 F06: Doses ranging from 100 to 600 mg PO or from 20 to 600 mg as aqueous suspension via NG/gastric tube or orally via a syringe daily Coated granules: Doses ranging from 100 to 600 mg PO daily	BICR-assessed ORR	Until disease progression, unacceptable toxicity, withdrawal of consent or death	N=6	Pediatric patients with *NTRK* or *ROS1* fusion-positive tumors	6 sites in 5 countries
STARTRK-02 (GO40782)	NCT02568267	Phase II, global, multicenter, open-label	600 mg PO daily	BICR-assessed ORR	Until disease progression, unacceptable toxicity, withdrawal of consent or death	N=2	Pediatric patients with locally advanced or metastatic solid tumors that harbor *ROS1* gene rearrangement [a]	2 sites in 2 countries (United States and Italy)

BICR=blinded Independent Central Review; BSA=body surface area; ORR=objective response rate; PO=orally.

The FDA's Assessment:
FDA agrees with the Applicant's description of clinical trials.

11 Statistical and Clinical Evaluation

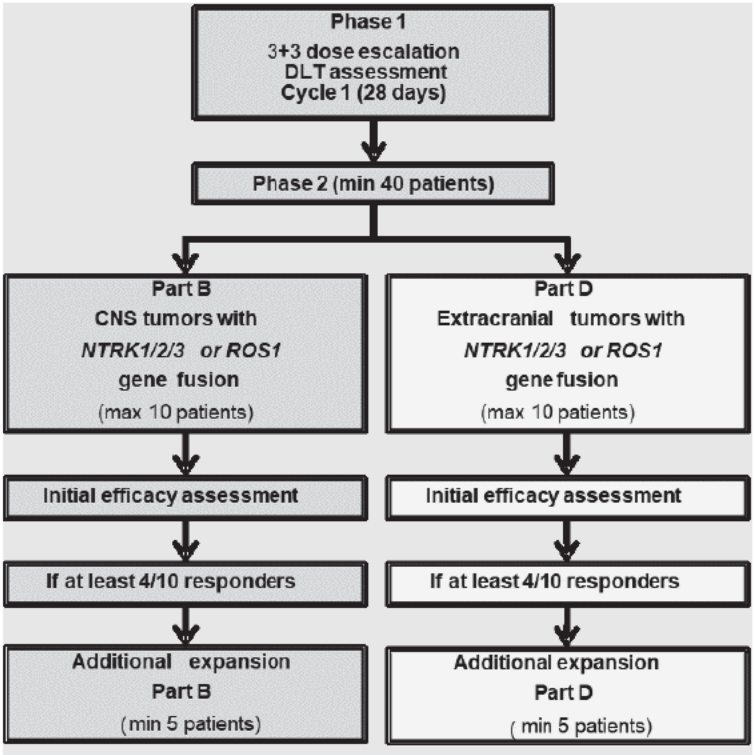
11.1. Review of Relevant Individual Trials Used to Support Efficacy

11.1.1. Study CO40778 (STARTRK-NG)

Trial Design

The Applicant's Description:
STARTRK NG is a Phase I/II multicenter, open label dose-escalation study in the rare population of pediatrics patients with relapsed or refractory extracranial solid tumors (Phase I; Part A), with additional expansion cohorts (Phase II) in patients with primary brain tumors harboring NTRK or ROS1 gene fusions (Part B), and extracranial solid tumors harboring NTRK or ROS1 gene fusions (Part D). An overview of the study design is shown in Figure 1.

Figure 4 STARTRK NG Study Schema



Phase I, Part A (dose escalation, completed December 2017) determined the MTD or RP2D, PK and safety profile of entrectinib, administered as the F1 formulation, in pediatric patients with relapsed or refractory extracranial solid tumors.

Phase II (dose expansion, ongoing) was opened after the determination of the RP2D (550 mg/m2, using the F1 formulation) in Phase I, Part A. In addition, patients were also able to be dosed with F06 formulation at the recommended dose of 300 mg/m2 (for patients ≥ 6 months), 250 mg/m2 (1–6 months), or 100 mg/m2 (newborn to <1 month), assessed by modeling and simulation.

The initial protocol design was characterized by five cohorts in the Phase II portion; however, from protocol amendment version 5 onward, only Parts B (primary brain tumors with gene fusions) and D (extracranial tumors with gene fusions) remained open.
The primary objective of the Phase II portion of the study is to evaluate the efficacy of entrectinib as assessed by Confirmed Objective Response Rate (ORR). Responses will be evaluated with use of the RANO for primary CNS tumors and RECIST v1.1 in patients with extracranial solid tumors, as assessed by blinded Independent Central Review (BICR).
Study Treatment: Phase II Cohorts B and D
All patients in this study received entrectinib administered orally or via nasogastric/gastric tube, as appropriate, QD, in repeated 4-week (28-day) cycles. Entrectinib was administered as an outpatient-based treatment. In this study, several formulations were used (i.e., F1, F06, and coated granules) based upon the patients' ability to swallow.

The FDA's Assessment:
FDA agrees with the Applicant's description of STARTRK-NG. For both Cohorts B and D, a two-stage design was implemented with 10 patients planned in Stage I and 5-10 patients planned in Stage II. A futility analysis was planned at the end of Stage I and the study was planned to continue to Stage II if 4 responses were observed out of 10 patients. Multiple formulations have been utilized during the clinical development of entrectinib. The initial formulation used in pediatrics was the F1 capsule, which does not contain acidulant and is sensitive to gastric conditions such as concomitant food intake and increased pH caused by concomitant medications. Subsequently, a capsule formulation (F06) containing an alternative acidulant (tartaric acid) was developed and is the current approved commercial formulation. Both F1 and F06 (available as 100 mg and 200 mg dose strengths) are used in pediatrics.

Later in clinical development, an age-appropriate formulation for younger children with difficulty swallowing was developed, which is a film-coated (b) (4) formulation initially described as granules, but during this review, has been finalized as pellets (F15/F17, 50 mg per packet) to be taken with food. Additionally, a new suspension presentation, prepared from contents of the approved F06 capsule, is intended for oral administration for patients unable to swallow

capsules, and via nasogastric tube for patients who require enteral administration. See Section 19.4.4.1.

Eligibility Criteria

The Applicant's Description:

Each patient met all of the following inclusion criteria to be eligible for study entry:

- Sex and age: male or female aged from birth to age < 18 years
- Tumor types included below harboring *NTRK1/2/3* or *ROS1* gene fusions as determined locally by an appropriately validated assay performed in a Clinical Laboratory Improvement Amendments-certified or equivalently-accredited diagnostic laboratory, or centrally by a [redacted] (b) (4) Clinical Trial Assay, or the alternative, approved central laboratory assay for that region:
  - Phase I portion: **Cohort A:** Relapsed or refractory extracranial solid tumors
  - Phase II portion:

    Cohort B: Primary brain tumors with *NTRK1/2/3* or *ROS1* gene fusions; gene fusions are defined as those predicted to translate into a fusion protein with a functional TRKA/B/C or ROS1 kinase domain, without a concomitant second oncodriver (e.g., known, activating mutations in EGFR, KRAS) as determined by a nucleic acid-based diagnostic testing method (e.g., NGS, Sanger, reverse transcriptase (RT) polymerase chain reaction [PCR], NanoString, EdgeSeq).

    Cohort D: Extracranial solid tumors (including NB) with *NTRK1/2/3* or *ROS1* gene fusions; gene fusions are defined as those predicted to translate into a fusion protein with a functional TRKA/B/C or ROS1 kinase domain, without a concomitant second oncodriver (e.g., known, activating mutations in EGFR, KRAS) as determined by a nucleic acid-based diagnostic testing method (e.g., NGS, Sanger, RT-PCR, NanoString, EdgeSeq).
- Histologic/molecular diagnosis of malignancy at diagnosis or the time of relapse
- Performance status: Lansky or Karnofsky performance score ≥60% and minimum life expectancy of at least 4 weeks
- Patients must have a disease that is locally advanced, metastatic, or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options for solid tumors and primary CNS tumors that are *NTRK* or *ROS1* gene fusion-positive.
- Patients must have recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to enrollment.
- Organ Function
  - Adequate bone marrow function:
  - **Cohorts A (closed; all), B (all), C (closed;** unknown or without documented tumor infiltration of bone marrow at enrollment), and **D (all):**

- ANC ≥1000 µL.
- Platelet count ≥75,000/µL (unsupported for 72 hours).
- Hemoglobin ≥8 g/dL (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE], Version 4.03) term anemia, transfusion permitted).
- **Cohort C (closed;** with documented tumor infiltration of bone marrow at enrollment)
- ANC ≥750µL.
- Not known to be refractory to platelet transfusions.
- Hemoglobin ≥8 g/dL (NCI-CTCAE v4.03) term anemia, transfusion permitted).

- Adequate liver function:
  - ALT <3 × upper limit of normal (ULN; ULN for protocol: 45 U/L)
  - Bilirubin <1.5 × ULN
- Adequate renal function:
  - Serum creatinine ≤1.5 × ULN for age or creatinine clearance (or radioisotope glomerular filtration rate) > 70 mL/min/1.73 m^2
- Adequate cardiac function:
  - electrocardiogram (ECG) with corrected QT interval (QTc) ≤450 msec
- Adequate neurologic function:
  - Peripheral motor or sensory neuropathy Grade ≤2 unless related to tumor or prior surgery
- Females of childbearing potential must have a negative serum pregnancy test during screening and be neither breastfeeding nor intending to become pregnant during study participation. A female is considered of childbearing potential if the first menarche has occurred.

The FDA's Assessment:
FDA agrees with the description of the eligibility crtieria.

Study Endpoints

The Applicant's Description:

Primary Endpoint

Confirmed Objective Response Rate (ORR)

The primary endpoint for these studies is confirmed ORR, as assessed by BICR using RECIST v1.1 or RANO criteria.

Confirmed ORR was defined as the proportion of patients with confirmed CR or PR; a confirmed response is a response that is sustained on repeat imaging ≥4 weeks after initial documentation of response. Such patients with a confirmed objective response (CR or PR) were referred to as responders. Patients without a confirmed objective response, or without a post-baseline tumor assessment, were counted as non-responders.

Secondary Endpoints
The following secondary endpoints were assessed by BICR using RECIST v1.1 or RANO:

Duration of Confirmed Response (DOR)

Time to Confirmed Response (TTR)

Clinical Benefit Rate (CBR)

Progression-Free Survival (PFS)

Overall Survival (OS)

The FDA's Assessment:
FDA agrees with the Applicant's description of the primary and secondary endpoints. FDA does not consider the endpoint of clinical benefit rate for regulatory decision-making as it includes the proportion of patients with stable disease which may be reflective of the natural history of the disease and not an effect of the drug. Additionally, FDA considers time to event endpoints, such as progression-free survival, overall survival, and time of confirmed response, to be uninterpretable in the context of a single arm study.
In addition, the analysis population is comprised of all patients who received at least 1 dose of study treatment.

Statistical Analysis Plan and Amendments

The Applicant's Description:
Changes in the planned analyses for the study that were implemented by protocol amendments are described in the protocol.

The FDA's Assessment:
FDA agrees with the Applicant's description of the statistical analysis plan.

Protocol Amendments

The Applicant's Description:
The CO40778 Protocol was amended 9 times since the first version (Version 1) dated 05 November 2015. Table 2 summarizes the key changes made to the protocol with each amendment.

Table 13 Summary of Protocol Amendments

Protocol Amendment (Date)	Rationale and Key Changes
Protocol Version 1 (05 November 2015)	Initial version
Protocol Version 2 (18 November 2015)	FDA feedback was incorporated to clarify dose modification criteria for DLTs. Patient enrollment in Phase I began under this amendment.
Protocol Version 3 (30 November 2016)	Phase 1b portion was expanded beyond neuroblastoma, to cancers which harbor *TRK*, *ROS1*, or *ALK* molecular alterations, especially gene fusions. Antitumor endpoints and statistical methods were added accordingly. Retrospective Blinded Independent Central Review of tumor assessments was introduced for gene fusion-positive patients and neuroblastoma responders. Part B (Primary Brain Tumors) was moved to the Phase 1b portion of the study, and Part E was created to accommodate patients with an age ≥2 years and < 22 years unable to swallow capsules and all patients < 2 years. Alternative dosing methods were specified. Nonclinical findings of embryo-fetal and ocular toxicities were incorporated in study design including additional contraceptive guidance and ophthalmologic exams. Additional collection of blood samples was added for entrectinib PK analysis.
Protocol Version 4 (24 March 2017)	Changes were made to incorporate FDA feedback: Starting dose for Part E patients changed to -1-dose level de-escalation from the RP2D with re-escalation to the pediatric RP2D starting from Cycle 3 onwards based onacceptable safety and PK exposure from Cycle 1. Update to stipulate that patients enrolled in Part E were to be dosed in the fed state with a meal that has a standardized fat content and volume. Moderate CYP3A inhibitors and inducers were included in Table 4 which lists drugs requiring caution when administered with entrectinib.
Protocol Version 5 (25 October 2018)	Changes were introduced to reflect a change in study design and Sponsor: Sponsor changed to F. Hoffmann-La Roche Ltd from Ignyta, Inc. Design changed from Phase Ib to Phase II. Enrollment expanded to include patients with *NTRK, ROS1,* or *ALK* fusion-positive tumors who had no acceptable standard first-line therapies. Dose expansion phase of the study updated to restrict enrollment to patients with tumors harboring *NTRK, ROS1,* or *ALK* fusions to maximise therapeutic intent. Design also streamlined with two main cohorts of CNS tumors harboring *NTRK, ROS1,* or *ALK* fusions and extracranial solid tumors harboring *NTRK, ROS1,* or *ALK* fusions. NB cohort (Cohort C) and Cohort E closed with Protocol Amendment Version 5. Statistical design modified to a two-step gated design to determine whether entrectinib has sufficient anti-cancer activity to warrant further development of Cohorts B and D.

Protocol Amendment (Date)	Rationale and Key Changes
	Additional information incorporated regarding the management of patients unable to swallow capsules due to the simplified expansion design including safety run-in. Information incorporated to describe the remit of the iDMC and frequency of meetings. Study objectives and endpoints were modified to align with the new study design. The inclusion criteria were updated to specify that archival tumor tissue is required for all patients. Patients will be enrolled via local molecular testing or through submission of tumor tissue and the independent central testing would be performed by (b) (4) laboratory. Details were included regarding a new formulation of the drug to be distributed in the trial. Per requirement from the European Regulatory Agency, a taste acceptability survey was included to be completed by patients receiving capsules and any pediatric-specific formulation and associatedsecondary objective added. The safety reporting requirements section was updated to incorporate relevant AESI information of Hy's Law events to be immediately reported to the Sponsor to ensure effective safety monitoring during the study.
Protocol Version 6 (21 May 2019)	The Sponsor decided to discontinue the enrollment of patients with solid tumors harboring *ALK* fusions to align with the adult indication and (b) (4) Details on dosing and administration of the F06 formulation were included. Tanner scale was added to define physical measurements of development. Measures to monitor neurological and neurocognitive status for children were included.. An integrated efficacy analysis for *NTRK1/2/3* fusion-positive patients was added to provide a comprehensive summary of efficacy in this population. Dose modifications and guidance for cognitive disorders or intolerable CNS toxicity, syncope, congestive heart failure, and QTc interval prolongation were added to align with current entrectinib risk language. Cardiac exclusion criteria were changed to align more closely with updated safety language and LVEF measurements were added at baseline (screening), Cycle 3, Day 1 and as clinically indicated.

Protocol Amendment (Date)	Rationale and Key Changes
Protocol Version 7 United Kingdom (22 August 2019), France (17 September 2019), Spain (7 November 2019), and Germany (6 February 2020) Only	Protocol CO40778 (RXDX-101-03) Version 7 was amended for the United Kingdom to ensure male and female patients are using highly effective contraceptive methods. Contraceptive language was updated accordingly. Additional cardiac exclusion criteria was also added to further clarify the enrollment criteria for patients with prolonged QTc or history of cardiac failure. Protocol CO40778 (RXDX-101-03), Version 7 was amended for France to be more precise concerning the indication under study. Text was also added to justify the efficacy of entrectinib after the second dose reduction of the F06 formulation. Contraceptive criteria were also revised to clarify the methods that are permitted during and after the study and additional ECG monitoring was added. Protocol CO40778 (RXDX-101-03), Version 7 was amended for Spain to clarify contraceptive and confidentiality language.
Protocol Version 8 (17 December 2019)	The title was revised to be more specific concerning the indication under study and inclusion criteria updated from < 22 years to < 18 years, and the reference to young adults removed. Details included regarding the dosing and administration of the film-coated granules/F15 formulation for patients unable to swallow intact capsules. Additional bone monitoring assessments were incorporated (as part of exploratory endpoints), including DXA scans, hand/wrist and knee X-rays, and biological markers of bone formation, bone resorption, and calcium metabolism. Exclusion criteria also added for patients with familial or personal history of congenital bone disorders, bone metabolism alterations or osteopenia.
Protocol Version 9 (09 June 2021)	Protocol CO40778 (RXDX-101-03), global version 8 was amended to incorporate changes from France and Germany-specific protocol updates to ensure alignment between the protocols including updates to the nonclinical overview section, addition of an Integrated Risk Assessment, addition of a risk assessment for the administration of COVID-19 vaccines to patients in the study and details added on the possibility for patients to interrupt the treatment after a minimum period of 24 months on treatment and in case of complete response with no evidence of disease for at least 6 months' treatment. Secondary objectives were also updated to include an evaluation of efficacy and safety as assessed by ORR, DOR, and TTR in subsets of efficacy-evaluable and safety-evaluable patients and dosing recommendations for the coated granule formulation were further broken down into [redacted] (b) (4) with updated values included. New adverse events of special interest that are immediately reportable to the Sponsor were added and the definition of the efficacy-evaluable population was clarified to include patients with measurable or evaluable disease at baseline.
Protocol Version 10 (22 September 2021)	Protocol CO40778 (RXDX-101-03), Version 9 was amended to correct errors mainly in the Schedule of Assessments and Coated Granule Dosing Tables.

AESI=adverse event of special interest; BMD=bone mineral density; DLT=dose-limiting toxicity; DOR=duration of response; DXA=dual X-ray absorptiometry; GI=gastrointestinal; iDMC=independent Data Monitoring Committee; LVEF=left ventricular ejection fraction; NB=neuroblastoma; ORR=objective response rate; PK=pharmacokinetic; QTc=corrected QT intervals; QTcF=QT/corrected QT interval with use of Fridericia's formula; RP2D=recommended phase 2 dose; TTR=time to response.

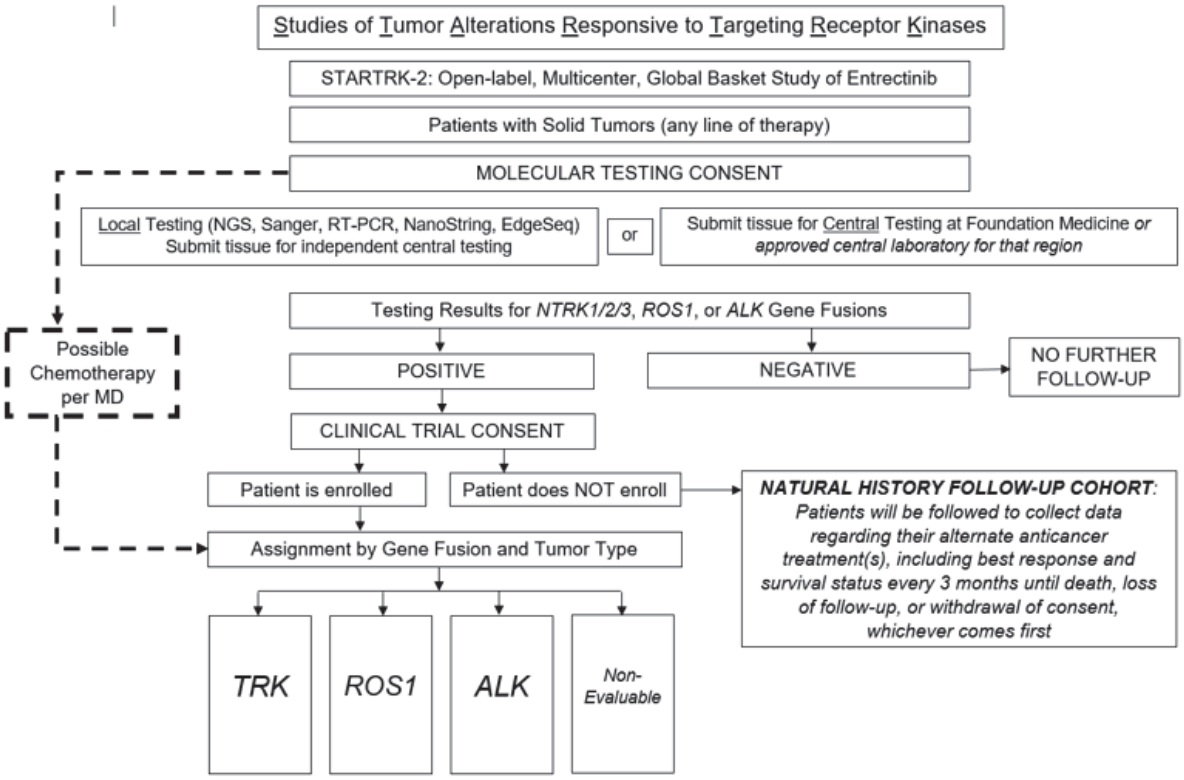
The FDA's Assessment:

FDA agrees with description of protocol amendments for STARTRK-NG (CO40778) .

11.1.2. Study GO40782 (STARTRK-02)

STARTRK-02 is a Phase II, global, multi-center, open-label basket study investigating the efficacy, safety, and PK of entrectinib for the treatment of patients with solid tumors that harbor an *NTRK, ROS1*, or *ALK* gene rearrangement (fusion). Entrectinib was self-administered orally at home (except on clinic days) on a continuous daily dosing regimen of 600 mg, in repeated 28-day cycles. An overview of the study design is shown in Figure 2.
Details about inclusion and exclusion criteria are provided in the GO40782 Data Memo, Section 2.

Figure 5 STARTRK-02 Study Schema



ALK=Anaplastic lymphoma kinase; MD=medical doctor; TRK=tropomyosin receptor kinase.

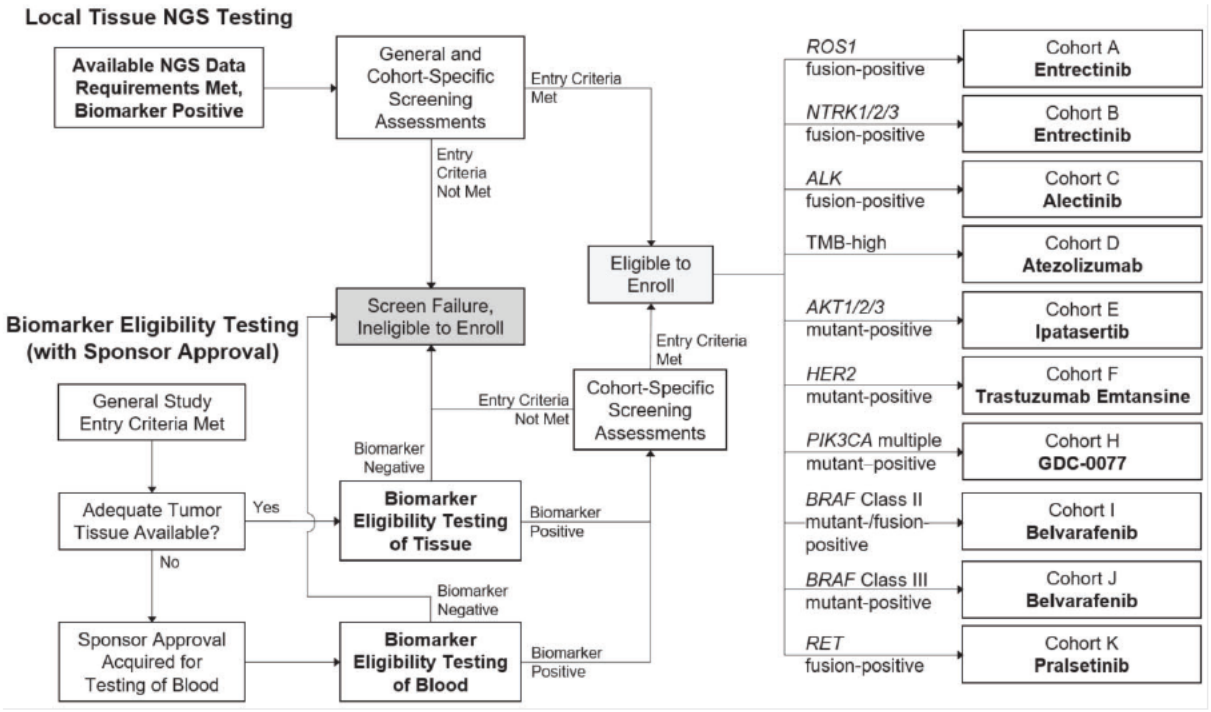
The FDA's Assessment: FDA agrees with the Applicant's description of Study GO40782 (STARTRK-02). No patients with NTRK fusions from this study were included in the efficacy analyses.

11.1.3. Study BO41932 (TAPISTRY)

TAPISTRY is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in patients with unresectable, locally advanced or metastatic solid tumors determined to harbor specific oncogenic genomic alterations or that are TMB-high as identified by a validated NGS assay. An overview of the study design is provided in Figure 3.

Details about inclusion and exclusion criteria are provided in the BO41932 Data Memo, Section 2.1.

Figure 6 TAPISTRY Study Schema



ALK = anaplastic lymphoma kinase; HER2 = human epidermal growth factor receptor 2; NGS = next-generation sequencing; NTRK = neurotrophic tyrosine receptor kinase; TMB = tumor mutational burden.

The FDA's Assessment:

FDA agrees with the Applicant's description of Study BO41932 (TAPISTRY). The primary endpoint is ORR as assessed by BICR per RANO for brain tumors and per RECIST 1.1 for solid tumors. Secondary endpoints include DOR, PFS and OS. No formal sample size calculation was provided, but up to 200 patients were planned to be included in the study. The analysis population is comprised of all patients who received at least one dose of study treatment.

11.1.4. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

Studies were conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP)

Guidelines

- Applicable laws and regulations

The Roche Clinical Quality Assurance group or designee conducted one service provider audit. No critical audit findings were observed. For all audit findings appropriate corrective and preventative were undertaken.

The FDA's Assessment:

FDA agrees with the Applicant's statement. See NDA submission Module 2.5 "Clinical Overview" Section 1.7 for declaration of GCP.

Financial Disclosure

The Applicant's Position:

Details of financial disclosures for STARTRK-NG (CO40778), STARTRK-2 (GO40782), and TAPISTRY (BO41932) are provided in Section 19.2.

The FDA's Assessment:

In accordance with 21 CFR 54, Genentech submitted financial disclosure certification documents in Module 1.3.4. Genentech provided Form 3454, attesting to the absence of financial interests and arrangements for investigators and sub-investigators in each study.

FDA agrees with the Applicant that the investigators involved in STARTRK-NG (CO40778), STARTRK-2 (GO40782), and TAPISTRY (BO41932) had no financial arrangements that would affect the outcome of the trial.

For further details see Section 19.2.

Patient Disposition

The Applicant's Position:

For Study STARTRK-NG, a total of 68 patients <18 years were enrolled in either Phase I or Phase II of this study across 25 sites in North America, Europe, and Asia and received at least 1 dose of entrectinib. The number of patients enrolled per region and country, followed by the number of centers (in parentheses), is summarized below in descending order:

- Europe: Spain 1 (1), Germany 2 (1), France 3 (2), Italy 2 (1), United Kingdom 2 (2)

- Asia: China 10 (2), Hong Kong 1 (1)
- North America: United States of America 45 (14), Canada 2 (1)

For Study STARTRK-02, a total of 2 pediatric patients <18 years were enrolled in two sites in the United States and Italy. For TAPISTRY, pediatric patients were enrolled in Australia 1 (1), Hong Kong 1 (1), Italy 1 (1), Republic of Korea 2 (2), and Switzerland 1 (1).

A total of 76 patients $<$ 18 years old from STARTRK-NG, TAPISTRY, and STARTRK-02 were included in this integrated analysis. At the CCOD (2 August 2022), of the 76 enrolled patients, 51 patients (67.1%) remained on study, and 25 patients (32.9%) had withdrawn from the study.

The FDA's Assessment:

Of the 33 patients involved in the efficacy population, 7 discontinued and 26 were still on study. Of the 7 discontinued patients, 6 died and 1 was lost to follow-up.

FDA agrees with the Applicant's disposition analysis of the pooled safety population (n=76) across STARTRK-NG, TAPISTRY, and STARTRK-02 (see Section 8.2).

Protocol Violations/Deviations

The Applicant's Position:

Critical and important protocol deviations included deviations that could have significant impact on the completeness, accuracy, and/or reliability of the study data or that significantly affected a patient's rights, safety, or well-being.

Study CO40778 (STARTRK-NG)
Overall, critical and important protocol deviations were reported in 60% of the safety-evaluable population . Among patients who had major protocol deviations, 54% had procedural deviations, 19% had medication deviations, and 3% had inclusion criteria deviations.
Additionally, 28% of patients had major protocol deviations related to the COVID-19 pandemic, out of which 27% had deviations related to subject movement restricted due to epidemic/pandemic, 3% had deviations for site action due to epidemic/pandemic, and 2% had deviations due to suspected epidemic/pandemic infection.

Study BO41932 (TAPISTRY)

There were 2 protocol deviations reported in 1 patient in the overall safety-evaluable population. Both were procedural deviations, one related to ICF/Assent and the other related to Tumor Assessment not done or done outside of the window.

The FDA's Assessment:

FDA agrees with the Applicant's statement regarding protocol deviations. Overall, the protocol deviations were not considered to have a significant impact on the efficacy or safety conclusions of the study.

Table of Demographic Characteristics

Data:

Table 14 Demographic and Baseline Characteristics Demographic and Baseline Characteristics, Patients (<18 years old), Safety-Evaluable Patients

Table Demographic and Baseline CharacteristicsDemographic and Baseline Characteristics, Patients (<18 years old), Safety-Evaluable Patients

Protocols: CO40778, BO41932, GO40782
Pooled Population

	STARTRK-NG (N=68)	TAPISTRY (N=6)	STARTRK-02 (N=2)	Total (N=76)
Sex				
n	68	6	2	76
Male	34 (50.0%)	2 (33.3%)	1 (50.0%)	37 (48.7%)
Female	34 (50.0%)	4 (66.7%)	1 (50.0%)	39 (51.3%)
Age (years)				
n	68	6	2	76
mean	6.56	3.67	15.00	6.55
std	4.64	4.03	0.00	4.79
median	6.00	2.50	15.00	6.00
Q1, Q3	3.00, 10.00	0.00, 7.00	15.00, 15.00	3.00, 10.00
Min, Max	0.0, 17.0	0.0, 10.0	15.0, 15.0	0.0, 17.0
Age group				
>= 0 to < 28 days	0	0	0	0
>= 28 days to < 24 months	12 (17.6%)	2 (33.3%)	0	14 (18.4%)
>= 24 months to < 12 years	45 (66.2%)	4 (66.7%)	0	49 (64.5%)
>= 12 years to < 18 years	11 (16.2%)	0	2 (100%)	13 (17.1%)
Ethnicity				
n	68	6	2	76
Hispanic or Latino	7 (10.3%)	0	1 (50.0%)	8 (10.5%)
Not Hispanic or Latino	51 (75.0%)	6 (100%)	1 (50.0%)	58 (76.3%)
Not Stated	3 (4.4%)	0	0	3 (3.9%)
Unknown	7 (10.3%)	0	0	7 (9.2%)
Race				
n	68	6	2	76
Asian	12 (17.6%)	3 (50.0%)	0	15 (19.7%)
Black or African American	5 (7.4%)	0	0	5 (6.6%)
White	46 (67.6%)	3 (50.0%)	2 (100%)	51 (67.1%)
Other	5 (7.4%)		0	5 (6.6%)
Weight (kg)				
n	68	6	2	76
mean	25.04	16.40	50.85	25.04
std	15.24	11.65	4.45	15.51
median	21.75	14.05	50.85	21.75
Q1, Q3	16.35, 33.40	7.50, 23.00	47.70, 54.00	14.95, 33.70
Min, Max	3.5, 79.2	3.8, 36.0	47.7, 54.0	3.5, 79.2

	STARTRK-NG (N=68)	TAPISTRY (N=6)	STARTRK-02 (N=2)	Total (N=76)
Height (cm)				
n	68	6	2	76
mean	116.01	93.60	167.20	115.59
std	30.41	32.61	3.11	31.73
median	114.90	95.20	167.20	114.90
Q1, Q3	98.00, 137.75	62.50, 124.70	165.00, 169.40	95.50, 137.75
Min, Max	52.0, 176.9	51.0, 133.0	165.0, 169.4	51.0, 176.9
BSA (m2)				
n	68	6	2	76
mean	0.88	0.64	1.55	0.88
std	0.37	0.34	0.04	0.38
median	0.82	0.62	1.55	0.82
Q1, Q3	0.68, 1.13	0.34, 0.88	1.52, 1.57	0.63, 1.15
Min, Max	0.2, 1.9	0.2, 1.2	1.5, 1.6	0.2, 1.9
BMI (kg/m^2)				
n	68	6	2	76
mean	17.06	16.68	18.23	17.06
std	3.45	2.67	2.27	3.35
median	16.18	16.01	18.23	16.23
Q1, Q3	14.98, 18.30	14.61, 19.20	16.62, 19.83	14.87, 18.36
Min, Max	11.3, 28.6	13.9, 20.4	16.6, 19.8	11.3, 28.6
Baseline Lansky/Karnofsky Score				
n	67	6	0	73
60	2 (3.0%)	0	0	2 (2.7%)
70	2 (3.0%)	0	0	2 (2.7%)
80	12 (17.9%)	2 (33.3%)	0	14 (19.2%)
90	20 (29.9%)	1 (16.7%)	0	21 (28.8%)
100	31 (46.3%)	3 (50.0%)	0	34 (46.6%)
			0	

The youngest patient at enrollment is 1.3 months.
Age is calculated as (Date of informed consent - Date of Birth + 1)/365.25. If the date of birth was partially collected, it was imputed to the 15th of June unless the patient
was born in the same year as the year of the informed consent. In this last case, the 1st of Jan. was used.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932, STARTRK-02 = study GO40782.
CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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25JAN2023 17:08
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Table 15 Demographics of US Pediatric Patients (<18 years old) in the Safety-Evaluable Population

	STARTRK-NG (N=45)	STARTRK-02 (N=1)	Total (N=46)
Sex			
n	45	1	46
Male	23 (51.1%)	0	23 (50.0%)
Female	22 (48.9%)	1 (100%)	23 (50.0%)
Ethnicity			
n	45	1	46
Hispanic or Latino	7 (15.6%)	1 (100%)	8 (17.4%)
Not Hispanic or Latino	35 (77.8%)	0	35 (76.1%)
Not Stated	1 (2.2.%)	0	1 (2.2%)
Unknown	2 (4.4%)	0	2 (4.3%)
Race			
n	45	1	46
Asian	0	0	0
Black or African American	5 (11.1%)	0	5 (10.9%)
White	37 (82.2%)	1 (100%)	38 (82.6%)
Other	3 (6.7%)	0	3 (6.5%)

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Oct 03 2022 (GO40782)

Pooled Population: Protocols CO40778, GO40782

This table presents the sex, ethnicity and race demographics for these US patients specifically; 57.9% (46/76) of the global safety-evaluable population are the US patients.

The Applicant's Position:

Among the 76 patients, 51% were female, 49% were male, and the majority were White (67%). The median age was 6.0 years (range: 0-17 years), and the majority of patients (65%) were ≥ 24 months to < 12 years old. The youngest patient at enrollment was 1.3 months old. The majority of patients (55 out of 76 patients [72%]) had a Karnofsky/Lansky performance score of at least 90 at screening.

The demographic data from the STARTRK-NG and STARTRK-2 US population is comparable with the estimated incidence of pediatric patients with *NTRK* fusion-positive tumors based on the SEER and FoundationCORE® data (STARTRK-NG and STARTRK-2 vs estimated: black (10.9% vs. 16.0%), white (82.6% vs. 76.0%), Asian (0% vs 4.0%) other (6.5% vs 4.0%)). In conclusion, the ethnic diversity represented, based on currently available data across studies STARTRK-NG and STARTRK-2, reflects the racial and ethnic diversity of the US pediatric patient population with *NTRK* fusion-positive tumors.

The FDA's Assessment:

The demographics described above are for the safety population. FDA analysis of the demographic of pediatric patients in the primary efficacy population are described below (n=33). Overall the median age range between the two studies is between 2-4 years old, with greater than 50% of the patients enrolled being from the U.S. Enrollment was highest among White (58%) and Asian (30%) patients; given the rarity of the population, there is no published literature describing the distribution of pediatric patients with solid tumors with NTRK fusions in the U.S. Further detail regarding demographic and baseline characteristics in the primary efficacy population are summarized below in Table 16. See Subpopulations in Section 8.16 for a more detailed summary of prior therapy.

Table 16. Demographics and Baseline Characteristics of Pediatric Patients in Efficacy Population

	STARTRK-NG N = 31 n (%)	TAPISTRY N = 2 n (%)	Combined N = 33 n (%)
Age, Median (range)	4 (0-15)	2.5 (2-3)	4 (0-15)

	STARTRK-NG N = 31 n (%)	TAPISTRY N = 2 n (%)	Combined N = 33 n (%)
Sex			
Female	16 (52)	0	16 (48)
Male	15 (48)	2 (100)	17 (52)
Race			
Asian	9 (29)	1 (50)	10 (30)
Black or African American	1 (3.2)	0	1 (3.0)
Other	3 (10)	0	3 (9)
White	18 (58)	1 (50)	19 (58)
Ethnicity, n (%)			
Hispanic or Latino	3 (10)	0	3 (9)
Not Hispanic or Latino	20 (65)	2 (100)	22 (67)
Not Reported or Unknown	8 (26)	0	8 (24)
Country, n (%)			
US	16 (58)	0	16 (55)
Non-US	15 (42)	2 (100)	17 (45)
Region, n (%)			
North American	18 (58)	0	18 (55)
Asian	8 (26)	1 (50)	9 (27)
Europe	5 (16)	0	5 (15)
Australia	0	1 (50)	1 (3.0)
Baseline BSA, Median (range)	0.74 (0.22-1.83)	0.62 (0.60, 0.63)	0.74 (0.22-1.83)
Type of Tumor, n (%)			
Extracranial Solid Tumor	12 (39)	0	12 (36)
Primary CNS Tumor	16 (52)	1 (50)	17 (52)
Non-extracranial Solid Tumor	3 (10)	0	3 (9)
Sarcoma	0	1 (50)	1 (3.0)
Prior Chemotherapy, n (%)			
Yes	19 (61)	1 (50)	20 (61)

	STARTRK-NG N = 31 n (%)	TAPISTRY N = 2 n (%)	Combined N = 33 n (%)
No	12 (39)	1 (50)	13 (39)
Prior Targeted Therapy, n (%)			
Yes	4 (13)	0	4 (12)
No	27 (87)	2 (100)	29 (88)
Prior Radiotherapy Therapy, n (%)			
Yes	7 (23)	0	7 (21)
No	24 (77)	2 (100)	26 (79)
Prior Immunotherapy Therapy, n (%)			
Yes	1 (3.2)	0	1 (3.0)
No	30 (97)	2 (100)	32 (97)
Prior Systemic Therapy, n (%)			
Yes	21 (68)	1 (50)	22 (67)
No	10 (32)	1 (50)	11 (33)
Prior Surgery, n (%)			
Yes	19 (61)	1 (50)	20 (61)
No	12 (39)	1 (50)	13 (39)

Source: adsl.xpt for individual studies separately and combined, response to IR on prior lines of therapy.
DCO: 09/30/2022 for CO40778 and 09/29/2022 for BO41932

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

The Applicant's Position:

Overall, 39 out of 76 patients (51.3%) had an *NTRK* altered kinase. The median time from diagnosis to start of treatment was 11.7 months (range: 0.3–164.7 months). At baseline, the majority of patients (67.6%) presented with locally advanced disease, while 32.4% of patients presented with metastatic disease.

The FDA's Assessment:

The baseline disease characteristics and prior lines of therapies of the 33 pediatric patients with *NTRK* fusion-positive solid tumors treated with entrectinib in the efficacy population is summarized in Table 16. Overall, 85% of patients received prior anti-cancer therapy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

As of the CCOD, the median relative dose intensity was 100% (range: 25.4%–383.1%). Dose intensity was defined as the (the Cumulative Dose/Number of planned days)/Planned Daily Dose at the beginning of treatment $\times$ 100. Because dose intensity is relative to the dose at the beginning of treatment, growing pediatric patients may have a dose intensity $>$ 100%. For example, one patient was 2 months old at enrollment and started treatment at 50 mg daily. As of the CCOD, this patient was $>$ 6 months old; and therefore, was receiving entrectinib at 200 mg daily. The median total duration of treatment was 8.7 months (range: 0.2–44.7 months). Overall, 74 patients (97.4%) received at least one concomitant medication in the study. The most frequently reported classes of medications ($\geq$ 40% of patients) were:

- Analgesics (52 patients [68.4%])
- Antibacterials for systemic use (49 patients [64.5%])
- Drugs for constipation (43 patients [56.6%])
- Antiemetics and antinauseants (39 patients [51.3%])
- Vitamins (31 patients [40.8%])

The FDA's Assessment: FDA agrees with the Applicant's assessment of concomitant medication use. We did not independently verify dose intensity.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

For primary endpoint, please refer to Section 8.1.6.

The FDA's Assessment: FDA agrees.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

For secondary and other endpoints, please refer to Section 8.1.6.

The FDA's Assessment: FDA does not have additional comments. The efficacy results are based on pooled analyses of the two studies STARTRK-NG (n=31) and TAPISTRY (n=2).

Dose/Dose Response

The Applicant's Position:

Refer to section 6.2.2.1 and 19.4.2.

The FDA's Assessment:

FDA agrees.

Durability of Response

The Applicant's Position:
Refer to Section 8.1.6, Duration of Confirmed Objective Response, Progression-Free Survival and Overall Survival.

The FDA's Assessment: FDA agrees.

Persistence of Effect

The Applicant's Position:
Refer to Section 8.1.6, Duration of Confirmed Objective Response, Progression-Free Survival and Overall Survival.

The FDA's Assessment: FDA doesnot have any comments. The efficacy results are based on pooled analyses of the two studies STARTRK-NG (n=31) and TAPISTRY (n=2). Time to event endpoints, such as progression-free survival and overall survival, are not interpretable in single arm studies due to the lack of a comparator arm.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:
Not applicable as PRO efficacy endpoints were not assessed in the CO40778 study

The FDA's Assessment:
FDA agrees.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:
Reffer to Section 8.1.6, Subpopulations.

The FDA's Assessment: FDA agrees with the Applicant's description of subpopulation analyses.

11.1.5. Integrated Review of Effectiveness

The FDA's Assessment: See Section 8.1.7. The clinical and statistical review teams conclude that the Applicant provided substantial evidence of effectiveness of entrectinib in pediatric patients older than 1 month of age with solid tumors with *NTRK*-fusions.

11.1.6. Assessment of Efficacy Across Trials

Studies STARTRK-NG and TAPISTRY recruited patients ≤18 years of age with locally advanced or metastatic solid or primary CNS tumors that harbor NTRK or ROS1 gene fusions.

As of the CCOD (2 August 2022), a total of 33 patients satisfying all of the following criteria were included in the NTRK integrated efficacy population:

- Age < 18 years
- Had tumors that harbor an NTRK gene fusion
- No prior treatment with TRK inhibitors
- Measurable or evaluable disease at baseline
- Received at least one dose of entrectinib
- Had at least 6 months of follow-up (i.e., enrolled before 2 Feb 2022)

At the CCOD, the median duration of survival follow-up was 15.0 months (range: 1 to 57 months).

Primary Endpoints

Data:

Table 17 Confirmed Objective Response Rate (BICR Assessment), NTRK Integrated Analysis Population

Protocols: CO40778, BO41932
Pooled Population

	Total (N=33)
Responders	23 (69.7%)
95% CI	(51.29, 84.41)
Complete Response (CR)	14 (42.4%)
95% CI	(25.48, 60.78)
Partial Response (PR)	9 (27.3%)
95% CI	(13.30, 45.52)
Stable Disease (SD)	6 (18.2%)
95% CI	(6.98, 35.46)
Non-CR/Non-PD	2 (6.1%)
95% CI	(0.74, 20.23)
Progressive Disease (PD)	2 (6.1%)
95% CI	(0.74, 20.23)
Not Evaluable (NE)	0
Missing	0

Confidence Interval is calculated using Clopper-Pearson exact confidence interval.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932)
Patients Enrolled up to February 02, 2022.

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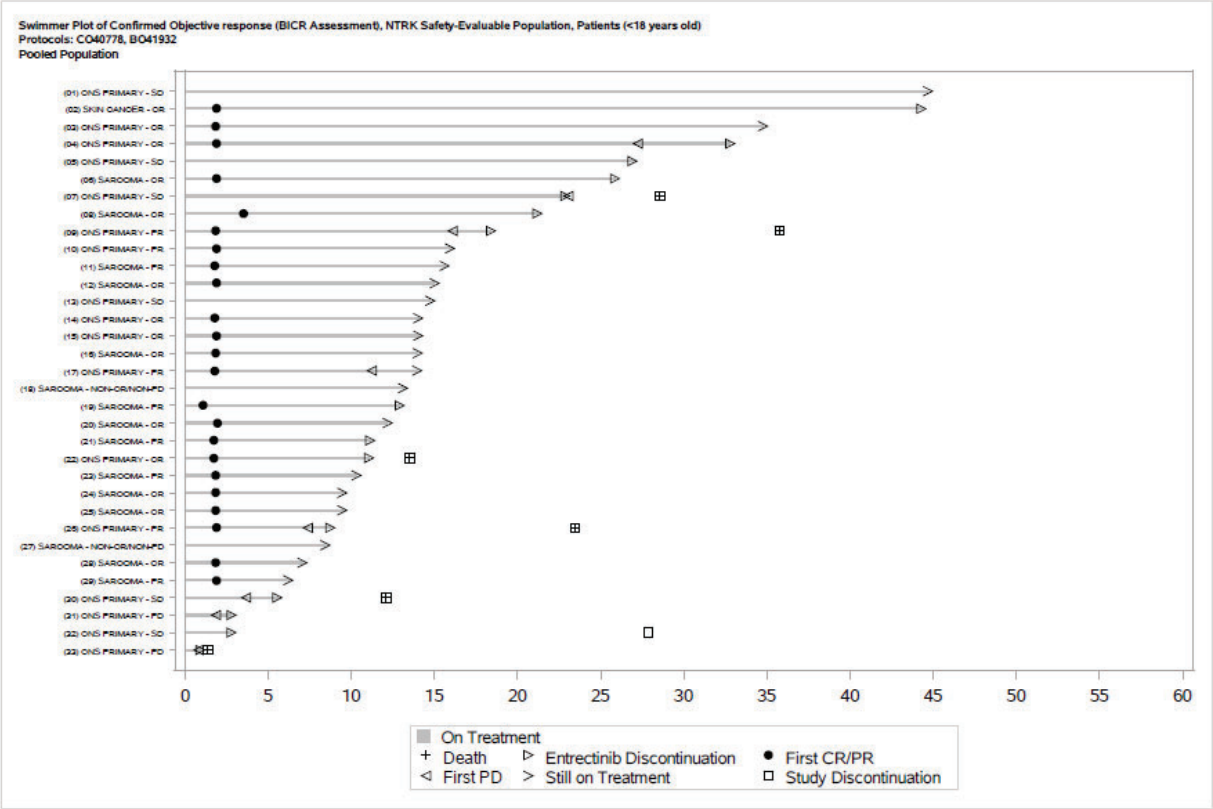
Figure 7 Swimmer Plot of Confirmed Objective Response (BICR Assessment), NTRK Integrated Analysis Population



The Applicant's Position:

Confirmed objective response rate by BICR was defined as the proportion of patients with a complete response or partial response on two consecutive occasions at least 4 weeks apart according to RECIST v1.1 or RANO by BICR assessment.

Confirmed objective responses were achieved in 23/33 patients (69.7%; 95% CI: 51.3, 84.4) in the NTRK integrated efficacy population (Table 12). The lower bound of the 95% CI excluded the reference ORR of 20%, demonstrating that entrectinib had a clinically meaningful effect in patients with NTRK fusion-positive tumors. Fourteen patients (42.4%) achieved a CR, and 9 patients (27.3%) achieved a PR. Two patients had progressive disease (6.1%) as their best response. Figure 4, a swimmer plot of the NTRK integrated efficacy population, shows durable responses.

The FDA's Assessment:

In general, FDA agrees with the Applicant's position. Efficacy was evaluated in each trial separately; however, the primary efficacy analysis was performed in a pediatric population derived from both STARTRK-NG and TAPISTRY. The efficacy analyses that

supported the indication in adult patients with *NTRK* fusion-positive solid tumors treated are also included in the table for context. The efficacy analyses supporting the original accelerated approval of entrectinib for patients 18 years of age and older were based on pooled data from three multicenter, single-arm, open-label clinical trials: LKA, STARTRK-1 and STARTRK-2.

Table 18. Efficacy Summary for Integrated Pediatric and Adult Patients with Solid Tumors Harboring NTRK Gene Fusions.

BICR-Assessed	STARTRK-NG N = 31	TAPISTRY N = 2	Combined N = 33	Patients > 18 n=54
ORR, n (%)	22 (71)	1 (50)	23 (70)	31 (57)
CR	14	0	14	4
PR	8	1	9	27
95% CI[1]	(52, 86)	-	(51, 84)	(43,71)
Duration of response				
Median in months (95% CI)	25.4 (14.3, NE)	9.3 (NE, NE)[3]	25.4 (14.3, NE)	10.4 (7.1, NE)
≥ 6 months, %[2]	86	100[3]	87	68
≥ 12 months, %[2]	45	0	43	45

Source: adrs.xpt, adtte.xpt for individual studies separately and combined
NR: not reached; +: censored observation;
DCO: 09/30/2022 for CO40778 and 09/29/2022 for BO41932;
[1]95% CI for ORR in Study BO41932 is not calculated due to small sample size;
[2]Based on observed proportion of responders;
[3]Based on one responder from Study BO41932

Secondary and Other Endpoints

Data:

Table 19 Duration of Confirmed Objective Response (BICR Assessment), NTRK Integrated Analysis Population

Protocols: CO40778, BO41932
Pooled Population

	Total (N=33)
Patients included in analysis	23
Patients with event (%)	5 (21.7%)
Earliest contributing event	
Death	1
Disease Progression	4
Patients without event (%)	18 (78.3%)

Time to Event (Months)	
Median	25.4
95% CI	(14.3, NE)
25% and 75%-ile	14.3 - NE
Range	4* - 42*
6 Months	
Patients remaining at risk	20
Event Free Rate (%)	95.24
95% CI	(86.13, 100.00)
9 Months	
Patients remaining at risk	16
Event Free Rate (%)	95.24
95% CI	(86.13, 100.00)
12 Months	
Patients remaining at risk	10
Event Free Rate (%)	82.42
95% CI	(64.03, 100.00)
18 Months	
Patients remaining at risk	4
Event Free Rate (%)	68.68
95% CI	(39.72, 97.64)
24 Months	
Patients remaining at risk	4
Event Free Rate (%)	68.68
95% CI	(39.72, 97.64)

* Censored observation
Summaries of events (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.

CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932)
Patients Enrolled up to February 02, 2022.

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The Applicant's Position:

Duration of Confirmed Objective Response

Among 23 patients who achieved a BICR-assessed confirmed objective response (OR [CR/PR]), 5 patients (21.7% of responders) subsequently had progressive disease or died (Table 11). Median BICR-assessed confirmed DOR for responders in the NTRK integrated efficacy population was 25.4 months (95% CI: 14.3, NE). At the CCOD, 20/23 patients (87.0%) had responses lasting longer than 6 months. Ten of these were still responders at 12 months. The maximum response duration was 42 months.

Time to Confirmed Objective Response

In the NTRK integrated efficacy population, the median time to BICR-assessed confirmed OR was 1.84 months (range: 1.1–3.5), demonstrating a rapid achievement of response after receiving entrectinib treatment.

Clinical Benefit Rate

In the NTRK integrated efficacy population, 28 patients had BICR-assessed responses (CR, PR) or stable disease at 6 months after the first dose of entrectinib, resulting in a

CBR of 84.8% (95% CI: 68.1, 94.9). This indicates an additional benefit of sustained stable disease in some patients.

Progression-Free Survival

The Kaplan-Meier (KM) estimated median PFS based on the BICR assessment in the NTRK integrated efficacy population was 27.2 months (95% CI: 16.1, NE). Nine patients (27.3%) experienced an event (8 disease progression and 1 death).

Overall Survival

At the time of the CCOD, the OS data were immature with 6 patients (<20%) experiencing events. The KM estimated median OS was not reached (95% CI: 35.7, NE). All deaths were due to disease progression.

The FDA's Assessment:

FDA agrees with the Applicant's description of DOR. FDA's calculation of proportion of patients who had at least 6 or 12 months is based on the observed rate rather than the proportion estimated using Kaplan-Meier curves (Table 13). As discussed in earlier sections, time to event endpoints are not considered interpretable in single arm studies. Additionally, clinical benefit rate, which includes stable disease, may reflect the natural history of disease and is not considered when evaluating clinical benefit for entrectinib.

Subpopulations

The Applicant's Position:

Efficacy by Age

BICR-assessed confirmed objective responses were observed in all pediatric subsets: in 5/9 patients (55.6%) in the $\geq$ 28 days to $<$ 24 months age group, 15/19 patients (78.9%) in the $\geq$ 24 months to $<$ 12 years age group, and 3/5 patients (60%) in the $\geq$ 12 years to $<$ 18 years age group.

Five responders from the $\geq$ 24 months to $<$ 12 years age group subsequently had progressive disease or died in the NTRK integrated efficacy population. BICR-assessed confirmed DOR for responders aged $\geq$ 24 months to $<$ 12 years was 25.4 months (95% CI: 11.8, NE). Median BICR-assessed confirmed DOR was not established for patients in the $\geq$ 28 days to $<$ 24 months and $\geq$ 12 years to $<$ 18 years age groups given that responses were still ongoing in these groups without disease progression/death at the time of the CCOD.

Efficacy by Tumor Type

BICR-assessed confirmed objective response in the NTRK integrated efficacy population was observed across most tumor types: 9/17 patients (52.9%) with primary CNS tumors, 7/8

patients (87.5%) with infantile fibrosarcoma, 6/6 patients (100%) with spindle cell sarcoma, and 1/1 patient (100%) with melanoma.

Five of 9 responders (55.6%) with primary CNS tumors subsequently had progressive disease or died. Median BICR-assessed confirmed DOR for responders in the group of patients with primary CNS tumors was 14.3 months (95% CI: 11.8, 25.4). Median BICR-assessed confirmed DOR was not established for patients with infantile fibrosarcoma, spindle cell sarcoma, and melanoma since no responders in those groups experienced disease progression/death.

The FDA's Assessment:

In general, FDA agrees with the Applicant's position. The efficacy results by baseline demographics (Table 15), by tumor types (Table 16), and by *NTRK* gene fusion partner (Table 17) are summarized below. Treatment effect, as demonstrated by ORR, is consistent across subgroups of base demographics, including age, sex, race and ethnicity. A total of 9 patients out of 17 patients with primary CNS tumors had either a CR (n =5) or a PR (n = 4) (Table 17). Of the 9 responders, only 1 patient (Subject ID (b) (6) in Study CO40778) received prior radiotherapy, 2 patients (Subject ID (b) (6) in Study CO40778 and Subject ID (b) (6) in Study BO41932) received prior chemotherapy, and 1 patient (Subject ID (b) (6) (b) (6) in Study CO40778) received both prior chemotherapy and targeted therapy within two months of study entry; the median DOR was 14.3 (95% CI: 11.8, 25.4) in these patients. Five responders had prior radiation therapy and 1 responder did not receive any prior systemic therapy. FDA acknowledges that prior therapy, particularly prior radiotherapy, may confound ORR in CNS tumors; however, most patients did not enroll on these studies until at least 3 months after completion of radiotherapy . Additionally, given the biologic rationale for the mechanism of action (NTRK inhibiton) and responses in other extracranial tumor types, FDA agrees with including these patients as responders.

Table 20 Efficacy Results for Integrated Pediatric Patients with Solid Tumors Harboring NTRK Gene Fusions by baseline demographics

	Values	Patients	ORR	
		n	n (%)	95% CI
Age	< 2	9	5 (56)	(21, 86)
	2 to < 6	13	10 (77)	(46, 95)
	6 to < 12	6	5 (83)	(36, 100)
	12 to <18	5	3 (60)	(15, 95)
Sex	Female	16	13 (81)	(54, 96)
	Male	17	10 (59)	(33, 82)
Race	White	19	14 (74)	(49, 91)
	African American	1	0	NA

	Values	Patients	ORR	
		n	n (%)	95% CI
	Asian or Other	13	9 (69)	(39, 91)
Ethnicity	Hispanic or Latino	3	2 (67)	(9, 99)
	Not Hispanic or Latino	22	14 (64)	(41, 83)
	Not Reported or Unknown	8	7 (88)	(47, 100)
Country	US	16	9 (56)	(30, 80)
	Non-US	17	14 (82)	(57, 96)

Table 21. Efficacy Results for Integrated Pediatric Patients with Solid Tumors Harboring NTRK Gene Fusions by Tumor Type

Tumor Type	Patients	ORR		DOR
	N = 33	%	95% CI	Range (months)
Primary CNS	17	53	28, 77	5.5, 30.4+
Infantile fibrosarcoma	8	88	47, 100	3.7+, 24+
Spindle Cell	6	100	54, 100	3.7+, 12.9+
Sarcoma (other)*	1	Non-CR/ Non-PD	NA	NA
Melanoma	1	CR	NA	42.4+

Source: adrs.xpt, adtte.xpt
NA: not applicable; +: censored observation;
DCO: 09/30/2022 for CO40778 and 09/29/2022 for BO41932
*This patient (Subject ID (b) (6) in Study CO40778) had non-measurable but evaluable disease at baseline per BICR, and is thus included as non-responder.

Table 22. Prior Cancer Therapy Information for CNS Responder Patients

Study ID	Subject ID	Responses	Anti-cancer therapy received	Time from completion of anti-cancer therapy to entrectinib (mos)	Type of last anti-cancer therapy	Prior radiation therapy	Time of completion of last dose of radiation therapy to entrectinib (mos)
CO40778	(b) (6)	CR	Y	3.2	Chemotherapy	Y	1.2
CO40778		PR	Y	10.7	Chemotherapy	Y	6.4
CO40778		CR	Y	7.9	Chemotherapy	N	NA

Study ID	Subject ID	Responses	Anti-cancer therapy received	Time from completion of anti-cancer therapy to entrectinib (mos)	Type of last anti-cancer therapy	Prior radiation therapy	Time of completion of last dose of radiation therapy to entrectinib (mos)
CO40778	(b) (6)	PR	Y	2.8	Chemotherapy	Y	13.5
CO40778		CR	Y	0.7	Targeted Therapy (CDK4/6 inhibitor and MEK inhibitor)	Y	3.4
CO40778		CR	Y	0.6	Chemotherapy	N	NA
CO40778		CR	N		NA	N	NA
CO40778		CR	Y	80.2	Chemotherapy and Targeted Therapy (VEGF inhibitor)	Y	Approximately 9 years or more
BO41932		PR	Y	0.9	Chemotherapy	N	NA

Source: applicant's response to IR on CNS primary tumors
NA: not applicable;

The ORRs observed across different fusions are summarized below in Table 18. Much like the adult and adolescent data that supported AA, ETV6 – NTRK3 is found to be the predominant gene fusion type in pediatric patients. A total of 25 out of 54 adult and adolscent patients were found to harbor ETV6 – NTRK3 gene fusion, with an ORR of 68% (95%CI: 74,85) compared to 7 out of 33 pediatric patients harboring the same gene fusion resulting in a greater ORR of 86% (95%CI:42,100).

Table 23. Efficacy Results for Integrated Pediatric Patients with Solid Tumors Harboring NTRK Gene Fusions by *NTRK* Gene Fusion Partner

***NTRK* Partner**	**Patients N = 33**	**ORR**		**DOR**
		%	**95% CI**	**Range (months)**
ETV6 – NTRK3	7	86	42, 100	11.9+ - 42.4+
LMNA – NTRK1	5	80	28, 99	7.4+ - 12.9+
TPM3 – NTRK1	3	100	29, 100	3.7+ - 24.0+
TPR – NTRK1	3	67	9, 99	8.1+ - 14.3
EML4-NTRK3	2	50	1.3, 99	13.8+
BCAN-NTRK1	1	CR	NA	11.8+
EML1-NTRK2	1	CR	NA	11.8
QKI-NTRK2	1	CR	NA	11.1+
TFG-NTRK3	1	CR	NA	3.7+
KANK1-NTRK2	1	PR	NA	5.5
KIF5B-NTRK2	1	PR	NA	12.9+
TNS3-NRTK2	1	PR	NA	9.5
ARHGEF2-NTRK1	1	SD	NA	NA
KIF21B-NTRK1	1	SD	NA	NA
BCR-NTRK2	1	SD	NA	NA
GKAP1-NTRK2	1	SD	NA	NA
DNM3-NTRK2	1	PD	NA	NA
PARP6-NTRK3	1	PD	NA	NA

Source: adsl.xpt, adrs.xpt, adtte.xpt
NA: not applicable; +: censored observation;
DCO: 09/30/2022 for CO40778 and 09/29/2022 for BO41932

Additional Efficacy Considerations

The FDA's Assessment:

During the review of this application, an update of efficacy data was provided with a data cutoff (DCO) date of March 8, 2023. In the updated analysis, a total of 39 pediatric

patients were included in the pooled efficacy population. The updated ORR was 72% (95% CI = 55, 85); however, FDA did not independently verify the updated results.

11.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

There is a clear unmet medical need for safe and effective molecularly targeted treatment options, especially those that are CNS active, for the rare population of pediatric cancer patients with relapsed or refractory *NTRK* fusion positive solid tumors.

Entrectinib has demonstrated a positive benefit risk with durable responses in both primary CNS and non-CNS tumors.
Responses have been seen in primary CNS, infantile fibrosarcoma, spindle cell and melanoma.
Considering unmet medical need, particularly for CNS tumors, the clinically significant ORR and durable responses observed with entrectinib treatment bring a new targeted therapeutic option to specifically treat the oncodriver-selected pediatric cancer patients with advanced or metastatic *NTRK* fusion positive tumors.
The efficacy benefits of entrectinib occurred in the context of a generally well-tolerated and manageable safety profile considering the pretreated and advanced nature of the disease of the cancer patient population under study. Adverse events were generally manageable through routine medical care and specific monitoring, and when necessary, transient dose interruption and/or reduction allowed resolution of the events to enable patients to continue receiving entrectinib treatment. These measures are considered adequate to manage the risks associated with entrectinib treatment. No new risks were identified. Additionally, it is anticipated that routine risk mitigation for the identified important risks proposed in the RMP are sufficient to manage the risks and maintain a positive benefit-risk profile for entrectinib.
In summary, considering the totality of evidence, the Applicant believes that the benefit risk balance of entrectinib is positive, and that entrectinib represents a promising treatment option for pediatric patients with locally advanced or metastatic solid tumors that are *NTRK* fusion-positive. The proposed indication wording is as follows:
Rozlytrek as monotherapy is indicated for the treatment of adult (b) (4) with solid tumours (b) (4) (b) (4)

The FDA's Assessment:

The efficacy evaluation of this application is primarily based on an analysis of 33 pediatric patients with unresectable or metastatic solid tumors with an *NTRK* gene fusion who were treated with entrectinib in one of two multicenter, open-label clinical trials: STARTRK-NG and TAPISTRY. Data was pooled from these two single arm trials due to the rarity of the population.

FDA considers ORR of sufficient magnitude and durability to be an endpoint reasonably likely to predict clinical benefit in patients with solid tumors. Among the 33 patients in the primary efficacy population, the ORR was 70% (95% CI 51,84) with a median duration of response (DOR) of 25.4 months (95% CI 14.3, not estimable [NE]).

Although standard treatment regimens exist for most patients with locally advanced or metastatic solid tumor malignancies, such treatment generally is not curative and additional treatment is needed. In refractory settings, when no treatment is available or, if available, such treatment would result in significant morbidity, entrectinib (with the outcomes described in the efficacy sections above) confers a meaningful advantage over available therapy for patients with solid tumors with an activating *NTRK*-rearrangement or mutation, particularly in the context of durable responses observed in patients greater than 12 years of age.

Due to the small sample size, there is uncertainty regarding the magnitude and durability of the treatment effect of entrectinib overall and in any one histologic subtype of solid tumors with an activating *NTRK* rearrangement. Under a postmarketing requirement, the Applicant will conduct clinical trial(s) intended to verify and describe the clinical benefit of entrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in a sufficient number of pediatric patients older than 1 month of age and less than 12 years of age with solid tumors with NTRK gene fusion and without a known acquired resistance mutation; that are metastatic or would require surgical resection that would result in severe morbidity; and have no satisfactory alternative treatment or have progressed following treatment. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months from the onset of response.

11.2. Review of Safety

The Applicant's Position

Study Populations

The integrated safety population includes 76 pediatric patients from STARTRK-NG, TAPISTRY, and STARTRK-02 studies who received any amount of entrectinib.

At the CCOD (2 August 2022), of the 76 enrolled patients, 51 patients (67.1%) remained on study, and 25 patients (32.9%) had withdrawn from the study.

The FDA's Assessment:

FDA agrees with the Applicant's position. The primary pediatric safety population consisted of pediatric patients (n=76) with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of three studies: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2). The Applicant's analyses of safety data from the clinical cut off date (CCOD) of August 2, 2022 were reviewed and verified by the FDA clinical reviewer. A 90 day safety update was submitted on July 26, 2023 for updated safety analysis of pediatric patients from all three studies with a CCOD of March 8, 2023.

11.2.1. Safety Review Approach

The Applicant's Position:

Safety assessments consisted of monitoring and recording AEs, including SAEs, adverse events of special interest (AESIs), measurement of protocol-specified clinical laboratory assessments and vital signs, bone monitoring, and cardiac monitoring. The definitions of AEs, SAEs (immediately reportable to the Sponsor), and AESIs (immediately reportable to the Sponsor) are provided in the CO40778 Protocol Section 9.1, BO41932 Protocol Section 5.2, and GO40782 Protocol Section 9.1.

Of note, in terms of safety reporting and analysis, for Ignyta-initiated studies (CO40778/STARTRK-NG and GO40782/STARTRK-2), due to clinical database limitations, each change in grade (severity) of a single AE reported in an individual was recorded as a new episode, leading to multiple records for a given event with potentially different outcome and actions taken for these adjacent episodes. In contrast, for study BO41932/TAPISTRY, per Roche convention, when there were grade changes of a single AE, only the AE grade at onset and the worst grade were collected within one record in the clinical database for the event thus avoiding any duplication in reporting. AE characteristics such as onset date, outcome, study drug relationship, and seriousness were collected for each episode per Ignyta reporting convention and collected once per Roche reporting convention. Full details are included in the SCS.

Adverse Events

For classification purposes in each study, verbatim descriptions of AEs were mapped to the Medical Dictionary for Regulatory Activities (MedDRA) version 25 terminology for AEs and diseases. Thesaurus terms for the STARTRK-NG, TAPISTRY, and STARTRK-02 studies were

graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, version 5, and version 4, respectively.

Adverse Events of Special Interest and Selected Adverse Events
Adverse events of special interest, regardless of seriousness, were required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). The AESI categories evolved over time as more information was gained over the course of the studies. The combined list of AESIs for STARTRK-02, STARTRK-NG, and TAPISTRY include the following:

- Bone fractures
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Cognitive disturbances Grade $>$ 2
- Congestive cardiac failure Grade $>$ 2
- QT prolongation Grade $>$ 2
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

For analysis purposes, the AESI terms listed above are presented under the broader category of Selected AEs, which also includes an analysis of weight changes.

Adverse Event Reporting Period
Investigators collected information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, were recorded in the patient's medical record and on the Adverse Event electronic Case Report Form.

After informed consent for the clinical trial was obtained but prior to initiation of study drug, only SAEs related to protocol-mandated assessments were reported.

After initiation of study drug, all AEs, regardless of relationship to study drug, were reported until at least 30 days after the last dose of study treatment. Any new-onset SAEs or AESIs occurring any time after the reporting period were promptly reported indefinitely if a causal relationship to the study drug was suspected.

The FDA's Assessment:
FDA's approach to the safety review included evaluation of the clinical study report, case report forms, selected narratives, the Integrated Summary of Safety, and the original datasets

submitted by the Applicant. The reviewers analyzed key safety datasets using several safety analysis queries. Subgroup analyses were performed as necessary to further characterize the safety profile of entrectinib and additional analyses were performed for specific safety issues.

11.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 24 Study Treatment Exposure

Study Treatment Exposure, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

	STARTRK-NG (N=68)	TAPISTRY (N=6)	STARTRK-02 (N=2)	Total (N=76)
Treatment duration (months)				
n	68	6	2	76
Mean (SD)	11.94 (10.99)	6.15 (4.43)	14.41 (18.70)	11.55 (10.80)
Median	9.46	4.55	14.41	8.71
Min - Max	0.2 - 44.7	2.0 - 14.0	1.2 - 27.6	0.2 - 44.7
Total cumulative dose (mg)				
n	68	6	2	76
Mean (SD)	116729.68 (139732.10)	38906.67 (26400.34)	260100.00 (337289.93)	114358.66 (141536.79)
Median	57600.00	47850.00	260100.00	54300.00
Min - Max	2400.0 - 834800.0	6540.0 - 71200.0	21600.0 - 498600.0	2400.0 - 834800.0
Dose intensity (%) (with respect to total dose)				
n	68	6	2	76
Mean (SD)	103.16 (41.10)	77.08 (33.13)	98.94 (1.50)	100.99 (40.41)
Median	100.00	91.88	98.94	100.00
Min - Max	28.8 - 383.1	25.4 - 104.8	97.9 - 100.0	25.4 - 383.1
Number of doses				
n	68	0	2	70
Mean (SD)	347.4 (317.1)	NE (NE)	433.5 (562.1)	349.8 (320.1)
Median	276.5	NE	433.5	276.5
Min - Max	6 - 1305	NE - NE	36 - 831	6 - 1305
Missed doses				
n	68	0	2	70
At least one missed dose	38 (55.9%)	0	1 (50.0%)	39 (55.7%)

Dose intensity (%) (with respect to total dose) is defined as (the Cumulative Dose/Number of planned days)/Planned Daily Dose at the beginning of treatment*100.
Total number of doses and Missed doses could not be determined for patients enrolled in TAPISTRY because this information was not collected for this study.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932, STARTRK-02 = study GO40782.
CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

Program: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/program/t_ex.sas / Output: root/clinical_studies/RO7102122/share/pool_aco_2022/prod/output/t_ex_AGE18_SE.out
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The Applicant's Position:

As of the CCOD, the median relative dose intensity was 100% (range: 25.4%–383.1%) Dose intensity was defined as the (the Cumulative Dose/Number of planned days)/Planned Daily Dose at the beginning of treatment $\times 100$. Because dose intensity is relative to the dose at the beginning of treatment, growing pediatric patients may have a dose intensity $>100\%$. For example, one patient was 2 months old at enrollment and started treatment at 50 mg daily. As of the CCOD, this patient was >6 months old; and therefore, was receiving entrectinib at 200 mg daily. The median total duration of treatment was 8.7 months (range: 0.2–44.7 months).

The FDA's Assessment:

FDA agrees with the Applicant's position. Of the 76 patients in the safety population, 58% were exposed to entrectinib for 6 months or longer and 38% were exposed to entrectinib for greater than one year. Patients received entrectinib 20 mg to 600 mg based on body surface area (BSA) orally or via enteral feeding tube once daily in 4-week cycles until unacceptable toxicity or disease progression.

Relevant characteristics of the safety population:

The Applicant's Position:

Among patients with *NTRK* gene fusions, the most common tumor types were CNS primary tumors (19 patients [25.0%]) and sarcoma (17 patients [22.4%]). Other tumor types represented with *NTRK* gene fusions were kidney, skin, and thyroid cancer. Among patients with ROS1 gene fusions, the most common tumor types were sarcoma (10 patients [13.2%]) and CNS primary tumors (8 patients [10.5%]). One patient with a *ROS1* gene fusion had NSCLC.

A total of 49 patients (64.5%) received previous systemic cancer therapy. The majority of patients (44/76 [57.9%%]) received a chemotherapy treatment, 15 patients (19.7%) received immunotherapy, 14 patients (18.4%) received targeted therapy, and 14 patients (18.4%) received other treatments. Twenty-six patients (34.2%) received radiotherapy, and 43 patients (56.6%) underwent surgery prior to study enrollment. For further details see Section 8.1.4.

The FDA's Assessment:

FDA agrees with Applicant's position that the most common tumor types within both the safety (n=76) and efficacy (n=33) populations were primary CNS tumors and extracranial solid tumors (i.e. infantile fibrosarcoma). Section 8.1.4 of the review describes the efficacy population. In this section FDA will provide a description of the primary safety population, comprised of 76 pediatric patients with NTRK gene fusions only. FDA did not analyze patients with ROS1 gene fusions for this review. Table 20 summarizes the key demographic characteristics of the pediatric safety population, including sex, country of enrollment, primary diagnosis and histology. Only tumor and histologic types in >1 patient were included.

Table 25 Demographics Characteristics of Safety Population

	STARTRK-NG N = 68 N (%)	**TAPISTRY N = 6 N (%)**	**STARTRK-2 N = 2 N (%)**	**Overall N = 76 N (%)**
Gender				
F	34 (50)	4 (67)	1 (50)	39(51)
M	34 (50)	2 (33)	1 (50)	37 (49)
Age				
Mean (SD)	7 (5)	4 (4)	15 (0)	7 (5)
Median (Min - Max)	6 (0 - 17)	2 (0 - 10)	15 (15 - 15)	6 (0 - 17)
Age Group				
	68 (100)	6 (100)	2 (100)	76 (100)
Race				
WHITE	46 (68)	3 (50)	2 (100)	51 (67)
ASIAN	12 (18)	3 (50)	0 (0)	15 (20)
OTHER	5 (7)	0 (0)	0 (0)	5 (7)
BLACK OR AFRICAN AMERICAN	5 (7)	0 (0)	0 (0)	5 (7)
Country				
USA	45 (66)	0 (0)	1 (50)	46 (61)
China	10 (15)	0 (0)	0 (0)	10 (13)
France	3 (4.4)	0 (0)	0 (0)	3 (3.9)
Canada	2 (2.9)	0 (0)	0 (0)	2 (2.6)

	STARTRK-NG N = 68 N (%)	TAPISTRY N = 6 N (%)	STARTRK-2 N = 2 N (%)	Overall N = 76 N (%)
Great Britain	2 (2.9)	0 (0)	0 (0)	2 (2.6)
Germany	2 (2.9)	0 (0)	0 (0)	2 (2.6)
Italy	2 (2.9)	1 (17)	1 (50)	4 (5)
Hong Kong	1 (1.5)	1 (17)	0 (0)	2 (2.6)
Spain	1 (1.5)	0 (0)	0 (0)	1 (1.3)
Korea	0 (0)	2 (33)	0 (0)	2 (2.6)
Australia	0 (0)	1 (17)	0 (0)	1 (1.3)
Switzerland	0 (0)	1 (17)	0 (0)	1 (1.3)
Primary Diagnosis				
PRIMARY CNS TUMORS	23 (34)	0 (0)	0 (0)	23 (30)
NEUROBLASTOMA	14 (21)	0 (0)	0 (0)	14 (18)
INFLAMMATORY MYOFIBROBLASTIC TUMOR	3 (4.4)	0 (0)	0 (0)	3 (3.9)
Histology				
SPINDLE CELL	10 (15)	0 (0)	0 (0)	10 (13)
INFANTILE FIBROSARCOMA	5 (7)	0 (0)	0 (0)	5 (7)
HIGH GRADE GLIOMA	3 (4.4)	0 (0)	0 (0)	3 (3.9)

Source: ADSL (Subject-Level Analysis Dataset) - 2023-04-28. Variables used: USUBJID, STUDYID, SAFFL, SEX, AAGE, AGEGR1, BECOG, RACE, ETHNIC, COUNTRY, DCSREAS, DCSREASP, DISCAE, TRTDRS, PRIMDIAG, EXTENT, HISTOL, NUMSURG, NUMRAD, NUMTHPED

Adequacy of the safety database:

The Applicant's Position:

The Applicant believes that the safety analysis set of the 76 patients pediatric < 18 years old with solid tumors is sufficient to adequately evaluate the incidence of toxicities and to support the proposed indication. The integrated dataset includes 39 patients with NTRK1/2/3 gene fusions and 19 patients with ROS1 gene fusions. Of the 76 pediatric patients in the integrated dataset, 14 are infants (0 to <2 years), 49 are children (≥ 2 to <12 years), and 13 are

adolescents (≥ 12 to <18 years). This safety analysis set (n=76) has been reflected in the proposed labeling of this submission in locations in the USPI where pediatric safety is described separately from the integrated safety population of adult and pediatric patients (Section 5.3 Skeletal Fractures and Section 8.4 Pediatric Use).

Adverse events were generally manageable through routine medical care and specific monitoring, and when necessary, transient dose interruption and/or reduction allowed resolution of the events to enable patients to continue receiving entrectinib treatment. These measures are considered adequate to manage the risks associated with entrectinib treatment. No new risks were identified. Additionally, it is anticipated that routine risk mitigation for the risks identified are sufficient to manage the risks and maintain a positive benefit-risk profile for entrectinib in pediatric patients of all ages.

The adequacy of the total pediatric patient exposure of entrectinib to support registration in the target population was discussed at theType B Pre-submission meeting with DO3 on 02 May 2022 (Ref. ID: 4990533) and the Type B Pre-submission meeting with DO2 on 06 March 2023 (Ref. ID: 5136816The FDA considered the planned safety database at that time to be reasonable.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the adequacy of the safety database. The integrated pediatric safety population consisted of pediatric patients (n=76) with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of three studies: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2).

11.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues relating to safety data integrity or quality were identified for Studies CO40778, BO41932 and GO40782

There were no reported major COVID-19-related protocol deviations with a potential impact on AE reporting.

The FDA's Assessment:

The data submitted was organized and adequate to perform a complete review of the safety of entrectinib. Overall, FDA agrees that there were no significant data quality or reporting issues identified during the review of this NDA. FDA issued multiple information requests during the review cycle to obtain clarification and additional information on safety data included in the NDA.

Categorization of Adverse Event

The Applicant's Position:

For classification purposes, lower level terms were assigned by the Sponsor to the original terms entered on the case report form (CRF), using the most up-to-date version of the MedDRA 25.0 terminology for AEs and diseases. and the Roche INN (International Non-proprietary Name) Drug

The FDA's Assessment:

For purposes of the FDA review of safety, incidences of adverse events were analyzed without consideration of relatedness. Common Terminology Criteria for Adverse Events (CTCAE) versions that were used across the contributing studies (v4.03 in STARTRK-NG and STARTRK-2, v5.0 in TAPISTRY).

Routine Clinical Tests

The Applicant's Position:

Laboratory data were classified according to NCI-CTCAE and summarized descriptively over time, including change from baseline. The highest NCI-CTCAE grades after baseline are also reported in addition to shift tables (from baseline to worst value after baseline). Normal ranges for laboratory values are provided.

The FDA's Assessment:

FDA agrees with the Applicant's position.

11.2.4. Safety Results

Deaths

The Applicant's Position:

A total of 18 deaths (23.7%) were reported, with the majority of patients (17/18) being among patients enrolled in Phase I of study CO40778, with tumors that did not harbor fusions. All deaths were due to progressive disease. The majority of deaths (14/18) occurred more than 30 days after the last dose of entrectinib.

The FDA's Assessment:

FDA agrees with the Applicant's position. Analyses of safety data from the clinical cut off date (CCOD) of August 2, 2022 performed by the Applicant were reviewed and verified by the FDA clinical reviewer. A total of 18 deaths were reported (24%), with all deaths due to progressive disease.

Serious Adverse Events

Data:

Table 26 Serious Adverse Events by System Organ Class and Preferred Term

Serious Adverse Events by System Organ Class and Preferred Term, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

MedDRA System Organ Class MedDRA Preferred Term	STARTRK-NG (N=68)	TAPISTRY (N=6)	STARTRK-02 (N=2)	Total (N=76)
Total number of patients with at least one adverse event	33 (48.5%)	0	1 (50.0%)	34 (44.7%)
INFECTIONS AND INFESTATIONS				
Total number of patients with at least one adverse event	16 (23.5%)	0	0	16 (21.1%)
PNEUMONIA	4 (5.9%)	0	0	4 (5.3%)
DEVICE RELATED INFECTION	3 (4.4%)	0	0	3 (3.9%)
SEPSIS	2 (2.9%)	0	0	2 (2.6%)
UPPER RESPIRATORY TRACT INFECTION	2 (2.9%)	0	0	2 (2.6%)
BRONCHIOLITIS	1 (1.5%)	0	0	1 (1.3%)
COVID-19	1 (1.5%)	0	0	1 (1.3%)
ENCEPHALITIS	1 (1.5%)	0	0	1 (1.3%)
INFECTION	1 (1.5%)	0	0	1 (1.3%)
LOWER RESPIRATORY TRACT INFECTION	1 (1.5%)	0	0	1 (1.3%)
NASOPHARYNGITIS	1 (1.5%)	0	0	1 (1.3%)
NOROVIRUS INFECTION	1 (1.5%)	0	0	1 (1.3%)
OSTEOMYELITIS	1 (1.5%)	0	0	1 (1.3%)
PNEUMONIA ASPIRATION	1 (1.5%)	0	0	1 (1.3%)
PNEUMONIA RESPIRATORY SYNCYTIAL VIRAL	1 (1.5%)	0	0	1 (1.3%)
RESPIRATORY TRACT INFECTION	1 (1.5%)	0	0	1 (1.3%)
VASCULAR ACCESS SITE INFECTION	1 (1.5%)	0	0	1 (1.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Total number of patients with at least one adverse event	12 (17.6%)	0	0	12 (15.8%)
FEMUR FRACTURE	4 (5.9%)	0	0	4 (5.3%)
FRACTURE	2 (2.9%)	0	0	2 (2.6%)
FALL	1 (1.5%)	0	0	1 (1.3%)
LIMB FRACTURE	1 (1.5%)	0	0	1 (1.3%)
LOWER LIMB FRACTURE	1 (1.5%)	0	0	1 (1.3%)
RADIATION VASCULITIS	1 (1.5%)	0	0	1 (1.3%)
SPINAL COMPRESSION FRACTURE	1 (1.5%)	0	0	1 (1.3%)
STRESS FRACTURE	1 (1.5%)	0	0	1 (1.3%)
THERMAL BURN	1 (1.5%)	0	0	1 (1.3%)
NERVOUS SYSTEM DISORDERS				
Total number of patients with at least one adverse event	7 (10.3%)	0	1 (50.0%)	8 (10.5%)
HYDROCEPHALUS	4 (5.9%)	0	0	4 (5.3%)
HEADACHE	1 (1.5%)	0	1 (50.0%)	2 (2.6%)
DEPRESSED LEVEL OF CONSCIOUSNESS	1 (1.5%)	0	0	1 (1.3%)
SEIZURE	1 (1.5%)	0	0	1 (1.3%)
SYNCOPE	1 (1.5%)	0	0	1 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total number of patients with at least one adverse event	7 (10.3%)	0	0	7 (9.2%)
PYREXIA	4 (5.9%)	0	0	4 (5.3%)
GAIT DISTURBANCE	2 (2.9%)	0	0	2 (2.6%)
PAIN	2 (2.9%)	0	0	2 (2.6%)
FACE OEDEMA	1 (1.5%)	0	0	1 (1.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total number of patients with at least one adverse event	6 (8.8%)	0	0	6 (7.9%)
HYPOXIA	3 (4.4%)	0	0	3 (3.9%)
DYSPNOEA	2 (2.9%)	0	0	2 (2.6%)
ALVEOLITIS	1 (1.5%)	0	0	1 (1.3%)
ATELECTASIS	1 (1.5%)	0	0	1 (1.3%)
BRONCHOSPASM	1 (1.5%)	0	0	1 (1.3%)
PLEURAL EFFUSION	1 (1.5%)	0	0	1 (1.3%)
PULMONARY OEDEMA	1 (1.5%)	0	0	1 (1.3%)
RESPIRATORY ACIDOSIS	1 (1.5%)	0	0	1 (1.3%)
RESPIRATORY FAILURE	1 (1.5%)	0	0	1 (1.3%)
GASTROINTESTINAL DISORDERS				

Total number of patients with at least one adverse event	3 (4.4%)	0	0	3 (3.9%)
PANCREATITIS	1 (1.5%)	0	0	1 (1.3%)
SMALL INTESTINAL OBSTRUCTION	1 (1.5%)	0	0	1 (1.3%)
VOMITING	1 (1.5%)	0	0	1 (1.3%)
MedDRA System Organ Class MedDRA Preferred Term	STARTRK-NG (N=68)	TAPISTRY (N=6)	STARTRK-02 (N=2)	Total (N=76)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Total number of patients with at least one adverse event	3 (4.4%)	0	0	3 (3.9%)
JOINT EFFUSION	1 (1.5%)	0	0	1 (1.3%)
PATHOLOGICAL FRACTURE	1 (1.5%)	0	0	1 (1.3%)
PERIOSTITIS	1 (1.5%)	0	0	1 (1.3%)
METABOLISM AND NUTRITION DISORDERS				
Total number of patients with at least one adverse event	1 (1.5%)	0	0	1 (1.3%)
HYPONATRAEMIA	1 (1.5%)	0	0	1 (1.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
Total number of patients with at least one adverse event	1 (1.5%)	0	0	1 (1.3%)
DERMATOFIBROSARCOMA PROTUBERANS	1 (1.5%)	0	0	1 (1.3%)
PRODUCT ISSUES				
Total number of patients with at least one adverse event	1 (1.5%)	0	0	1 (1.3%)
DEVICE FAILURE	1 (1.5%)	0	0	1 (1.3%)
PSYCHIATRIC DISORDERS				
Total number of patients with at least one adverse event	1 (1.5%)	0	0	1 (1.3%)
MANIA	1 (1.5%)	0	0	1 (1.3%)
RENAL AND URINARY DISORDERS				
Total number of patients with at least one adverse event	1 (1.5%)	0	0	1 (1.3%)
URINARY RETENTION	1 (1.5%)	0	0	1 (1.3%)

Subjects with more than one adverse event within a particular system organ class and preferred term are counted once for that system organ class and preferred term.
Coded using MedDRA version 25.
STARTRK-NG = study CO40778, TAPISTRY = study BO41932, STARTRK-02 = study GO40782.
CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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The Applicant's Position:

A total of 34 patients (44.7%) experienced at least one SAE. Eleven patients (14.5%) experienced at least one treatment-related SAE.

The most frequent SAEs by system organ class (SOC) (≥5% of patients) were:

- Infections and infestations (16 patients [21.1%])
- Injury, poisoning, and procedural complications (12 patients [15.8%])
- Nervous system disorders (8 patients [10.5%])
- General disorders and administration site conditions (7 patients [9.2%])
- Respiratory, thoracic, and mediastinal disorders (6 patients [7.9%])

The most frequent SAEs by PT (≥2 patients) were:

- Pneumonia, femur fracture, hydrocephalus, pyrexia (4 patients each [5.3%])
- Device related infection, hypoxia (3 patients each [3.9%])

- Sepsis, upper respiratory tract infection, fracture, headache, gait disturbance, pain, dyspnea (2 patients each [2.6%])

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

SAEs were observed in 45% of patients in the primary safety population. The most frequent SAEs (> 2% of patients) were skeletal fractures (12%), pneumonia (5%), pyrexia (5%), hydrocephalus (5%), device related infection (4%), hypoxia (4%), dyspnea (3%), headache (3%), gait disturbance (3%), pain (3%), upper respiratory infection (3%), and sepsis (3%).

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

The most frequent AEs by SOC (≥2 patients) that led to discontinuation of treatment were injury, poisoning, and procedural complications (5 patients [6.6%]) and Respiratory, thoracic, and mediastinal disorders (2 patients [2.6%]).

The most frequent AEs by PT (≥2 patients) were femur fracture and tibia fracture (2 patients each).

The FDA's Assessment:

FDA independently verified the AEs leading to permanent discontinuation for the primary safety population (N=76); permanent discontinuation of entrectinib due to an AE occurred in 13% of patients. FDA agrees with the Applicant's position that the most frequent AE (≥ 2 patients) leading to treatment discontinuation was skeletal fractures.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Sixteen patients (21.1%) experienced AEs leading to dose reduction of entrectinib.

The most frequent AEs by SOC (≥2 patients) that led to dose reduction were:

- Investigations (10 patients [13.2%])
- Injury, poisoning, and procedural complications (2 patients [2.6%])
- Nervous system disorders (2 patients [2.6%])

The most frequent AEs by PT (≥2 patients) that led to dose reduction were:

- Weight increased (6 patients [7.9%])

- Blood creatinine increased (2 patients [2.6%])

A total of 30 patients (39.5%) experienced AEs leading to dose interruption of entrectinib. The most frequent AEs by SOC (≥5% of patients) that led to dose interruption were as follows:

- Infections and infestations (14 patients [18.4%])
- Investigations (13 patients [17.1%])
- Gastrointestinal disorders (9 patients [11.8%])
- General disorders and administration site conditions (7 patients [9.2%])
- Respiratory, thoracic, and mediastinal disorders (5 patients [6.6%])
- Blood and lymphatic system disorders (4 patients [5.3%])
- Musculoskeletal and connective tissue disorders (4 patients [5.3%])

The most frequent AEs by PT (≥ 5% patients) that led to dose interruption were as follows:

- Neutrophil count decreased (7 patients [9.2%])
- Vomiting (5 patients [6.6%])
- Pyrexia (5 patients [6.6%])
- Diarrhea (4 patients [5.3%])

The FDA's Assessment:

FDA agrees with the Applicant's analyses regarding dose reductions and interruptions.

Dose reductions due to an adverse reaction occurred in 21% of patients who received entrectinib. Adverse reactions which required dose reductions in > 2% of patients were increased blood creatinine and increased weight.

Dosage interruptions due to an adverse reaction occurred in 39% of patients who received entrectinib. AEs requiring dosage interruption in ≥ 5% of patients were decreased neutrophil count, pyrexia, vomiting, and diarrhea.

Significant Adverse Events

Table 27 Safety Summary of Selected Adverse Events

Safety Summary, Selected Adverse Events, Patients (<18 years old), Safety-Evaluable Patients
Protocols: CO40778, BO41932, GO40782
Pooled Population

	STARTRK-NG (N=68)		TAPISTRY (N=6)		STARTRK-02 (N=2)		Total (N=76)	
Patients With Selected Adverse Events	63	(92.6%)	2	(33.3%)	2	(100%)	67	(88.2%)
Patients With Related Selected Adverse Events	56	(82.4%)	2	(33.3%)	1	(50.0%)	59	(77.6%)
Patients With Serious Selected Adverse Events	19	(27.9%)	0		1	(50.0%)	20	(26.3%)
Patients With Related Serious Selected Adverse Events	11	(16.2%)	0		0		11	(14.5%)
Patients with NCI-CTCAE >= Grade 3 Selected Adverse Events	41	(60.3%)	1	(16.7%)	1	(50.0%)	43	(56.6%)
Patients with Related NCI-CTCAE >= Grade 3 Selected Adverse Events	32	(47.1%)	1	(16.7%)	1	(50.0%)	34	(44.7%)
Patients with Selected Adverse Events Leading to Discontinuation	7	(10.3%)	0		0		7	(9.2%)
Patients with Related Selected Adverse Events Leading to Discontinuation	7	(10.3%)	0		0		7	(9.2%)
Patients with Selected Adverse Events Leading to Dose Reduction	14	(20.6%)	0		0		14	(18.4%)
Patients with Related Selected Adverse Events Leading to Dose Reduction	13	(19.1%)	0		0		13	(17.1%)
Patients with Selected Adverse Events Leading to Dose Interruption	22	(32.4%)	1	(16.7%)	0		23	(30.3%)
Patients with Related Selected Adverse Events Leading to Dose Interruption	17	(25.0%)	1	(16.7%)	0		18	(23.7%)
Patients with Selected Adverse Events Leading to Death	0		0		0		0	

STARTRK-NG = study CO40778, TAPISTRY = study BO41932, STARTRK-02 = study GO40782.
CCOD: Aug 02 2022, DBL: Sep 30 2022 (CO40778), Sep 29 2022 (BO41932), Oct 03 2022 (GO40782)

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The Applicant's Position:

For analysis purposes, selected AEs include the AESIs and weight changes.

A summary of selected AEs is provided below. Of the 76 patients in the pooled safety population, 67 patients (88.2%) experienced a selected AE. Selected AEs led to treatment discontinuation in 7 patients (9.2%), dose reduction in 14 patients (18.4%), and dose interruption in 23 patients (30.3%).

A total of 19 out of 76 patients (25%) experienced a bone fracture event. Thirteen patients experienced more than one bone fracture event. Of the 13 patients with more than one bone fracture event, 6 patients experienced multiple fractures at the same time point. A majority of fractures occurred in patients $<$ 12 years (17/19 patients).

Eleven patients (14.5%) experienced a Grade 1-2 bone fracture. Eight patients (10.5%) experienced a Grade 3 bone fracture. There were no Grade 4 or 5 bone fracture events.

The majority of fractures occurred in the lower body. The most frequent bone fracture events by PT (≥5% of patients) were as follows:

- Tibia fracture (10 patients [13.2%])
- Femur fracture (4 patients [5.3%])
- Fibula fracture (4 patients [5.3%])
- Foot fracture (4 patients [5.3%])

Of the 19 patients with a bone fracture event, 9 (47%) patients experienced a bone fracture that was serious (SAE). SAEs by PT included: femur fracture (4 patients), fracture (2 patients), limb fracture, lower limb fracture, pathological fracture, spinal compression fracture, and stress fracture (1 patient each). Bone fracture SAEs were assessed as related to entrectinib in 7 patients.

Five patients (6.6%) experienced bone fractures that led to treatment discontinuation. One patient (1.3%) experienced a bone fracture that led to dose reduction of entrectinib, and 3 patients (3.9%) experienced a bone fracture that led to dose interruption of entrectinib.

A full description of the fractures including narratives can be found in the clinical study report (CSR) for studies CO40778 and BO41932.

The FDA's Assessment:

FDA agrees with the Applicant's analyses of skeletal fractures in the pediatric safety population. Through several informational requests, FDA and the Applicant agreed upon the preferred terms utilizied to capture skeletal fractures and the verification of the number of skeletal fractures. Out of 76 pediatric patients who received entrectinib, 5% of adult patients and 25% of pediatric patients experienced fractures. In two pediatric

patients, bilateral femoral neck fractures occurred. A total of 41 fracture events were reported in 19 pediatric patients, with 13 patients who experienced more than one occurrence of fracture. Among the 19 pediatric patients who experienced fractures, 17 patients were less than 12 years of age. The median time to fracture was 3.8 months (range 0.3 to 18.5 months) in adults and 4.3 months (range: 2 months to 28.7 months) in pediatric patients. Entrectinib was interrupted in 41% of adults and 16% of pediatric patients who experienced fractures. Five pediatric patients discontinued treatment due to fractures.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 28 Adverse Reactions (≥ 10%) in Patients Receiving ROZLYTREK in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG

Adverse Reactions	**ROZLYTREK** **n = 355**	
	All Grades (%)	**Grade ≥ 3* (%)**
General		
Fatigue[1]	48	5
Edema[2]	40	1.1
Pyrexia	21	0.8
Gastrointestinal		
Constipation	46	0.6
Diarrhea	35	2.0
Nausea	34	0.3
Vomiting	24	0.8
Abdominal pain[3]	16	0.6
Nervous System		
Dysgeusia	44	0.3

Adverse Reactions	**ROZLYTREK** **n = 355**	
	All Grades (%)	**Grade ≥ 3* (%)**
Dizziness[4]	38	0.8
Dysesthesia[5]	34	0.3
Cognitive impairment[6]	27	4.5
Peripheral sensory neuropathy[7]	18	1.1
Headache	18	0.3
Ataxia[8]	17	0.8
Sleep[9]	14	0.6
Mood disorders[10]	10	0.6
Respiratory, Thoracic and Mediastinal		
Dyspnea	30	6*
Cough	24	0.3
Musculoskeletal and Connective Tissue		
Myalgia[11]	28	1.1
Arthralgia	21	0.6
Muscular weakness	12	0.8
Back pain	12	1
Pain in extremity	11	0.3
Metabolism and Nutritional		
Increased weight	25	7

Adverse Reactions	**ROZLYTREK** **n = 355**	
	All Grades (%)	**Grade ≥ 3* (%)**
Decreased appetite	13	0.3
Dehydration	10	1.1
Eye		
Vision disorders[12]	21	0.8
Infections		
Urinary tract infection	13	2.3
Lung infection[13]	10	6*
Vascular		
Hypotension[14]	18	2.8
Skin and Subcutaneous Tissue		
Rash[15]	11	0.8

* Grades 3 – 5, inclusive of fatal adverse reactions, including 2 events of pneumonia and 2 events of dyspnea.
[1]Includes fatigue, asthenia
[2] Includes face edema, fluid retention, generalized edema, localized edema, edema, edema peripheral, peripheral swelling
[3] Includes abdominal pain upper, abdominal pain, lower abdominal discomfort, abdominal tenderness
[4] Includes dizziness, vertigo, dizziness postural
[5] Includes paresthesia, hyperesthesia, hypoesthesia, dysesthesia, oral hypoesthesia, palmar-plantar erythrodysesthesia, oral paresthesia, genital hypoesthesia
[6] Includes amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, visual hallucination, memory impairment, mental disorder, mental status changes
[7] Includes neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy
[8] Includes ataxia, balance disorder, gait disturbances
[9] Includes hypersomnia, insomnia, sleep disorder, somnolence
[10] Includes anxiety, affect lability, affective disorder, agitation, depressed mood, euphoric mood, mood altered, mood swings, irritability, depression, persistent depressive disorder, psychomotor retardation
[11] Includes musculoskeletal pain, musculoskeletal chest pain, myalgia, neck pain
[12] Includes blindness, cataract, cortical cataract, corneal erosion, diplopia, eye disorder, photophobia, photopsia, retinal hemorrhage, vision blurred, visual impairment, vitreous adhesions, vitreous detachment, vitreous floaters

Adverse Reactions	ROZLYTREK n = 355	
	All Grades (%)	Grade ≥ 3* (%)

[13] Includes lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection
[14] Includes hypotension, orthostatic hypotension
[15] Includes rash, rash maculopapular, rash pruritic, rash erythematous, rash papular

The Applicant's Position:

The current treatment emergent adverse reactions presented in the ROZLYTREK USPI (Section 6.1 Clinical Trial Experience) is presented in Table 15. Please note that this table summarizes the adverse reactions observed in 355 patients presented in the original NDA filings.

Clinically relevant adverse reactions occurring in ≤ 10% of patients include dysphagia (10%), fall (8%), pleural effusion (8%), fractures (6%), hypoxia (4.2%), pulmonary embolism (3.9%), syncope (3.9%), congestive heart failure (3.4%), and QT prolongation (3.1%).

This pooled adult and pediatric ADR table is not planned to be updated with the pediatric NDA submission.

The FDA's Assessment:

FDA disagreed with pooling of adult and pediatric safety data as a detailed description of safety data specific to pediatric patients may be important information for prescribers. For the purposes of this review, FDA considered the primary safety population to be comprised of pediatric patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three multicenter, open-label clinical trials: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2) who received at least one dose of entrectinib.

The most common (≥20%) treatment-emergent adverse events (TEAEs) were pyrexia, constipation, increased weight, vomiting, diarrhea, nausea, cough, fatigue, pain in extremity, skeletal fractures, decreased appetite, headache, abdominal pain, urinary tract infection, upper respiratory tract infection, and nasal congestion.

Table 29 Adverse Reactions (≥20%) in Pediatric Patients Who Received Entrectinib in STARTRK-NG, TAPISTRY and STARTRK-2

Adverse Reaction	ROZLYTREK (n=76)	
	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal Disorders		

Constipation	41	1.3
Vomiting	38	0
Diarrhea	37	0
Nausea	34	0
Abdominal Pain	20	2.6
Investigations		
Increased Weight	39	18
General Disorders		
Pyrexia	43	1.3
Fatigue[1]	30	2.6
Infections		
Upper Respiratory Tract Infection	20	1.3
Urinary Tract Infection	20	2.6
Nervous System Disorders		
Headache	22	2.6
Metabolism And Nutrition Disorders		
Decreased Appetite	24	1.3
Musculoskeletal And Connective Tissue Disorders		
Pain in Extremity	26	2.6
Skeletal Fracture[2]	25	11
Respiratory, Thoracic And Mediastinal Disorders		
Cough	33	1.3
Nasal Congestion	20	0

Source: ADSL (Subject-Level Analysis Dataset) - 2023-04-28, ADAE (Adverse Events Analysis Dataset) - 2023-04-28. Variables used: USUBJID, STUDYID, SAFFL, TRTEMFL, AEDECOD, ATOXGR, AEACN, AEACNOT1, AEACNOT2, AEACNOT3, AEBODSYS, AESER

[1]Includes fatigue, asthenia
[2]Includes clavicle fracture, tibia fracture, femur fracture, fibula fracture, foot fracture, fracture, pathological fracture, limb fracture, lower limb fracture, pelvic fracture, spinal compression fracture, stress fracture, ulna fracture

Clinically relevant adverse reactions in <20% of patients who received entrectinib included pruritus, rash, urinary incontinence, eye pain, and photophobia.

Laboratory Findings

The Applicant's Position:

See Section 11 about strategy to update USPI.

Clinical laboratory evaluations were analyzed at the study level.

In study STARTRK-NG, the most frequent (≥ 2 patients) shifts observed from Grade 0-2 at baseline to Grade 3-4 post-baseline for the specific hematology parameters were neutrophils decreased (15 patients [22%]), hemoglobin decreased (5 patients [7%]), lymphocytes increased (2 patients [3%]), and platelets decreased (2 patients [3%]). In studies TAPISTRY and STARTRK-02, the majority of patients who experienced post baseline shifts in hematology parameters had shifts to Grade 1 or 2.

Based on laboratory data, in study STARTRK-NG, the most frequent (≥ 2 patients) shifts observed from Grade 0-2 at baseline to Grade 3-4 post-baseline for the specific chemistry parameters were albumin decreased (6 patients [9%]), calcium increased (6 patients [9%]), creatinine increased (4 patients [6%]), potassium decreased (4 patients [6%]), phosphorus decreased (3 patients [4%]), ALT increased (3 patients [4%]), sodium decreased (3 patients [4%]), magnesium increased (2 patients [3%]), potassium increased (2 patients [3%]), and AST increased (2 patients [3%]). No clinically relevant shifts of Grade ≥3 post baseline were observed in study TAPISTRY, and 1 patient (2 events) experienced clinically relevant shift of Grade ≥3 post baseline in study STARTRK-02.

The FDA's Assessment:

According to the Applicant, two versions of CTCAE were used across the contributing studies (v4.03 in STARTRK-NG and STARTRK-2, v5.0 in TAPISTRY). In order to generate a cohesive table describing commonly reported adverse reactions, adverse event listings from the two STARTRK studies were updated to CTCAE v5.0 by the Applicant. With this update, the criteria for each grade of hypophosphatemia were revised such that clinical information was needed to grade the event. Since correspoinding clinical information was not required for events of hypopohosphatemia according to CTCAE v4.03 , these data were not captured in in STARTRK-NG and STARTRK-2, and as such, hypophosphatemia could not be assessed using CTCAE v5.0. The FDA and the Applicant agreed to report decreased phosphorus based on laboratory data rather than adverse event reporting.

The most common (≥20%) Grade 3 or 4 laboratory abnormalities were increased creatinine, increased aspartate aminotransferase (AST) decreased neutrophils,decreased hemoglobin, increased alanine aminotransferase (ALT), decreased leukocytes, increased sodium, increased lymphocytes, increased magnesium,increased glucose,increased potassium, increased alkaline phosphatase, decreased albumin, increased calcium, increased bilirubin.

Data:

Table 30 Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Receiving ROZLYTREK in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG

Laboratory Abnormality	Entrectinib[1]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased Hemoglobin	53	7
Decreased Neutrophils	53	22
Decreased Leukocytes	46	1.3
Increased Lymphocytes	33	3
Chemistry		
Increased Creatinine	84	5
Increased AST	61	2.7
Increased ALT	53	2.6
Increased Sodium	38	1.4
Increased Magnesium	32	5
Decreased Glucose	26	0
Increased Alkaline Phosphatase	25	0
Increased Potassium	25	2.7
Decreased Albumin	24	9
Increased Calcium	21	8
Increased Bilirubin	20	8

Source: adlbir.xpt, adsl.xpt.
Variables used: USUBJID, STUDYID, ATOXGRV5, ABLFL, ANRHI, ANRLO, ADY, ADT, TRTSDT, TRTEDT, PARCAT1, PARAM, AVAL.

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase
[1] The denominator used to calculate the rate varied from 67 to 76 based on the number of patients with a baseline value and at least one post-treatment value. All values based on NCI CTCAE v5.0

Other clinically relevant laboratory abnormalities in patients who received entrectinib included decreased phosphorous (22).

Vital Signs

The Applicant's Position:

STARTRK-NG

The most frequently reported vital sign abnormalities (≥20%) were:

- Heart rate decreased from baseline > 20 bpm
- Diastolic blood pressure decrease from baseline >20 mmHg
- Heart rate increase from baseline >30 bpm

TAPISTRY

The most frequently reported post-baseline vital sign changes were changes in respiration and blood pressure (3 patients each). Full details of vital sign abnormalities are provided in the BO41932 Data Memo, Section 8.3.1.

STARTRK-02

The most frequently reported post-baseline vital sign changes were changes in temperature, blood pressure, and heart rate (2 patients each).

Full details of vital sign abnormalities are provided in the GO40782 Data Memo, Section 8.3.1.

The FDA's Assessment:

No new significant findings were identified in FDA's evaluation of the vital signs dataset.

Electrocardiograms (ECGs)

The Applicant's Position:

STARTRK-NG

Among the 59 patients with baseline corrected QT interval (QTc) values ≤ 450 ms, 4 patients had post-baseline QTc values > 450 ms - ≤ 480 ms, and 2 patients had post-baseline QTc values > 480 ms - ≤ 500 ms.

Among the 9 patients with baseline QTc values > 450 ms - ≤ 480 ms, 1 patient had a post-baseline QTc value > 480 ms - ≤ 500 ms.

TAPISTRY

Post-baseline, 3 patients had abnormal ECGs. Full details are provided in the BO41932 Data Memo, Section 8.3.2.

STARTRK-02

Post-baseline, 2 patients had abnormal ECGs. Full details are provided in the GO40782 Data Memo, Section 8.3.2

The FDA's Assessment:
ECG results showed no unexpected safety findings. QT interval prolongation is appropriately labeled as a Warning and Precuation and Section 2 provides dose modifications for events of QT interval prolongation.

QT

The Applicant's Position:
See section above.

The FDA's Assessment:
See review above regarding ECG results

Immunogenicity

The Applicant's Position:
Immunogenicity is not applicable.

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

11.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Specific Adverse Events

The Applicant's Position:

See Section Significant Adverse Events

The FDA's Assessment:
The characterization of skeletal fractures is still ongoing. The current product labeling for entrecitnib includes skeletal fractures in Section 5 (Warnings and Precautions); this section was updated based on data provided in this submission. The exact mechanism for which entrectinib may cause skeletal fractures is not fully undestood In vitro data suggest that entrectinib has the potential to affect the osteoclast/osteoblast remodeling balance under the conditions tested; however these studies are exploratory in nature. A PMR for the further assessment of skeletal fractures was issued as part of the original approval and is ongoing.

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

The Applicant's Position:

Neurocognitive Assessments

Neurocognitive assessments were performed in CO40778 only in the 26 patients who enrolled after protocol v6 or re-consented to v6 once available. The specific assessment conducted was based on the normative age range for the assessment. For children between 2.5–6 years of age, the Wechsler Preschool and Primary Scale of Intelligence - Fourth Edition (WPPSI-IV) was administered. For children >6 years of age, the Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II) was administered. Neurocognitive assessments were conducted once every 12 months. The mean score on the WPPSI and WASI is 100 and scores between 90-110 are considered average performance (Wechsler 2011, 2012).

Six children were expected to and completed the WPPSI-IV at baseline. Only 2, 3, and 2 patients were expected to complete the WPPSI-IV at Cycles 12, 24, and 36, respectively. One to two patients completed assessments at the later cycles. The average WPPSI scale scores at baseline were within the average range. Change scores were not described for patients at Cycle 12 and beyond due to small number of patients contributing data.

Fourteen children were expected to complete the WASI-II at baseline, with the rate of completion being 57.1%. Six patients did not complete the WASI-II at baseline due to the site not administering the WASI-II (4 patients) and the translation was not available (2 patients). At Cycle 12, all 7 eligible patients completed the assessment. Only 3 patients were expected to complete at Cycle 24 with one patient completing. Only one patient was expected to complete Cycle 36 and 48 assessments, but did not. The average WASI-II baseline scores were within the average range. Change scores are not described for patients at Cycle 12 and beyond due to small number of patients contributing data.

Patients in general exhibited average neurocognitive assessment scores at baseline, but due to the small number of patients at one, two, and three-year follow-up, further interpretation was not possible.

The FDA's Assessment:

In the absence of comparative analyses for these non-randomized studies, it is difficult to attribute any observed within-patient differences of patient reported outcomes (PRO) exclusively to the experimental therapy, as the results cannot be adequately contextualized for this patient population. These data were not used to support claims in the USPI.

11.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Intrinsic Factors

- **Age** – Patients ≥ 28 days to < 24 months had a higher proportion of SAEs (10/14 patients [71.4%]) compared with patients ≥ 24 months to < 12 years and patients ≥ 12 years to 18 years (21/49 patients [42.9%] and 3/13 patients [23.1%], respectively). Patients ≥ 28 days to < 24 months had a higher proportion of AEs leading to dose interruption (10/14 patients [71.4%]) compared with patients ≥ 24 months to < 12 years and patients ≥ 12 years to 18 years (18/49 patients [36.7%] and 2/13 patients [15.4%], respectively). Additionally, there were no patients ≥ 28 days to < 24 months and patients ≥ 12 years to 18 years who experienced AEs leading to discontinuation.

Patients < 6 months had a higher proportion of SAEs (7/9 patients [77.9%]) compared with patients ≥ 6 months to < 2 years, patients ≥ 2 years to < 12 years, and patients ≥ 12 years to < 18 years (3/5 patients [60%], 21/49 patients [42.9%], and 3/13 patients [23.1%], respectively). Patients < 6 months had a lower proportion of AEs leading to dose interruption (6/9 patients [66.7%]) compared with patients ≥ 6 months to < 2 years (4/5 patients [80%]) but had a higher proportion of AEs leading to dose interruption compared with patients ≥ 2 years to < 12 years, and patients ≥ 12 years to < 18 years (18/49 patients [36.7%] and 2/13 patients [15.4%], respectively). Patients < 6 months did not have any AEs leading to discontinuation or AEs leading to dose reduction.

- **Sex** – The overall safety profile of entrectinib was generally comparable across sexes. In males, the proportion of SAEs (14/37 patients [37.8%]) was lower compared with females (20/39 patients [51.3%]).
- **Race** – Overall, the proportion of SAEs was higher in Other patients (4/5 patients [80%]) and White patients (28/51 patients [54.9%]) compared with Asian patients (1/15 patients [6.7%]) and African American patients (1/5 patients [20%]). The proportion of Grade ≥ 3 AEs was lower in Asian patients (6/15 [40%]) compared with White patients (40/51 patients [78.4%]), African American patients (3/5 patients [60%]), and Other patients (4/5 patients [80%]). The proportion of AEs leading to dose interruption was lower in Asian patients (2/15 patients [13.3%]) compared with White patients (22/51 patients [43.1%]), African American and Other patients (3/5 patients each [60%]). Additionally, there were no related SAEs, or AEs leading to dose reduction in Asian patients. There were no AEs leading to discontinuation in Asian and Other patients.
- **Performance Status** – Overall, the safety profile of entrectinib was generally comparable across all baseline Lansky-Karnofsky performance status. Consistent with the impact of the overall underlying disease burden on a patient's general performance, a higher proportion of patients experienced Grade ≥3 AEs with lower Lansky-Karnofsky performance status (2/2 patients [100%], 2/2 patients [100%] and 12/14 patients [85.7%] for Lansky-Karnofsky performance status 60, 70 and 80, respectively) at baseline.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that there were no apparent clinically meaningful differences regarding demograhic subgroups that would require further investigation and analyses. See Section 6.3.2.1.

It is not possible to draw meaningful conclusions for subgroups based on race for those subgroups with a small number of patients (Black and other non-reported races). The clinical meaningfulness of these findings is difficult to interpret given the small patient numbers.

11.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:

FDA agrees with Applicant's position.

11.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No signal for increased malignancy has been identified.

The FDA's Assessment:

FDA agrees with Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies were reported

The FDA's Assessment:

FDA agrees with Applicant's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Data collection for the long term effects of entrectinib on growth and development related to the post marketing requirement is ongoing in all pediatric age groups. Data collected to date is presented in the clinical study report for CO40778 and the data memo for study BO41932. To date, there have been no safety signals detected related to entrectinib with regard to effects on growth and development.

The FDA's Assessment:

FDA agrees with Applicant's statement. A postmarketing requirement was issued at the time of accelerated approval for the NTRK indication to further assess the risk of skeletal fractures with entrectinib.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There were no reported cases of overdose of entrectinib in the study.

No dedicated studies on the potential for entrectinib to cause dependence were performed. However, the pharmacological properties of entrectinib suggest that there are no risks of abuse.

There was no information regarding the potential for withdrawal and rebound to entrectinib.

The FDA's Assessment:

FDA agrees with the Applicant's position.

11.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

There have been no new safety concerns identified through postmarketed experience.

The FDA's Assessment:

FDA agrees with the Applicant's position that no new safety concerns have been identified.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

It is expected that safety issues can be adequately managed through labeling, routine risk minimization measures and routine postmarketing surveillance.

The FDA's Assessment:

The Applicant has a pharmacovigilance system for collecting, monitoring, evaluating, and communicating/reporting information regarding AEs in patients treated with entrectinib during the pre- and post-approval period.

FDA agrees with the Applicant's statement that no new risks have been identified in the postmarketing experience.

11.2.11. Integrated Assessment of Safety

The Applicant's Position:

The efficacy benefit occurred in the context of a tolerable and manageable safety profile which supports a positive benefit-risk relationship for entrectinib in pediatric patients.

The AEs reported in the integrated safety population were generally considered to be manageable and there were no fatal events. Grade $\geq$ 3 AEs were experienced by 69.7% of patients, and SAEs by 44.7% of patients treated with entrectinib,.

All deaths were due to progressive disease with the majority of deaths occurring more than 30 days after the last dose of entrectinib and primarily occurred in patients from Part I of CO40778 with no gene fusion.

The tolerability of entrectinib was evident by the low discontinuation rates. Out of 76 patients, 10 patients (13.2%) discontinued entrectinib due to AEs. Most AEs requiring intervention could be adequately managed with dose interruptions (withholding of dose) (39.5%), dose reduction (21.1%), and/or supportive care. Dose interruptions were transient, and generally did not prevent patients continuing to receive their planned entrectinib dose for the majority of the duration of treatment.

Overall, AEs were found to be manageable through routine medical care and specific monitoring for events of bone fractures, CHF, QT prolongation, cognitive disorders, changes in weight, and DILI.

Bone fractures were reported in 25% of pediatric patients in the integrated safety population, with no Grade 4 or 5 bone fracture events. The majority of patients continued treatment with entrectinib during the fracture and a large proportion of the events resolved.

There were no new safety findings and the safety profile is consistent with the known safety profile of entrectinib in pediatric patients.

The FDA's Assessment:

The primary safety population included 76 pediatric patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of three studies: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2).

Significant safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. The most common (≥20%) treatment-emergent adverse events (TEAEs) were pyrexia, constipation, increased weight, vomiting, diarrhea, nausea, cough, fatigue, pain in extremity, skeletal fractures, decreased appetite, headache, abdominal pain, urinary tract infection, upper respiratory tract infection, and nasal congestion. These adverse reactions are consistent with the safety profile observed in patients greater than 12 years of age observed in the original application that supported the accelerated approval of entrectinib..

Entrectinib appears to have an acceptable safety profile when assessed in the context of a life--threatening disease. In addition, although entrectinib can cause serious and severe toxicities

(including skeletal fractures), the safety concerns are described and dose modification recommendations included in product labeling; entrectinib will be prescribed by oncologists who are trained to monitor and treat serious treatment-related toxicities. There were no new significant safety concerns identified during this review requiring additional risk management tools such as a Risk Evaluation and Mitigation Strategy (REMS).

11.3. Statistical Issues

The FDA's Assessment:

Data were analyzed according to the plan pre-specified in the statistical analysis plan. There were no major statistical issues in the application. The efficacy evaluation of entrectinib is based on pooled analyses of two studies, STARTRK-NG (n=31) and TAPISTRY (n=2), that included pediatric patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion. Entrectinib is currently approved for adult and pediatric patients 18 years of age and older with unresectable or metastatic solid tumors with a *NTRK* gene fusion based on the results of pooled data from three multicenter, single-arm, open-label clinical trials: ALKA, STARTRK-1 and STARTRK-2. The data provided in this application is intended to support extension of the approved indication to pediatric patients aged 1 month or older.

Due to the single arm nature of the two pediatric studies, blinded independent central review (BICR) was implemented to assess the primary endpoint of ORR for both CNS and non-CNS tumors to minimize potential measurement bias.

Of the 33 patients included in the analysis population, 17 patients had a primary CNS tumor with responses evaluated per RANO criteria and 16 patients had a non-CNS primary tumor with responses evaluated per RECIST 1.1. The ORR observed in the 17 patients with primary CNS tumor is 53%, with a lower bound of the 95% CI of 28%; the ORR observed in the 16 non-CNS tumor patients is 88%, with a lower bound of the 95% CI of 62%. However, given the small sample size of the analysis population, it is difficult to determine if there are differential response rates by primary tumor type (CNS vs. non-CNS), and the response rate in each group is relatively high.

11.4. Conclusions and Recommendations

The FDA's Assessment:

Studies STARTRK-NG (NCT02650401) and TAPISTRY (NCT04589845) are multicenter, open label, non-randomized trials of entrectinib that included pediatric patients with solid tumors with

NTRK fusions. The ORR observed in the primary efficacy population (n=33) was 70% (95% CI 51, 84) with a median duration of response (DOR) of 25.4 months (95% CI 14.3, not estimable [NE]). A total of 43% of responders had a DOR of ≥ 12 months. This ORR is consistent with the ORR observed in patients greater than 12 year of age that supported the original approval of entrectinib for patients 12 years of age and older with solid tumors with NTRK fusions [ORR 57% (95% confidence interval: 43, 71)].

The overall safety population included 76 pediatric patients treated with entrectinib in one of three clinical trials: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2). Significant safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. The most common (≥20%) treatment-emergent adverse events (TEAEs) were pyrexia, constipation, increased weight, vomiting, diarrhea, nausea, cough, fatigue, pain in extremity, skeletal fractures, decreased appetite, headache, abdominal pain, urinary tract infection, upper respiratory tract infection, and nasal congestion. Overall the toxicity profile of entectinib is considered acceptable when assessed in the context of the treatment of this life-threatening disease.

Although data from pediatric patients with only 5 tumor types, including primary CNS tumors (n=17), fibrosarcoma (n=8), spindle cell carcinoma (n=6), sarcoma (n = 1), and melanoma (n = 1), were provided in this application, considering the rarity of the *NTRK* gene fusion in solid tumors, the mechanism of action of this targeted therapy, and the efficacy observed in adult patients with solid tumors with NTRK gene fusions, the small number of tumor types is considered acceptable.

Based on the favorable benefit:risk assessment of entrectinib for this population with a serious, life-threatening disease, the review team recommends expansion of the currently approved indication for patients 12 years of age and older with solid tumors with an NTRK gene fusion to pediatric patients older than 1 month of age. In addition, an adequate scientific bridge has been established between the coated granule (pellet packet) and oral capsule formulations, and between the oral capsule administered as suspension, either orally or via gastric/nasogastric tube, compared to the intact oral capsule formulation. Therefore, the FDA review team recommends accelerated approval of entrectinib for the following indication:

> *Adult and pediatric patients greater than 1 month of age with solid tumors that: have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory alternative therapy.*

A postmarketing requirement will be issued for additional clinical studies or data to verify the clinical benefit for this pediatric patient population (See Section 16).

X	X
Primary Statistical Reviewer Xiaoxue Li	Statistical Team Leader Pallavi Mishra-Kalyani
X	X
Primary Clinical Reviewer Marjilla Seddiq	Clinical Team Leader Amy Barone

12 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Not applicable. The review team did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review which required external input for the proposed indication.

13 Pediatrics

The Applicant's Position:

The Applicant has proposed changes to the pediatric sections of the ROZLYTREK label, which include Section 1.2, Section 2.1, Section 2.4, Section 2.5, Section 5.3, Section 8.4, and Section 14.2. In addition to the updates proposed within the Full Prescribing Information and Patient Information, the Applicant has introduced two Instructions for Use to support HCPs, patients and caregivers with guidance on preparation and administration of the two formulations of ROZLYTREK (capsules and coated granules).

For details on the proposed labeling changes, please refer to the Labeling Recommendations below in Section 11 of the Assessment Aid.

The FDA's Assessment:

FDA agrees with the Applicant's proprosal to update certain portions of section 1, 2, 3, 8 and 14 of the USPI after negaotions through IRs and labeling changes. The Applicant initially proposed (b) (4) FDA did not agree with this approach and recommend describing safety information for pediatric patients in Section 6. The Applicant agreed and revised the the USPI to capture the pediatric safety population in Section 6. For further detail see Section 11 of the Assessment Aid.

Orphan drug designation was granted on July 5, 2017 for entrectinib for the treatment of NTRK fusion positive tumors and, as such, it is exempt from PREA requirements.

14 Labeling Recommendations

The Applicant's Position:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1.2 *NTRK* Gene Fusion-Positive Solid Tumors	Changes proposed to extend the current indication for Rozlytrek in patients with solid tumors that have an NTRK gene fusion to include (b) (4)	FDA revised the indication statement to: "adult and pediatric patients older than 1 month of age" (b) (4)
2.1 Dosage and Administration Overview	Additional language to describe the recommended patient population for the capsules, capsules prepared as an oral suspension and coated granules.	Section 2 required complete revision for consistency with the newly published draft guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry.* FDA revisions include new sections: 2.1 Patient Selection, 2.2 Recommended Evaluation and Testing Before Initiating ROZLYTREK, 2.3 ROZLYTREK Dosage Form Overview, and 2.4 ROZLYTREK Administration Overview.
2.4 Recommended Doasge for *NTRK* Gene Fusion-Positive Solid Tumors	Additional language to provide recommended dosage for pediatric patients: Older than 6 months (changes to BSA categories for pediatric patients (b) (4) >1 month to ≤6 months (b) (4)	FDA removed (b) (4). Table 6 Preparation of ROZLYTREK Capsules as an Oral Suspension, FDA added rows to provide suspension information

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

		for dose 110 mg to 140 mg *(these were omitted by the Applicant).*
2.5 Dosage Modifications for Adverse Reactions	(b) (4) [redacted]	Revisions for clarity and brevity, (b) (4) [redacted]
2.5 Dosage Modifications for Drug Interactions	Additional language and table to describe recommended dose reduction of Rozlytrek if co-adminsitration of CYP3A inhibitors cannot be avoided. Dose reduction recommendations have been expanded from adult and pediatric patients 12 years and older with BSA greater than 1.50 m^2 to adult and pediatric patients 2 years and older with a starting dose of 200 mg or higher.	Moved to Section 2.8.
5.3 Skeletal Fractures	Updated language for the description of the adverse reaction and outcome in pediatric patients based on the integrated safety population with a clinical cutoff date of 2 Aug 2022 (n=76).	FDA adjudicated the numbers in this section.
8.4 Pediatric Use	Additional language to reflect the (b) (4) [redacted] effectiveness of Rozlytrek that has been established in pediatric patients based on available data. Additional language to describe pediatric (b) (4) [redacted].	FDA revised Section 8.4 and (b) (4) [redacted] Additionally, safety from a Juvenile Animal study was included to highlight adverse reactions not demonstrated in clinical studies: decreased body weight gain and delayed sexual maturation, deficits in neurobehavioral assessments, and decreased femur length.
14.2 *NTRK* Gene Fusion-Positive Solid Tumors	Efficacy subsection for pediatric patients has been added based on the pooled efficacy data (n=33) from the pivotal Phase I/II	Section 14.2 Efficacy in Pediatric Patients: FDA added complete demographic information, and limited Duration of

	study STARTRK-NG and one Phase II study TAPISTRY.	Response to the 12 month time point. FDA added a new Table 18. Efficacy Results for Pediatric Patients with Solid Tumors Harboring NTRK by Gene Fusion Partner to provide ORR and DOR by mutation.

The FDA's Assessment:

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

FDA included a new section in 6.1 Clinical Trial Experience, "Safety in Pediatric Patients" to describe the safety observed in pediatrics in the following studies: STARTRK-NG (N=68), TAPISTRY (N=6) and STARTRK-2 (N=2).

FDA revised Section 12.3 Pharmacokinetics to include exposure during fed and fasted conditions for both ROZLYTREK capsules and ROZLYTREK oral pellets. Also, FDA included exposure by age group.

15 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There were no significant safety concerns identified during the review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Entrectinib will be prescribed by oncologists who are skilled in monitoring, diagnosing, and managing serious toxicities caused by antineoplastic drugs including targeted therapies. Safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. Standard practice in oncology dictates that patients be apprised of risks related to treatment prior to receiving antineoplastic drugs.

16 Postmarketing Requrements and Commitment

The FDA's Assessment:

The Applicant has agreed to the following postmarketing requirements (PMRs). Please refer to the approval letter for expected completion dates.

4532-1 Conduct an integrated analysis from completed and ongoing trialsintended to verify and describe the clinical benefit of entrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in adult and pediatric patients 12 years of age and older with solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion and without a known acquired resistance mutation; that are metastatic or would require surgical resection that would result in severe morbidity; and that have no satisfactory alternative treatment or have progressed following treatment. A sufficient number of patients will be evaluated to more precisely characterize response and durability of response for each of the following tumor types: pediatric solid tumors, colorectal cancer, central nervous system cancers, gynecological cancers, and melanoma. A minimum of 40 patients with cancers other than pediatric solid tumors, colorectal cancer, central nervous system cancers, gynecological cancers, melanoma, soft tissue sarcoma, non-small cell adenocarcinoma lung cancer, mammary analogue secretory carcinoma, and secretory breast cancer will also be studied. Overall response rate and duration of response will be assessed by

independent central review and all responding patients will be followed for at least 12 months from the onset of response.

4532-2 Conduct an integrated analysis from ongoing trials intended to verify and describe the clinical benefit of entrectinib, through more precise estimation of the overall response rate and mature response duration per independent review assessment, in a sufficient number of pediatric patients older than 1 month of age and less than 12 years of age with solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion and without a known acquired resistance mutation; that are metastatic or would require surgical resection that would result in severe morbidity; and have no satisfactory alternative treatment or have progressed following treatment. Overall response rate and duration of response will be assessed by independent central review and all responding patients will be followed for at least 12 months from the onset of response.

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:	__ Yes X No

17 Division Director (DHOT) (NME ONLY)

X

18 Division Director (OCP)

X

19 Division Director (OB)

X

20 Division Director (Clinical)

X

21 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

22 Appendices

22.1. References

The Applicant's References:

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The FDA's References:

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22.2. Financial Disclosure

The Applicant's Position:

Study STARTRK-NG:

For the pivotal study, STARTRK-NG, a total of 432 out of 443 (97.5%) principal investigators and sub-investigators responded. Detailed tables that list each investigator with his or her accompanying financial disclosure state are provided in Section 1.3.4.4. Despite Genentech/Roche acting with due diligence to obtain the information, a signed financial disclosure was not obtained for 10 sub-investigators and 1 principal investigator in STARTRK-NG. Of these there were:

3 sub-investigators whom did not enroll any patients or perform any study-related duties.

1 sub-investigator for whom a signed financial disclosure was collected for Ignyta but a signed financial disclosure with Genentech/Roche was not possible to obtain.

1 sub-investigator for whom a positive disclosure was collected but subsequent attempts to collect further details about exact payment dates and amounts was not possible to obtain.

2 sub-investigators for whom a signed financial disclosure was not possible to obtain and whom received payments from (b) (6) in excess of $25,000 based on a review of Sunshine Act data. These disclosures are summarized in Table 1.

Genentech/Roche has generated Notes to File stating the reason that the information could not be collected, and performed a risk of bias assessment for the two investigators who received payments in excess of $25,000 based on the Sunshine Act data. These Notes to File are provided in Section 1.3.4.5.

Of the investigators who responded, disclosable financial interests were recorded in 0 out of 432 investigators in STARTRK-NG.

Summary of Financial Disclosures for Study STARTRK-NG

Study Protocol Number	Clinical Site Number	Number of Patients Enrolled at Site	Investigator Name	Investigator Type	Disclosure
CO40778	(b) (6)	(b) (6)	(b) (6)	Principal Investigator	$33,980 Amount identified through Sunshine Act data
CO40778	(b) (6)	(b) (6)	(b) (6)	Sub-Investigator	(b) (6) received payments from (b) (6) exceeding $25,000 (b) (6)

					(b) (4)
CO40778	(b) (4)	(b) (4)	(b) (4)	Sub-Investigator	$50,000 Amount identified through Sunshine Act data

Study STARTRK-2:

For the supportive Study STARTRK-2, a total of 26 out of 31 (83.9%) principal investigators and sub-investigators who enrolled pediatric patients responded. Despite Genentech/Roche acting with due diligence to obtain the information, a signed financial disclosure was not obtained for 5 sub-investigators. Notes to File stating the reason that the information could not be collected have been generated and provided in Section 1.3.4.5. No disclosable financial interests were recorded.

Study TAPISTRY:

For the supportive Study TAPISTRY, a total of 36 out of 36 (100%) principal investigators and sub-investigators who enrolled pediatric patients responded. No disclosable financial interests were recorded.

Information on financial disclosures for STARTRK-NG, STARTRK-2, and TAPISTRY are provided in Module 1.3.4 of the NDA.

The FDA's Assessment:

In accordance with 21 CFR 54, Genentech submitted financial disclosure certification documents in module 1.3.4. Genentech provided Form 3454, attesting to the absence of financial interests and arrangements for investigators and sub-investigators in each study.

The financial disclosures of the three investigators (1 principal investigator and 2 sub-investigators) listed above by the Applicant were reviewed by the FDA and verified. Two responders in the primary efficacy population were reported from sites 8 and 9.

FDA agrees with the Applicant that the investigators involved in the STARTRK-NG (CO40778), STARTRK-2 (GO40782), and TAPISTRY (BO41932) had no financial arrangements that would affect the outcome of the trial.

Covered Clinical Study (Name and/or Number): STARTRK-NG (CO40778)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 443		
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): 3		

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: N/A Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: Genentech, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Details were unable to obtain. Due diligence attempts documented on Note to Files are included in this application)
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): 11		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number): STARTRK-02 (GO40782)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 31		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: Genentech, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (N/A – no investigators with disclosable financial interest)
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): 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number): TAPISTRY (BO41932)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)

Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Sponsor of covered study: Genentech, Inc.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (N/A – no investigators with disclosable financial interest)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Since all investigators have provided a financial disclosure form, no Note to Files have been generated for Unable to Obtain Investigators)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

22.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Refer to Section 5.

The FDA's Assessment:

FDA has no additional comments.

22.4. OCP Appendices (Technical documents supporting OCP recommendations)

22.4.1. Population PK Analysis

22.4.2. Executive Summary

The FDA's Assessment:

Population PK analysis was conducted by the Applicant and evaluated by FDA. The PK of entrectinib was characterized by a 1-compartment model with sequential zero- and first-order absorption and linear elimination corresponding to M5 formation. The population PK model described the observed concentrations of entrectinib and M5 reasonably well except for underprediction in pediatrics 6 months and younger. The underprediction was only observed for population predicted concentrations not individual predicted concentrations, therefore the prediction for individual exposure used in E-R analysis is considered adequate.

To evaluate the proposed dosage for age and BSA categories from PK perspective, combined exposure of entrictinib and its active metabolite M5 due to equal in vitro potency was compared. Due to the lack of clinical data in pediatrics over 6 months old with BSA of 0.5 m^2 or less and the expected exposure with the proposed dose of (b) (4) mg being (b) (4)% of adults, FDA had efficacy concern for this subgroup and conducted independent simulation for alternative doses. Simulation suggests a dose of 300 mg/m^2 best match the exposure in other BSA groups. Based on exposure comparability and no major concern for worsening safety, FDA recommended a dose of 300 mg/m^2 in pediatric patients with BSA of 0.5 m^2 or less which was accepted by the Applicant.

22.4.3. PPK Assessment Summary

The Applicant's Position:

[Highlight the key findings in the white cells.]

General Information	
Objectives of PPK Analysis	• Update the existing popPK model of entrectinib and M5, including all available data from pediatric cancer patients treated with entrectinib collected until the clinical cutoff date (CCOD) of August 2nd, 2022. • Evaluate the impact of patient's characteristics on the PK of entrectinib and M5. • Determine individual exposure metrics to be used in the exposure-efficacy and safety analyses.
Study Included	• GO40784, GO40782, CO40778, GO40785, BO41932 (only pediatric data).
Dose(s) Included	Adults: 200-800 mg total daily dose Pediatrics: 50-1100 mg total daily dose

Population Included		Adult and pediatric patients with solid malignancies
Population Characteristics (Table 25)	General	Table 25
	Organ Impairment	Table 25
	Pediatrics (if any)	73 pediatric patients, see Table 25 Age: median 6.69 yr (range, 0.17-20.1 yr; 6 subj. <6 months, 6 subj. 0.5-2 yr, 47 subj. 2-12 yr, 14 subj. >12 yr) Weight: median 22 (range, 3.5-90) kg
No. of Patients, PK Samples, and BLQ		343 patients (incl. 73 pediatric patients) 5289 entrectinib and 5219 M5 non-BLQ PK observations 74 (1.4%) entrectinib and 121 (2.3%) M5 BLQ observations all post-first dose
Sampling Schedule	Rich Sampling	See ITT Population for pediatric population
	In ITT Population	CO40778 (main source of pediatric data): C1 and C2 (or C3): pre-dose, and 1, 2, 4 and 6, and 24 hours post-dose; C1 Days 8, 15, 22: pre-dose; C3 and beyond: Day 1 at pre-dose.
Covariates Evaluated	Static	Sex, race, ethnicity, fusion protein, hepatic impairment, renal impairment, BSA
	Time-varying	Age, body weight

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM 7.4.3	Yes
Model Structure	1-compartment model with sequential zero- and first-order absorption for entrectinib and linear elimination corresponding to M5 formation; 1-compartment model with linear elimination for M5.	Yes
Model Parameter Estimates	Table 26	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	RSEs: ≤15% on all model parameters IIV: moderate (32-46%CV) except on KA (163%); Shrinkage: <25% Variability accounted for in simulations.	Yes
BLQ for Parameter Accuracy	BLQ data ignored, no impact expected given their low proportion	Yes
GOF, VPC	GOF: Figure 5 VPCs: Figure 6	Generally acceptable. Reviewer noted a trend of underprediction for M5 in the pediatric population. GOF by age group (19.4.1.3) indicated that underprediction of the model mainly occurred in pediatrics <=6 months. This underprediction was not observed for individual predicted concentrations thus individual predicted

		exposures are still considered adequate for E-R analysis.
Significant Covariates and Clinical Relevance	Body weight (allometric scaling), pediatric age on bioavailability and M5 clearance. Impact summarized in simulation results.	Yes
Analysis Based on Simulation (optional)	Figure 7	FDA does not agree that the simulated exposures for pediatrics <=6 months align with observed exposures (see 19.4.1.4).
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	(b) (4)	Minor edits for specific populations. Age was regrouped to "pediatric patients >6 months" and "pediatric patients (b) (4) given the data for pediatrics (b) (4)

Table 31 Summary of Baseline Characteristics in the Dataset, Stratified by Population (Adults vs Pediatrics).

Variable [unit]	Population	Mean	Standard deviation	Minimum	Maximum	IQR	P5	Median	P95
Age [years]	Adult	55.7	14.2	18.2	86.3	19.4	29.2	57.7	76.6
	Pediatric	7.53	5.12	0.17	20.1	7.28	0.318	6.69	16.6
Body surface area [m^2]	Adult	1.79	0.263	1.17	2.6	0.347	1.38	1.79	2.25
	Pediatric	0.917	0.4	0.22	1.98	0.52	0.326	0.83	1.67
Body weight [kg]	Adult	70.4	17.8	31.6	136	21.9	44.9	70	105
	Pediatric	26.8	17.3	3.5	90	18.6	6.19	22	62.6

Variable	Adult	Pediatric
Japanese		
No	265 (98%)	73 (100%)
Yes	5 (1.9%)	0 (0%)
Hepatic function		
Normal	228 (84%)	60 (82%)
Mild or moderate impairment	41 (15%)	13 (18%)
Severe	1 (0.4%)	0 (0%)
Renal function		
Normal	145 (54%)	70 (96%)
Mild or moderate impairment	125 (46%)	3 (4.1%)
Sex		
Male	121 (45%)	36 (49%)
Female	149 (55%)	37 (51%)
Race		
Asian	78 (29%)	10 (14%)
Black or African American	12 (4.4%)	5 (6.8%)
Not reported	17 (6.3%)	0 (0%)
Other	2 (0.7%)	5 (6.8%)
White	161 (60%)	53 (73%)
Ethnicity		
Hispanic or Latino	7 (2.6%)	8 (11%)
Not Hispanic or Latino	242 (90%)	55 (75%)
Not reported	8 (3.0%)	3 (4.1%)
Unknown	13 (4.8%)	7 (9.6%)

FUSION		
No fusion	29 (11%)	17 (23%)
NTRK	65 (25%)	36 (49%)
ROS1	128 (50%)	17 (23%)
ALK	36 (14%)	3 (4.1%)
Unknown	12	0 (0%)
CYP3A moderate inhibitor*		
No	256 (95%)	71 (97%)
Yes	14 (5.2%)	2 (2.7%)
pH modifier		
No	236 (87%)	68 (93%)
Yes	34 (13%)	5 (6.8%)
Proton pump inhibitor		
No	212 (79%)	68 (93%)
Yes	58 (21%)	5 (6.8%)

Data shown as number (%). Source: Applicant's PopPK report (Report 1121816) , Table 6. IQR, interquartile range; P5, 5th percentile; P95, 95th percentile.

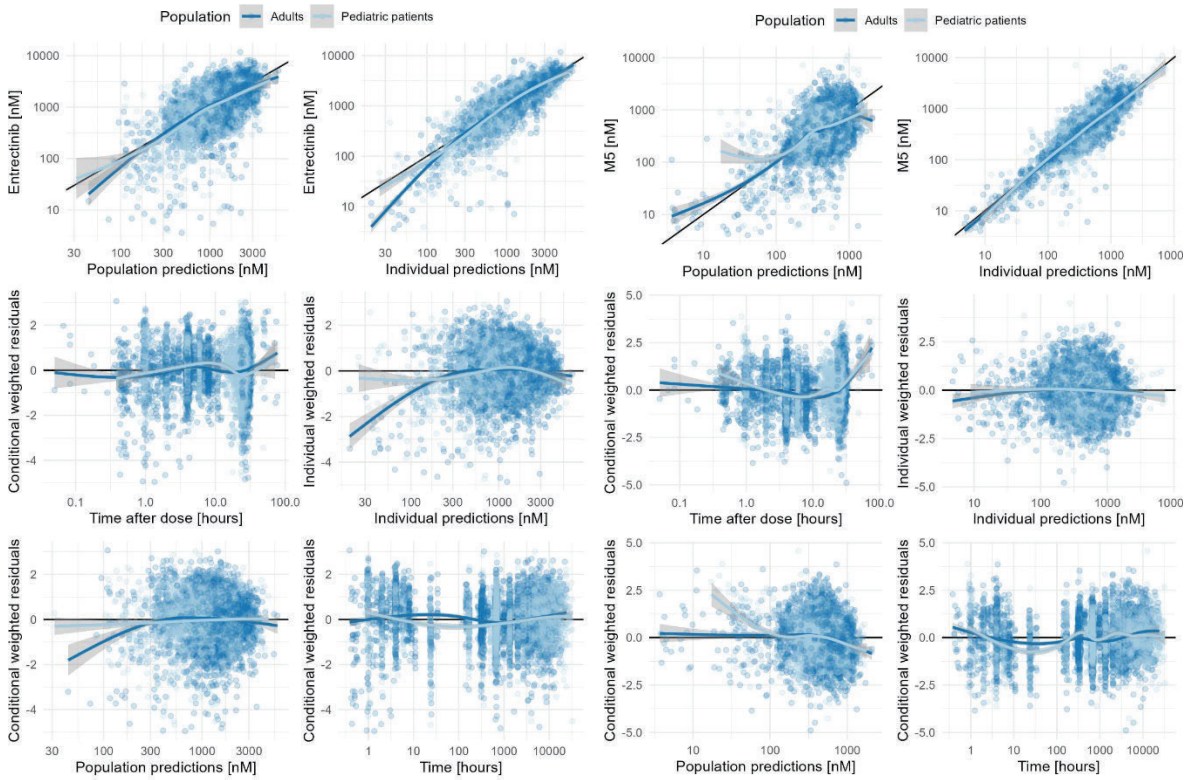
Source: Applicant's PopPK report (Report 1121816) , Table 4.

Table 32 Parameter Estimates and uncertainty from Final Population PK Model (Run 11).

Parameter [units]	Value	RSE [%]	Shrinkage [%]
Apparent clearance of entrectinib, CL/F [L/h/70kg]	20.4	3.0	-
Apparent volume of entrectinib, V/F [L/70kg]	613	3.2	-
Absorption rate constant, Ka [1/h]	1.48	8.4	-
Bioavailability, F [-]	1.00 fixed	-	-
Duration of the zero-order absorption process, D1 [h]	1.66	7.1	-
Effect of age on bioavailability [-]	0.432	12	-
Apparent clearance of M5, CLM/F [L/h/70kg]	54.0	3.6	-
Apparent volume of M5, VM/F [L/70kg]	78.8	9.4	-
Age at which maturation is 50% of the adult value,T50 [years]	0.989	15	-
Hill coefficient [-]	1.00 fixed	-	-
IIV in apparent clearance of entrectinib [%CV]	31.8	5.3	14.5
IIV in absorption rate constant [%CV]	163	5.8	24.4
IIV in bioavailability [%CV]	40.6	5.3	11.9
IIV in apparent clearance of M5 [%CV]	46.2	5.3	9.6
IIV in residual variability [%CV]	36.9	5.2	2.7
Residual variability (entrectinib) [%CV]	42.9	3.2	0.8
Residual variability (M5) [%CV]	39.8	2.8	0.8

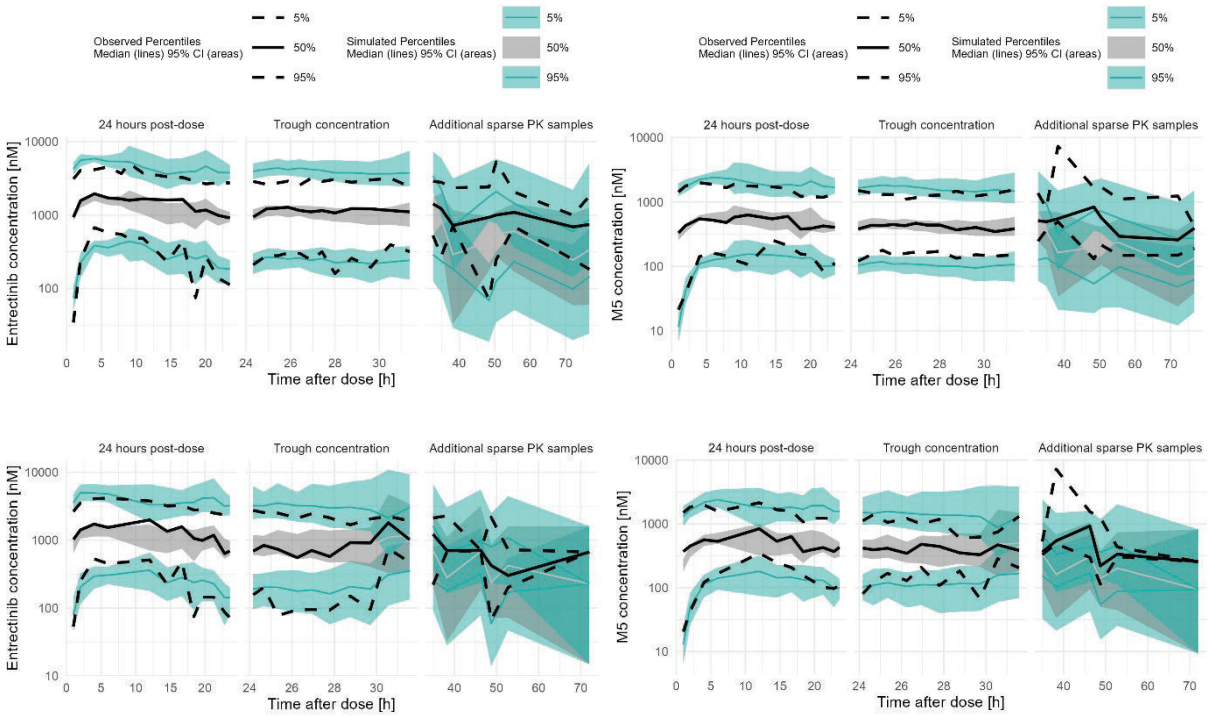
Abbreviations: IIV, inter-individual variability; RSE, relative standard error, as obtained from NONMEM Sandwich covariance matrix; CV, coefficient of variation. Source: Applicant's PopPK report (Report 1121816) , Table 9.

Figure 8 Goodness-of-fit Plots for Entrectinib (two left columns) and M5 (two right columns) for the Final Population PK Model (Run 11) .



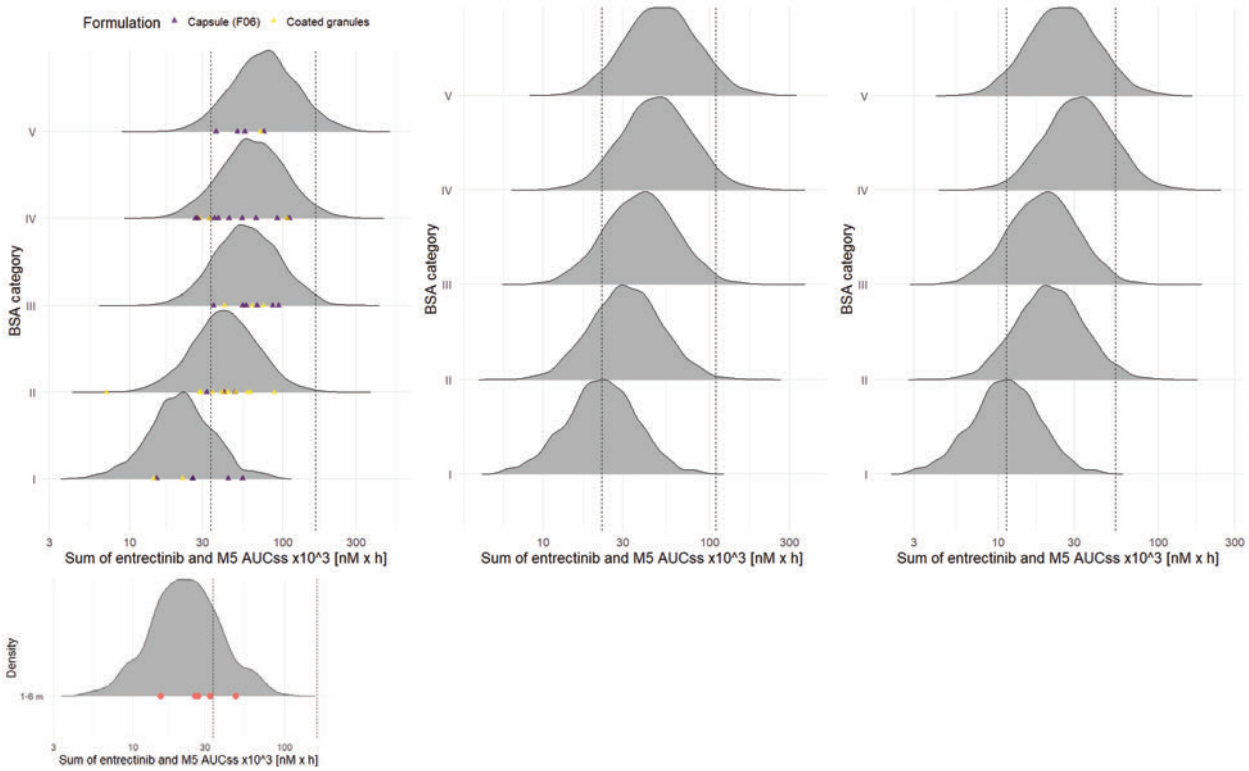
Data are shown as symbols, colored by population. Diagonal lines are lines of identity. Horizontal lines represent the zero lines. Colored bold lines are smooth to the data, and grey shaded areas are the corresponding 95% confidence intervals.
Source: Applicant's PopPK report (Report 1121816) , Figures 8-9.

Figure 9 Prediction-corrected VPC of Final Population PK Model for Entrectinib (left) and M5 (right) in the Overall Population (top) and in Pediatric Patients only (bottom).



Source: Applicant's PopPK report (Report 1121816) , Figures 11-14.

Figure 10 Simulation results for sum AUCss of entrectinib and M5 in pediatric patients aged 6 months or older (top) for the starting dose (left), first dose reduction (middle) and second dose reduction (right), and in patients aged 1-6 months following the starting dose (bottom).



AUCss, area under the plasma concentration-time curve at steady state; BSA, body surface area. BSA categories were defined as follow: I, 0.43-0.50 m^2; II, 0.51-0.80 m^2; III, 0.81-1.10 m^2; IV, 1.11-1.50 m^2; V, ≥1.51 m^2. Grey shaded areas represent the kernel distributions of AUCss obtained from simulations from the updated population pharmacokinetic model. Individual predicted AUCss for patients treated with the recommended dosing regimen are shown as symbols, colored by formulation (top). The vertical dashed lines represent the 5th and 95th percentiles of the simulated exposures in adults. Source: Applicant's PopPK report (Report 1121816) , Figures 33-34, 37, 40.

The FDA's Assessment:

Population PK analysis was used to propose (b) (4) FDA generally agrees with doses proposed for all evaluable groups based on PK simulation except for pediatrics over 6 months old with BSA of (b) (4) FDA recommended a dosage of 300 mg/m^2 for pediatrics over 6 months old with BSA of 0.5 m^2 and less based on evaluations of PK, efficacy, and safety (refer to 19.4.1.3 for details). Labeling for the recommended dosages was updated accordingly.

22.4.4. PPK Review Issues

Underprediction of the model identified in pediatrics >1 to 6 months

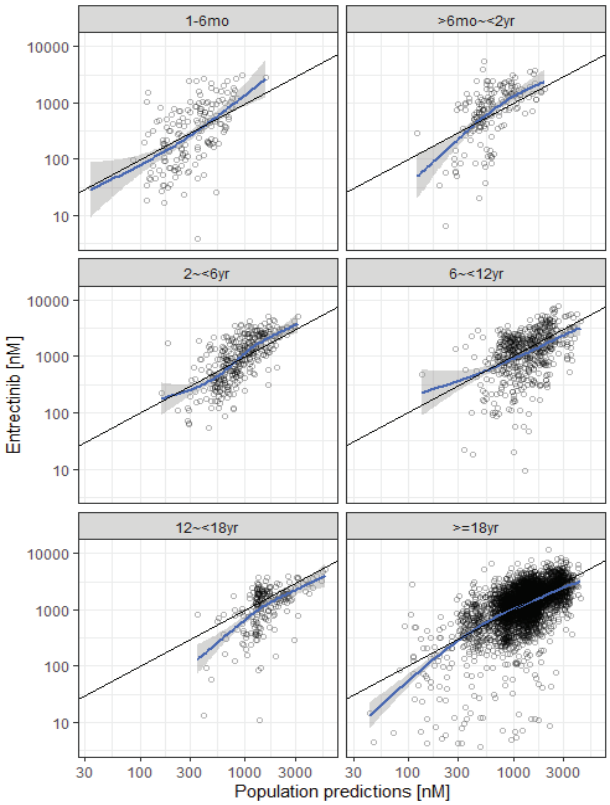
In GOF plots of entrectinib and M5, an underprediction was noted for M5 in pediatric population. Therefore, the Reviewer generated GOF plots by age group to further assess the attributing age group for this bias.

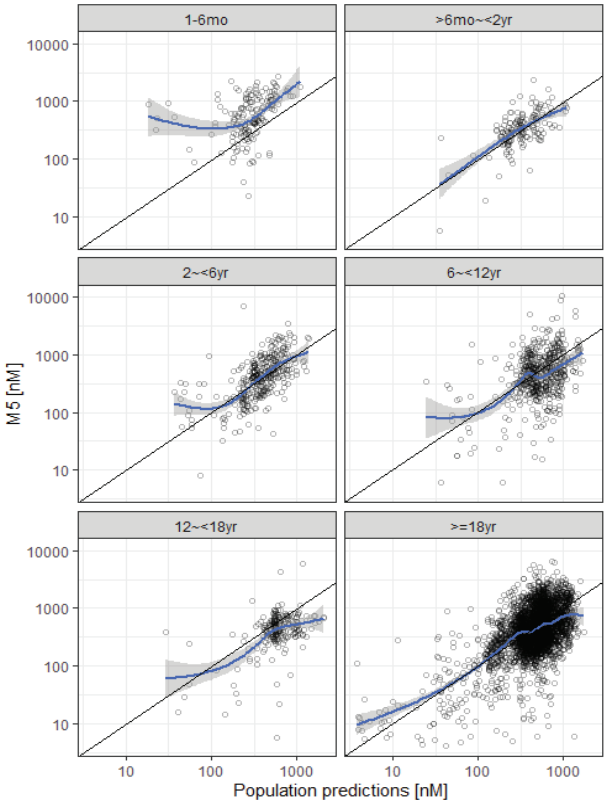
As shown in Figure X1, a discordance between population predictions and observations was only identified in pediatrics >1 to 6 months old. This discordance is for the active metabolite M5 not entrectinib. The observations in this subgroup are from 7 patients, 5 with an NTRK fusion. Fusion type was not identified as a covariate in popPK analysis, thus not a likely attribute to the bias.

In Study GP44192, AUC and Cmax of F06 oral suspension in milk were found ~40% and 48% higher than that of F06 capsules for M5 with upper 90% CI of ~160% and ~184%, respectively. The vehicle for drug administration may result in an increased exposure of M5, which could not be assessed as a covariate in popPK analysis as this information was not curated in the popPK dataset. The underprediction is not present for individual predictions, thereby not affecting E-R analysis.

For exposure comparison, since pediatrics of this age group are expected to be fed frequently in which case the milk is likely to increase exposure on a routine basis, the observed exposures are deemed more appropriate than population predicted exposures when considering PK matching.

Figure X1. Population prediction by age group for entrectinib and M5.





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

The FDA's Assessment:

The E-R analysis for efficacy based on data mainly from flat doses targeting a single dose level of 300 mg/m^2 is considered exploratory. No evident ER relationship was present for BOR in patients with NTRK fusion.

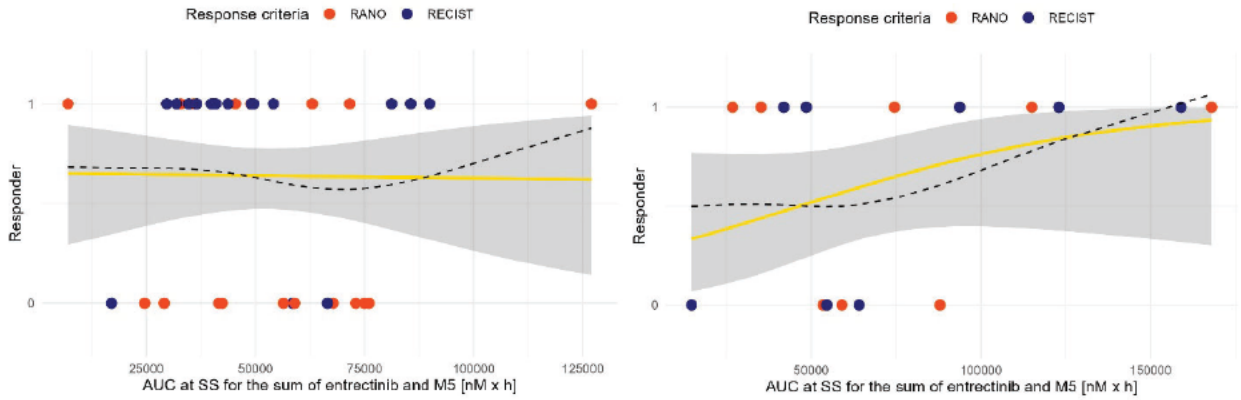
22.4.8. ER (efficacy) Assessment Summary

The Applicant's Position:

[Highlight the key findings in the white cells.]

General Information			
Goal of ER analysis		Characterize the ER relationship for efficacy in pediatric patients with NTRK or with ROS1 fusion	
Study Included		Pediatric patients from CO40778, GO40782, BO41932	
Endpoint		Responder status (PR or CR vs PD, SD or non-CR/non-PD)	
No. of Patients (total, and with individual PK)		N=36 with NTRK fusion, N=16 with ROS1 fusion All patients with evaluable PK and BOR available	
Population Characteristics ()	General	Only pediatrics	
	Pediatrics (if any)		
Dose(s) Included		All available from patients with PK and BOR data	
Exposure Metrics Explored (range)		Sum of steady state AUC or Cmax for entrectinib and M5	
Covariates Evaluated		NA	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		*Logistic regression*	Yes
Model Parameter Estimates		-	
Model Evaluation			
Covariates and Clinical Relevance		-	
Simulation for Specific Population		-	
Visualization of E-R relationships		Figure 8	Yes
Overall Clinical Relevance for ER		Absence of ER relationship in NTRK and in ROS1 patients	Yes. A trend was observed for ROS1 fusion with small sample size (n=16).
Labeling Language		**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		NA	Yes

Figure 11. ER Curves of clinical response vs sum of AUC_{ss} for entrectinib and M5 in pediatric Patients with NTRK (left) and ROS1 (right) fusion.



AUC, area under the concentration-time curve, RANO, Response Assessment in Neuro-Oncology Criteria; RECIST, Response Evaluation Criteria In Solid Tumors. Symbols: observed data. Solid yellow line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% confidence interval. Red dashed line: spline fitted to the observed data. Source: Applicant's PopPK report (Report 1121816) , Figures 18 and 20.

22.4.9. ER (safety) Executive Summary

The FDA's Assessment:

The E-R analysis for efficacy based on data mainly from flat doses targeting a single dose level of 300 mg/m^2 is considered exploratory. No evident ER relationship was present for SAE or Gr3+ TEAE. A shallow positive ER relationship was observed for bone fracture with age also identified as a risk factor.

22.4.10. ER (safety) Assessment Summary

The Applicant's Position:
[Highlight the key findings in the white cells.]

General Information		
Goal of ER analysis		Characterize the ER relationship for treatment-emergent AE Grade 3 or higher, SAEs and bone fractures
Study Included		Pediatric patients from CO40778, GO40782, BO41932
Population Included		All patients with evaluable PK
Endpoint		Treatment-emergent AE Grade 3 or higher, SAEs and bone fractures
No. of Patients (total, and with individual PK)		73 pediatric patients, 73 with available PK
Population Characteristics (Table 25)	General	Only pediatrics
	Organ impairment	(Pediatric patients)
	Pediatrics (if any)	73 pediatric patients, see Age: median 6.69 yr (range, 0.17-20.1 yr; 6 subj. <6 months, 6 subj. 0.5-2 yr, 47 subj. 2-12 yr, 14 subj. >12 yr) Weight: median 22 (range, 3.5-90) kg
	Geriatrics (if any)	-

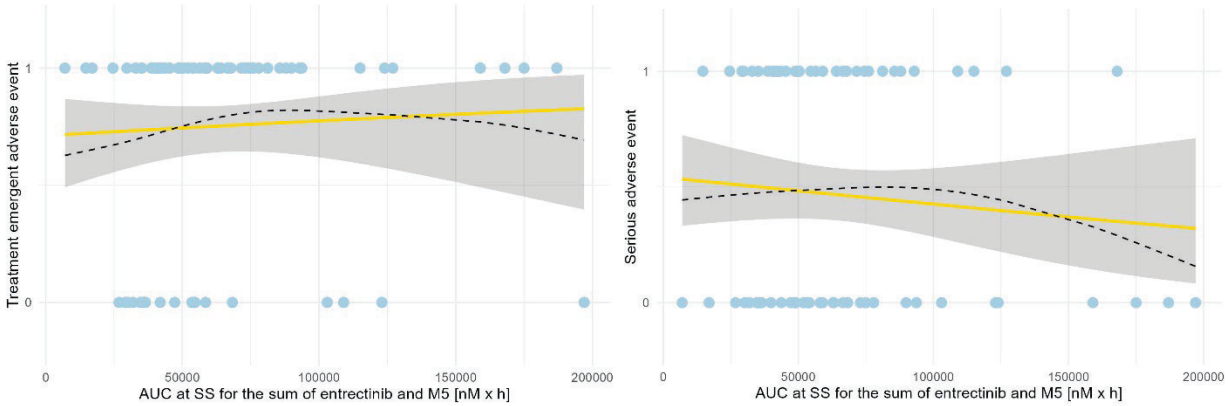
Dose(s) Included	50-1100 mg total daily dose	
Exposure Metrics Explored (range)	Cmax and AUC for entrectinib, M5, and their sum on Day 1 and at steady state	
Covariates Evaluated	Age for bone fractures	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Logistic regression analyses	Yes
Model Parameter Estimates	ER bone fractures:	Yes
Model Evaluation	-	
Covariates and Clinical Relevance	Age categories on bone fractures. Higher risk of bone fractures in 6-12 years old. May be a spurious association.	Yes
Simulation for Specific Population	-	
Visualization of E-R relationships	Figure 9	Yes
Overall Clinical Relevance for ER	A positive association between entrectinib exposure and risk of bone fracture may exist based on the univariate logistic regression.	Yes. Pediatrics age 6-11 years old had an increased risk for bone fracture.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	N/A	Yes

Table 33 Parameter Estimates from logistic regression Model of bone fractures.

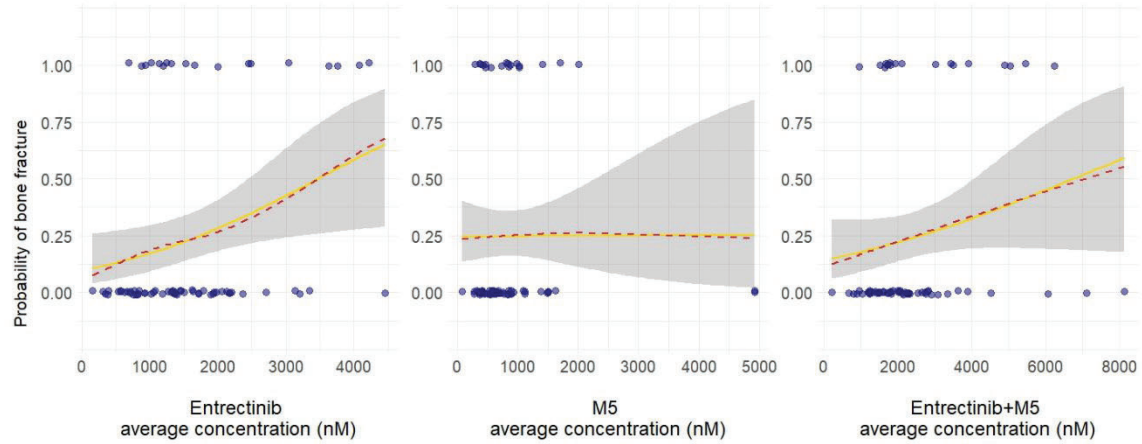
Scale	Analyte	Metrics	Slope (p value)
Original	Entrectinib	$C_{av,event}$	0.000636 (0.018)
Log10	Entrectinib	$C_{av,event}$	1.10 (0.017)

$C_{av,event}$, average concentration up to the time of the first bone fracture or censoring. On the original scale, slope has units of nM.
Source: Applicant's PopPK report (Report 1121816) , Table 23.

Figure 12 ER Curves of treatment emergent AEs Grade 3 or higher (top left), SAEs (top right), and bone fracture vs exposure in pediatric Patients.



AE, adverse event; AUC, area under the concentration-time curve, nM, nanomolar; h, hour. Symbols: observed data. Solid yellow line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% confidence interval. Red dashed line: spline fitted to the observed data. Source: Applicant's PopPK report (Report 1121816) , Figures 24, 26.



Average concentrations of entrectinib (left), M5 (middle), and their sum (right) were calculated from the first entrectinib dose up to the time of the event (first bone fracture or censoring) using the updated population pharmacokinetic model. Blue symbols: observed data. Solid yellow line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% confidence interval. Red dashed line: spline fitted to the observed data. Source: Applicant's PopPK report (Report 1121816) , Figure 29.

The FDA's Assessment:

FDA agrees with the Applicant's position.

22.4.11. *ER Review Issues*

Evaluation of bone fracture for alternative doses for pediatrics over 6 months with BSA of 0.5m^2 Univariate and multivariate analyses were both conducted to predict increase in bone fracture risk for alternative doses. The representative subset for prediction is pediatrics over 6 months whose BSA is exactly 0.5m^2 which is intended to capture the largest possible difference in exposure between flat dose and BSA based dose.

For univariate analysis that included Cavg from the first administration of entrectinib till the occurrence of bone fracture based on actual individual dosing history, the bone fracture risk is expected to increase by 1.3% when dose is increased from 100 mg to 300 mg/m^2 (Table X1).

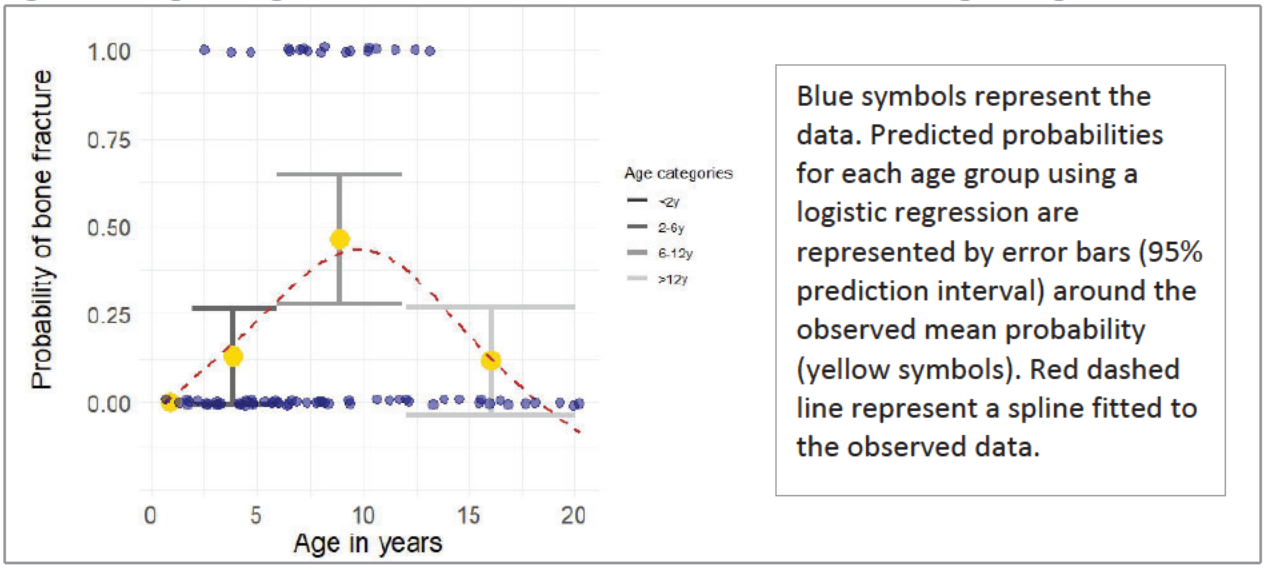
For multivariate analysis, age was included as a covariate. A quadratic term of age was included in the regression model given an obvious bell shape of probability of bone fracture with increasing age (Figure X3). The ROC curve for the logistic regression model was shown in Figure X4. The bone fracture risk is expected to increase by 0.68% when dose is increased from 100 mg to 300 mg/m^2 (Table X1). The average risk for bone fractures is predicted to be small (≤ 3%) for pediatrics of 2 years old with BSA of 0.5 m^2.

Table X1. Comparison of summary statistics of simulated AUCss of entrectinib and associated risk of bone fractures between 100 mg, 250 mg/m^2, and 300 mg/m^2 in pediatric patients over 6 months old with BSA of 0.5m^2.

Category	Dose	Entrectinib AUCss (nM*h), Median [P5-P95]	Probability of bone fracture (%), Average [95% CI]	
			Univariate	Multivariate
BSA 0.5 m^2	100 mg	12200 [5220-27600]	13.1 [5.82-27.1]	2.04 [0.21-16.8]
	250 mg/m^2	13800 [5760-30700]	13.6 [6.22-27.4]	2.30 [0.25-17.9]
	300 mg/m^2	16300 [6880-36600]	14.4 [6.89-27.9]	2.72 [0.32-19.6]
BSA 0.51-0.8m^2	200 mg	27000 [11200-64200]	18.3 [10.3-30.5]	4.47 [0.57-27.5]

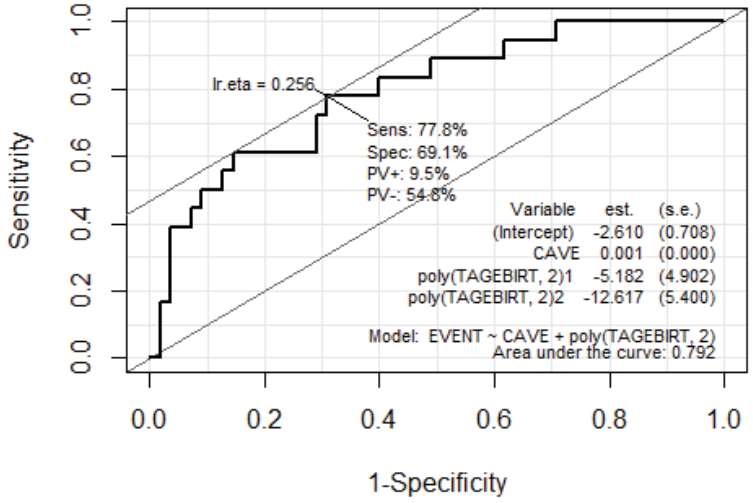
Source: IR response received on 8/17/2023 (Table 3). Multivariate analysis was conducted by the Reviewer. Age of 2 years (99th percentile of age in pediatrics over 6 months old with BSA of 0.5m^2 based on NHANES) was assumed to predict the highest bone fracture risk for the positive effect of age under 6 years.

Figure X3. Logistic regression for the occurrence of bone fracture versus age categories.



Source: PopPK and ER report (Figure 30).

Figure X4. Multivariate logistic regression for the occurrence of bone fracture.



Source: Reviewer's analysis.

22.4.12. *Reviewer's Independent Analysis*

None.

22.4.13. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The updated popPK model (popPK Report 1121816) predicts comparable exposures between pediatric patients receiving 300 mg/m^2 in BSA categories III, IV and V and adults receiving 600 mg once daily. This is also consistent with the observed NCA results showing pediatric exposure within the range of the adult exposure (Section 3.1.3 in SCP). These data together with the reported clinical efficacy and safety in the pediatric population confirm the appropriateness of the entrectinib 300 mg/m^2 QD dose in BSA categories III–V.

For BSA categories I, II, and patients < 6 months receiving 250 mg/m^2, lower exposures for entrectinib are predicted compared to adults and pediatric patients in the higher BSA categories. This is consistent with the NCA results, where patients ≤ 1 year old showed exposure levels that were at the lower end of the range of adult systemic levels (Section 3.1.3 in SCP). Further dose adjustment in these two BSA categories to generate exposures closer to the adult range is not recommended, because the exposures generated within these two BSA categories (I and II), remain within the exposure range where similar efficacy was observed in adults. In addition, The positive trend between the probability of bone fracture and entrectinib exposure (popPK Report 1121816) together with the higher frequency of AEs of Grade ≥ 3 or SAEs observed at higher exposures in the adult population (initial popPK Report 1091319, and popPK Report 1121816) suggest that increasing the pediatric systemic exposure to match the

adult systemic exposure may increase the risk of bone fractures, (popPK Report 1121816; 2.7.4 SCS, Section 2.1.8.1).
Hence, the current available clinical safety and efficacy data in the pediatric population confirm the adequacy of the recommended dose(s) to maintain a positive benefit risk ratio.

The FDA's Assessment:

FDA generally agrees except for the dose proposed for the patients (b) (4) due to efficacy concern (refer to 19.4.1 for details). The labeling was updated to reflect the change in the recommended dosage for this subgroup.

22.4.14. Physiologically Based PK Analysis

22.4.15. Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to:

- predict the pharmacokinetic (PK) profile of entrectinib and its major circulating metabolite M5 in pediatrics
- evaluate the drug-drug interaction (DDI) potential of entrectinib and M5 as victims of strong and moderate CYP3A inhibitors at steady state in pediatrics ≥ 2-year-old

The Division of Pharmacometrics has reviewed the PBPK report (report 1119857), FDA IR Clinical Pharmacology Response Documents (seq 0021, 0022, 0031, and 0033), and the modeling supporting files, and concluded that

- PBPK models of entrectinib and M5 are inadequate (b) (4)
- PBPK analyses are adequate to predict the effects of strong and moderate CYP3A inhibitors on the exposure of entrectinib and M5 in pediatric patients ≥ 2 years old. Strong and moderate CYP3A inhibitors were predicted to increase the combined exposure of entrectinib and M5 approximately 6- and 3-fold, respectively. However, the effect of itraconazole may be overestimated because the concentrations of itraconazole and its hydroxy metabolite reported in the literature were much lower than that predicted in pediatric patients < 12 years old.

22.4.16. Background

Entrectinib (RO7102122; ROZLYTREK; formerly known as RXDX-101, NMS-1191372, and NMSE628) is a kinase inhibitor and was approved in 2019 for the treatment of adult patients with *ROS1*-positive metastatic non-small cell lung cancer and for adults and pediatric patients 12 years of age and older with solid tumors that have neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion. The 100 and 200 mg capsules are approved dosage strength and form. The

recommended dosage for adult and pediatric patients is shown in **Table 34**. Entrectinib and its equally potent metabolite M5 are primarily metabolized by CYP3A. Avoiding coadministration with strong or moderate CYP3A inhibitors and inducers is recommended. If coadministration of moderate or strong CYP3A inhibitors cannot be avoided, a reduced dose is recommended (**Table 34**).

Table 34 Recommended Dosing in adult and pediatric patients 12 years and older

Patients	**Dosage** (Orally once daily)	**Dosing with strong or moderate CYP3A inhibitors**	**Dosing with strong or moderate CYP3A inducers**
Adult	600 mg	Avoid, or reduce to 100 or 200 mg with strong or moderate inhibitors, respectively	Avoid
Pediatric (based on body surface area)			
Greater than 1.50 m^2	600 mg		
1.11 to 1.50 m^2	500 mg	Avoid	
0.91 to 1.10 m^2	400 mg	Avoid	

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/212725s007lbl.pdf

Dedicated DDI studies with moderate CYP3A inhibitors or inducers have not been conducted. In the original NDA submission (NDA 212725/212726), PBPK analyses were performed and the entrectinib PBPK model was considered adequate to evaluate the effects of moderate CYP3A inhibitors or inducers on the PK of entrectinib. However, the PBPK model was considered inadequate to predict the PK of entrectinib in pediatric population. (b) (4)

In this submission, the Applicant proposed to expand the current indication to pediatric patients (b) (4) The recommended dosing regimen is as follows:

(b) (4)

From > 1 month to ≤ 6 months, a dose of 250 mg/m^2

For 6 months, a dose of 300 mg/m^2 with a maximum dose of 600 mg for pediatrics with 1.51 m^2 body surface area (BSA)

In addition, based on the PBPK analyses (report 1119857), dose reductions and/or a less frequent dosing are being proposed in pediatric patients when entrectinib is co-administered

with either strong CYP3A4 or a moderate CYP3A4 inhibitor (**Table 35**) if coadministration cannot be avoided.

Table 35 Recommended dose modifications of entrectinib for concomitant used with moderate or strong CYP3A inhibitors for adults and pediatric patients 2 years and older

Starting dose*	Moderate CYP3A inhibitor	Strong CYP3A inhibitor
200 mg	50 mg once daily	50 mg on alternate days
300 mg	100 mg once daily	50 mg once daily
400 mg	200 mg once daily	50 mg once daily
600 mg	200 mg once daily	100 mg once daily
* For pediatric patients with a starting dose less than 200 mg, avoid coadministration with moderate or strong CYP3A inhibitors		

Source: Table 5 in the proposed product information

(b) (4)

For pediatrics aged >1 month and < 2 years old, the recommended dosing regimen was based on population PK of pediatric and adult PK and exposure-response data.

22.4.17. Methods

The Applicant updated the Simcyp model in the original submission (b) (4)

The final model input parameters of entrectinib and M5 were summarized in **Table 36** and **Table 37**. The entrectinib PBPK model consists of an Advanced Dissolution, Absorption and Metabolism (ADAM) model for describing drug absorption in each gut segment, a full PBPK model for distribution, and an enzyme kinetics model and renal clearance for elimination. The Simcyp library files itraconazole and metabolite (SV-Itraconazole_Fed Capsule and SV-OH-Itraconazole), erythromycin, fluconazole, rifampin (SV-Rifampicin-MD), were used without any modification. All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Versions 21, Certara, Sheffield, UK). Simulations in healthy adults or adult patients with cancer were performed using healthy subject population (sim-Healthy Volunteers) models since clinical

data showed that the PK of entrectinib and M5 was comparable between adult cancer patients and healthy adult subjects (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%20212726Orig1s000MultidisciplineR.pdf). For simulations in pediactrics, the hepatic ontogeny function of Upreti and Wahlstrom was applied, and intestinal CYP3A4 maturation was described using parameters and the equation shown in ***Table 38***. Age, sex, subject number, and dosing regimens were consistent with the actual trial design. Ten trials were simulated for each simulation scenario.

Table 36 Final input parameters in the entrectinib model

Input parameters	Description	Units	Value	Remarks
1.Physicochemical and binding properties				
MW	Molecular weight	g/mol	560.64	
Log P	Octanol-water partition	-	3.96	
Compound type	Acid,base or neutral	-	Diprotic base	
pKa		-	2.54 / 5.3 [1]	
B/P ratio	Blood to plasma concentration ratio	-	1.3	[26]
fu	Fraction unbound in plasma	-	0.0022	[26]
HSA or AGP	Main plasma binding protein	-	HSA	[26] [2]
2.Absorption	[6]			
Absorption model	ADAM model			
Peff,man	Human jejunum permeability	10^{-4} cm/s	0.67	[3]
P caco-2	Caco-2 permeability (pH 6.5:7.4)	10^{-6} cm/s	1.07	[47]
fu(gut)	Unbound fraction in enterocytes	-	0.022	Optimized
Q(gut)	Nominal flow in gut model	L/h	4.21	[3]
CV Q(gut)	Coefficient of variation Q(gut)	%	30	[4]
Formulation	Solid formulation – immediate release – salt micelle-mediated component			(b) (4)
Particle size (µm)		15 (radius; monodispersed)		
Intrinsic solubility		0.012 (mg/mL)		[5]
Solubility-pH profile		1.674 (mg/mL) at pH 2; 1.213 (mg/mL) at pH 3; 0.215 (mg/mL) at pH 4.5; 0.032 (mg/mL) at pH 5; 0.014 (mg/mL) at pH 6; 0.012 (mg/mL) at pH 7, 8, 9 and 10		[5]
Intrinsic solubility scalar		7000		[5]
Particle surface pH in stomach		1.3 (fasted) and 6.5 (fed)		[5]
Bile micelle mediated solubilization enhancement coefficient (Km:w)		5.2 (neutral); 5.6 (ion)		[6]
3.Distribution				
Distribution model	Full PBPK model			
Tissue model	Perfusion limited model			
Vss	Volume of distribution at steady-state	L/kg	2.46	[29]
CV Vss	Coefficient of variation Vss	%	30	[4]

Input parameters	Description	Units	Value	Remarks
4.Enzyme phenotyping				
Recombinant CYP enzymes				
CLint (CYP3A4)	In vitro clearance (M5)	µL/min/pmol	11.4	
CLint (CYP3A4)	In vitro clearance (others)	µL/min/pmol	2.87	
CLint (UGT1A4)	In vitro clearance (M11)	µL/min/pmol	3.02	
fu(mic)	Fraction unbound in vitro	µL/min/pmol	1	
5.Other Distribution and Elimination property				
***In vivo* CL**				
CLr	Renal clearance in 20-30yr healthy male	L/h	0.102	1.70 (mL/min) [30]

Note: input parameters from an original compound file were reported in [5].

1) A reported pKa2 (7.54) was adjusted to 5.3 to capture a measured pH-dependent solubility profiles in vitro.

2) Assumption. Entrectinib binds to human serum albumin as well as α-glycoprotein in vitro.

3) A Peff,man was calibrated with GastroPlus using an in vitro P Caco-2, followed by predicting absorption parameters as fa, ka and Qgut using SimCYP Version 21.

4) SimCYP Version 21.

5) To recover the solubility-pH profile using the SIVA toolkit, a reported pKa2 (7.54) was adjusted to 5.3 by setting an intrinsic solubility scalar to 7000. In GastroPlus model the stomach bulk pH was adjusted to capture the slowed dissolution due to changes in surface pH as determined based on in vitro dissolution. Remaining gastrointestinal pH are the defaults for SimCYP.

6) Manually optimized using the SIVA toolkit to capture the measured FaSSIF and FeSSIF solubilities where FeSSIF (3.14 mg/mL) considerably higher solubility than FaSSIF (0.131 mg/mL).

Source: Table 2 in the PBPK report

Table 37 Final input parameters in the M5 model

Input parameters	Description	Units	Value	Remarks
1.Physicochemical and binding properties				
MW	Molecular weight	g/mol	546.6	
Log P	Octanol-water partition	-	3.73	
Compound type	Acid,base or neutral	-	Diprotic base	
pKa		-	2.56 / 8.55	
B/P ratio	Blood to plasma concentration ratio	-	1	[26]
fu	Fraction unbound in plasma	-	0.0031	[26]
HSA or AGP	Main plasma binding protein	-	HSA	[26] 1)
2.Absorption				
Absorption model	ADAM model			
fu(gut)	Unbound fraction in enterocytes	-	1×10^{-6}	Optimized
3.Distribution				
Distribution model	Full PBPK model			
Tissue model	Perfusion limited model			
Vss	Volume of distribution at steady-state	L/kg	5.18	[29]
CV Vss	Coefficient of variation Vss	%	30	2)
4. Enzyme phenotyping				
Recombinant CYP enzymes				
CLint (CYP3A4)	In vitro clearance	µL/min/pmol	32.3	Optimized
fu(mic)	Fraction unbound in vitro	-	1	
5.Other Distribution and Elimination property				
In vitro CL				
CLint HLM	In vitro additional clearance in HLM	µL/min/mg	80.9	Optimized 3)
fu(mic)	Fraction unbound in vitro	-	1	
In vivo CL				
CLr	Renal clearance in 20-30yr healthy male	L/h	0.213	3.55 (mL/min) [30]

Note: input parameters from an original compound file were reported in [5].
1) Assumption. M5 binds to human serum albumin as well as α-glycoprotein in vitro.
2) SimCYP Version 21.
3) Represent biliary excretion clearance CLbile.

Source: Table 2 in the PBPK report 1119857

Table 38: Ontogeny function used in this study

	Reference	F_{birth}	Age_{50}	n	F_{max}
Hepatic CYP3A4	[16]	0.15	0.1	1.3	1.7
Intestinal CYP3A4	SimCYP V21	0.42	2.357	1	1.059
UGT1A4	SimCYP V21	0.05	1.042	1.36	1.028
P-gp	[18]	0.366	2.94	0.78	1.0

$$Fraction\ of\ adult = Fbirth + \frac{(Fmax - F\ birth) \cdot Age^{n}}{Age_{50}^{n} + Age^{n}} \quad (1)$$

where F_{max} is the maximal response from adults, F_{birth} is the fraction of adult response at birth, Age_{50} is the age at which half-maximal adult response is obtained, Age is the age if the subject at the time of sample collection in years, and n is an exponential factor with an age cap of 25 years.

Source: Table 1 in the PBPK report 1119857

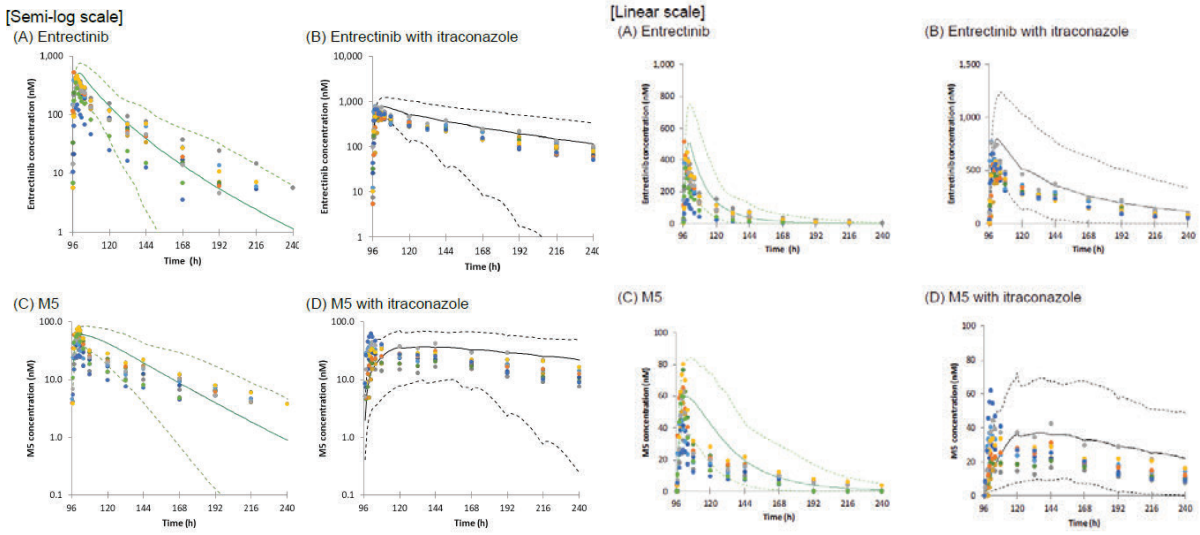
22.4.18. Results

1. **Can the PBPK model adequately describe the PK profiles of entrectinib and M5 in adults?**

Clinical DDI data with itraconazole, conducted using entrectinib formulation F06, were used in model development so that the PBPK models of entrectinib and its metabolite M5 could

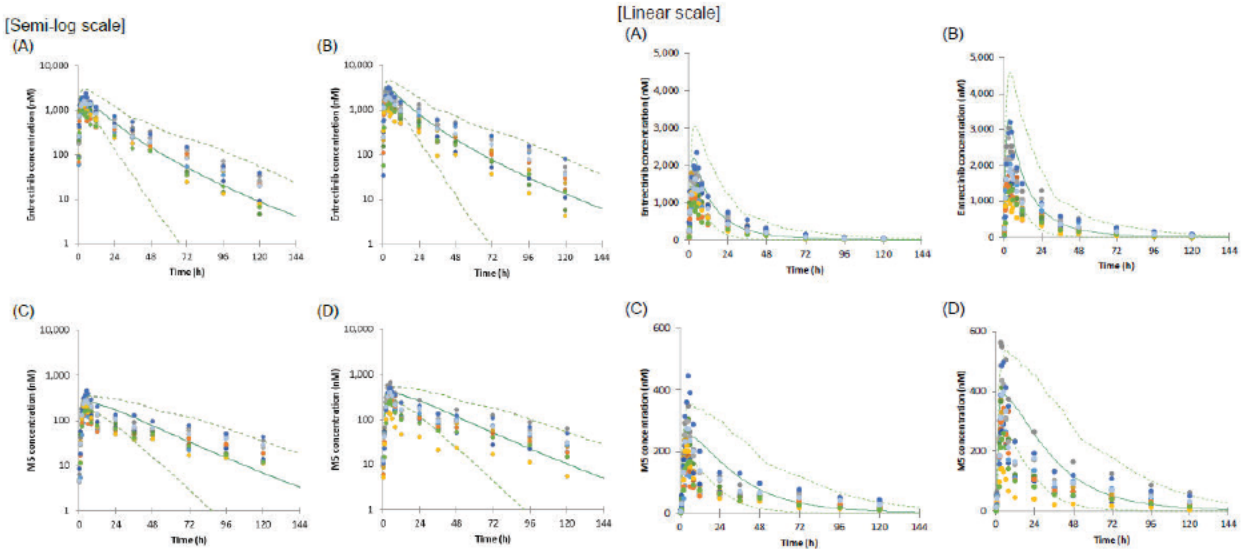
reproduce the plasma-concentration profiles of entrectinib and M5 (Figure *14*). These models could reasonably well describe the PK profiles and PK parameters of entrectinib following single oral doses of entrectinib in healthy adult subjects (Figure *15* and Table 39). Following multiple oral administration of entrectinib, the predictive performance of the PBPK models of entrectinib and M5 is formulation dependent, which may also affect by the large interindividual variability in entrectinib and M5 PK in cancer patients (Figure 16 and Table 40). The PBPK models of entrectinib and M5 reasonably well captured the PK of entrectinib and M5 (Figure 16) when the formulation F1 was used, but these models significantly underpredicted the PK of entrectinib and M5 when the formulation F06, the approved formulation, was used (Table 40).

Figure 14 Plasma concentration-time profiles of entrectinib and M5 following coadministration with itraconazole in adult healthy subjects



Entrectinib at 100 mg (single dose) was orally administered at day 5 over multiple oral administration of itraconazole at 200 mg once daily for 10 days. Each individual data with interactions [1090086] are represented as circles (n=9-10). Green and black are simulated mean plasma concentrations profiles for entrectinib (A, B) and M5 (C, D) of 100 virtual subjects (n=10×10 trials) with (B, D) and without interactions (A, C), respectively. Broken lines represent the respective 95th/5th percentiles.
Source: Figure 7 in the PBPK report 1119857

Figure 15. Plasma concentration-time profiles of entrectinib and M5 following oral administration of single doses of entrectinib in adult Caucasian subjects



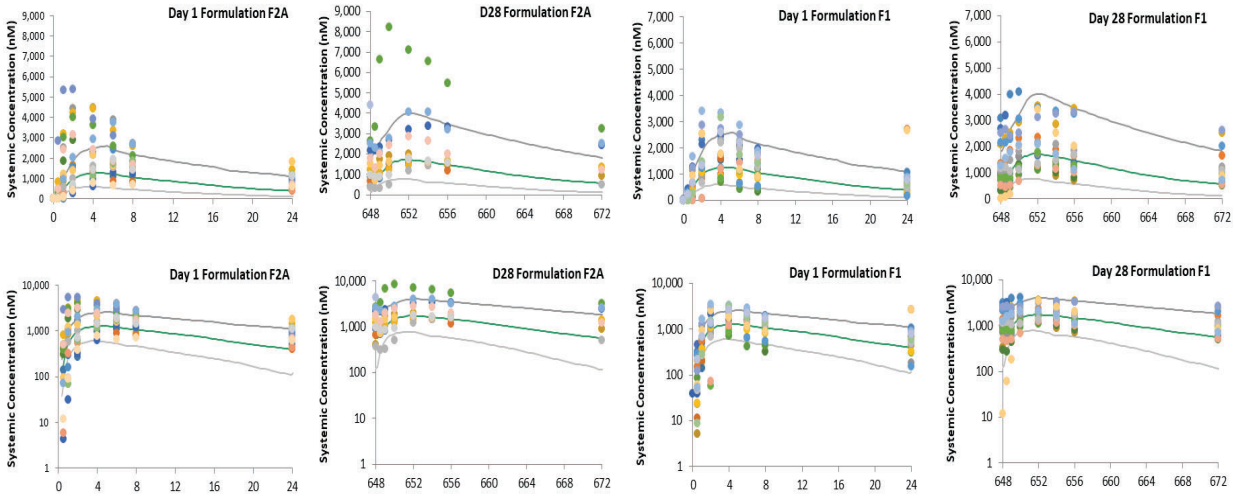
PK profiles of entrectinib (A, B) and M5 (C, D) over time after a single oral administration of entrectinib at 400 (A, C) and 600 mg (B, D) were simulated using the updated models of entrectinib and M5. Each individual observed data [1090090.] are represented as circles (n=12). Green lines are simulated mean plasma concentrations profiles of 120 virtual subjects (n=12×10 trials). Broken lines represent the respective 95th/5th percentiles.
Source: Figure 9 in the PBPK report 1119857

Table 39 Summary of PK parameters of entrectinib and M5 following oral administration of single doses of entrectinib in adult Caucasian subjects

Entrectinib dose (p.o.)		N	C_{max} (nM) [geomean (CV%)]		AUC_{inf} (nM*h) [geomean (CV%)]	
			Entrectinib	M5	Entrectinib	M5
400 mg	Simulated	120	2173 (26.0)	268 (20.0)	35284 (50.0)	9095 (48.0)
	observed	10	1560 (23.9)	260 (33.2)	33600 (30.9)	8450 (42.3)
	Sim/Obs		1.4	1.0	1.1	1.1
600 mg	Simulated	120	3257 (26.0)	406 (20.0)	52892 (50.0)	13758 (48.0)
	Observed	10	2030 (35.1)	374 (34.9)	44800 (40.3)	11900 (44.9)
	Sim/Obs		1.6	1.1	1.2	1.2

Source: Table 5 in the PBPK report 1119857

Figure 16 Mean plasma concentration-time profile of entrectinib and M5 after multiple oral administration of entrectinib in adult patient subjects



Each individual data is represented by closed circles (PK using F01 formulation: n=11-22; PK using F2A formulation: n=4-19). Green solid lines are simulated mean plasma concentration profiles of 100 virtual subjects (n=10 × 10 trials). Broken lines represent the respective 95th/5th percentiles.
Source: Figure 1 in the response-fda-ir-pbpk-20230831 (seq0022)

Table 40 Simulated and observed geometric mean with CV% for C_{max} and AUC of entrectinib plasma concentrations after multiple-dose administration in adult Caucasian subjects

Entrectinib dose (p.o.)	Formulation	Trials	$C_{max,ss}$ (nM) at Day 28 or Day 14		$AUC_{0\text{-}t,ss}$ (nM*h) at Day 28 or Day 14	
			Entrectinib	M5	Entrectinib	M5
the last dose of 600 mg QD, 28 days		simulated	1903 (50%)	379 (52%)	28421 (60%)	7773 (61%)
	F01	observed†	2170 (50%)	535 (56%)	32600 (77%)	9020 (46%)
		sim/obs	0.88	0.71	0.87	0.86
	F2A	observed‡	2660 (64%)	703 (83%)	26500 (158%)	7400 (225%)
		sim/obs	0.72	0.54	1.07	1.05
the last dose of 600 mg QD, 14 days	F06	observed‡	3644 (38%)	931 (89%)	61278 (45%)	17043 (96%)
		sim/obs	0.52	0.41	0.46	0.46

Geometric means were reported. †Study 1090209 (RXDX-101-01). ‡ Study 1096318 (RXDX-101-14)
Source: Table 1 in the response-fda-ir-pbpk-20230831 (seq0022)

2. Can PBPK analyses predict the effects of CYP3A perpetrators on the PK of entrectinib and M5?

Yes. The entrectinib PBPK models could be used to predict the effects of CYP3A inhibitors. The ability of the updated models to reproduce the effects of the strong CYP3A inhibitor itraconazole and strong CYP3A inducer rifampin has been verified (Table **41)**. In addition, the predicted effects of moderate inhibitors erythromycin and fluconazole using these updated models were similar to that predicted using the original model (data not shown, Table 2 in the response-fda-ir-pbpk-20230831).

Table 41 Predicted geometric mean with 90% confidence interval (90% CI) for C_{max} and AUC ratio of entrectinib and M5 following coadministration of strong CYP3A perpetrators in healthy adults

Victim (single dose, p.o.)	Perpetrator	N	Study	C_{max} (nM) [geo mean with CV(%)]		AUC_{inf} (nM·h) [geo mean with CV(%)]		C_{max} ratio [geo mean with 90% CI]		AUC_{inf} ratio [geo mean with 90% CI]	
				Entrectinib	M5	Entrectinib	M5	Entrectinib	M5	Entrectinib	M5
Entrectinib 100 mg at day 5	Alone	10	Observed [25]	373 (25.4)	55.1 (31.9)	6740 (38.2)	1520 (33.1) 1)	-	-	-	-
	+itraconazole (200 mg p.o. once daily for 10 days)	9		622 (16.4)	33.9 (40.7)	36500 (17.2)	2860 (25.9) 1)	1.73 (1.37-2.18)	0.60 (0.45-0.79)	6.04 (4.54-8.04)	1.88 1)
	Alone	10×10	Predicted	503 (29.0)	62.0 (22.0)	8904 (52.0)	2219 (50.0) 1)	-	-	-	-
	+itraconazole (200 mg p.o. once daily for 10 days)			811 (25.0)	43.1 (49.0)	45232 (90.0)	3860 (50.0) 1)	1.61 (1.57-1.65)	0.69 (0.64-0.75)	5.08 (4.76-5.42)	1.74 1) (1.57-1.93)
Entrectinib 600 mg at day 12	Alone	10	Observed [25]	1860 (21.5)	445 (71.8)	37600 (28.8)	12000 (51.5)	-	-	-	-
	+rifampicin (600 mg p.o. once daily for 16 days)	10		829 (24.3)	110 (21.1)	8750 (27.5)	1580 (23.2)	0.44 (0.35-0.56)	0.28 (0.20-0.40)	0.23 (0.18-0.30)	0.14 (0.11-0.18)
	Alone	10×10	Predicted	1571 (46.0)	202 (40.0)	28756 (63.0)	7353 (62.0)	-	-	-	-
	+rifampicin (600 mg p.o. once daily for 16 days)			555 (68.0)	114 (56.0)	5052 (76.0)	1466 (73.0)	0.35 (0.33-0.38)	0.57 (0.54-0.59)	0.17 (0.16-0.19)	0.20 (0.19-0.21)

Trial design parameters for the simulation were taken from Section 3.5. CI: confidence interval.
1) AUC_{last}
Source: Table 4 in the PBPK report 1119857

Reviewer's comments:

- In the previous submission, the fraction metabolized by CYP3A ($f_{m,CYP3A}$) in the entrectinib PBPK model was optimized to 0.76 using the data from the clinical DDI study with itraconazole (report 1091399). Since then, a new reaction phenotyping study was conducted (report 1095945). CYP3A4 was involved in the formation of all the metabolites studied except for the glucuronide M11, which represented <0.5% of the administered dose in the human ADME study (CSR RXDX-101-05). In the updated entrectinib model, the $f_{m,CYP3A}$ value was optimized to 0.92, in the meanwhile, the $f_{u,gut}$ value was (b) (4) 0.0022 (b) (4) in the original model to reproduce the observed effects of itraconazole on the exposure of entrectinib. This adjustment to the $f_{u,gut}$ value appears to be reasonable because entrectinib is highly bound to plasma protein with fraction unbound in plasma close to 0.00022. This model is verified by its ability to reproduce the effect of rifampin on entrectinib exposure (**Table 41**).
- The updated models underpredicted the induction effects of rifampin on the C_{max} of M5 by approximately 2-fold. The Applicant stated that this was likely because one subject had an extremely high exposure. However, the geometric mean C_{max} ratio excluding this subject was 0.32 and the predicted C_{max} ratio was 73% higher than this recalculated value. Therefore, the reasons for this underprediction remain unclear. Considering that C_{max} is not the metric for dose adjustment and the predicted effect (0.18) of rifampin on the combined exposure of entrectinib and M5 was similar to the observed effect (0.21),

the models of entrectinib and M5 are considered adequate to evaluate the effects of CYP3A inhibitors.

3. **Can PBPK analyses be used to simulate the pharmacokinetics of entrectinib and M5 in pediatric patients?**

The models could reasonably well describe the PK profiles (data not shown) and PK parameters of entrectinib and M5 following single and multiple oral doses in pediatric patients older than 4 years old (**Table 42)** . For pediatrics aged 2-4 years old, entrectinib AUC and C_{max} were overpredicted though still within 2-fold of the observed exposure (**Table 42)**. For pediatrics younger than 2 years old, the predicted PK profiles and PK parameters of entrectinib and M5 were compared with the observed in (**Table 43)** and **Figure 17**. Most of the observed concentrations were around or below the 5th percentile of the predicted concentration-time profiles of entrectinib. Entrectinib exposure was 2- to 4-fold overpredicted and M5 exposure was underpredicted up to 2.5-fold. Given the performance of the entrectinib and M5 models and knowledge gap in the gut physiology in infants, it is inappropriate to use these models to [redacted] (b) (4)

Table 42 Pharmacokinetic parameters of entrectinib and M5 after multiple oral administration of entrectinib at steady state in adults and pediatrics older than 2 years of age

Entrectinib (p.o.,once daily)	Age (yrs)		N	Entrectinib: C_{max} at the last dose (nM)					Entrectinib: $AUC_{(0-t)}$ at the last dose (nM·h)				
				Median	Normalized to 100 mg dose	Ratio: simulated /observed	Min	Max	Median	Normalized to 100 mg dose	Ratio: simulated /observed	Min	Max
150 mg	IIa: 2-4	Simulated	100	2571	1714	1.71	748	5805	28498	18999	1.46	7032	93674
200 mg	IIb: 4-7		100	2549	1275	1.37	721	5915	29768	14884	1.09	7031	99649
300 mg	III: 7-10		100	2718	906	1.19	733	6692	33257	11086	0.85	8184	102474
400 mg	IV: 10-12		100	2785	696	0.95	732	7211	36140	9035	0.77	8858	114951
600 mg	V: 12-18		100	2741	457	1.15	986	7797	41772	6962	1.11	9090	129735
600 mg	18-65		100	2194	366	0.76	587	9107	32908	5485	0.63	8535	175274
298 mg [2)]	IIa: 2-4	Observed	10	2979	1000	NA	1106	5230	38734	12998	NA	18140	72771
304 mg [2)]	IIb: 4-7		13	2818	927	NA	1106	5030	41529	13661	NA	18140	72771
321 mg [2)]	III: 7-10		10	2435	759	NA	1428	4352	41862	13041	NA	16218	72517
396 mg [2)]	IV: 10-12		5	2890	730	NA	1962	5565	46290	11689	NA	26772	96601
495 mg [2)]	V: 12-18		5	1962	396	NA	1698	2890	30986	6260	NA	25937	50036
600 mg	18-65		203	2870	478	NA	1040	13700	51900	8650	NA	13100	254000

Entrectinib (p.o.,once daily)	Age (yrs)		N	M5: C_{max} at the last dose (nM)					M5: $AUC_{(0-t)}$ at the last dose (nM·h)				
				Median	Normalized to 100 mg dose	Ratio: simulated /observed	Min	Max	Median	Normalized to 100 mg dose	Ratio: simulated /observed	Min	Max
150 mg	IIa: 2-4	Simulated	100	499	333	1.22	159	1143	7420	4947	1.05	1786	24659
200 mg	IIb: 4-7		100	501	251	1.30	137	1165	7660	3830	1.14	1783	26116
300 mg	III: 7-10		100	530	177	0.71	137	1315	8482	2827	0.66	2074	27405
400 mg	IV: 10-12		100	548	137	0.59	138	1452	9328	2332	0.60	2217	30993
600 mg	V: 12-18		100	561	94	0.78	176	1575	10579	1763	0.69	2265	34791
600 mg	18-65		100	428	71	0.44	126	2070	8424	1404	0.46	2166	47585
298 mg [2)]	IIa: 2-4	Observed	9	810	272	NA	256	2031	14106	4734	NA	4850	38071
304 mg [2)]	IIb: 4-7		13	584	192	NA	256	2177	10258	3374	NA	4850	40783
321 mg [2)]	III: 7-10		10	797	248	NA	291	2177	13855	4316	NA	4187	40783
396 mg [2)]	IV: 10-12		5	917	232	NA	595	1828	15458	3904	NA	12618	35821
495 mg [2)]	V: 12-18		5	595	120	NA	435	821	12618	2549	NA	8671	14808
600 mg	18-65		203	975	163	NA	186	5280	18200	3033	NA	3950	111000

2) Nominal doses (300-550 mg/m^2) in each population (mg/m^2) were converted using the reported BSA data, followed by taking the median value: 183-451 mg at 2-4 years, 219-517 mg at 4-7 years, 237-632 mg at 7-10 years, 348-660 mg at 10-12 years, and 381-549 mg at 12-18 years

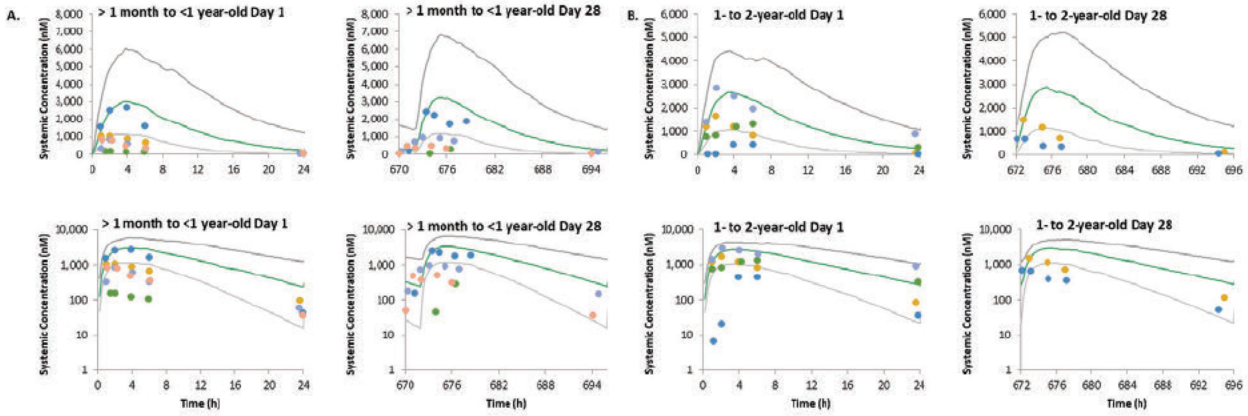
Source: Table 5 in the response-fda-ir-pbpk-20230831 (seq0022)

Table 43 Predicted and observed pharmacokinetic parameters of entrectinib and M5 after multiple oral administration of entrectinib at steady state in pediatrics less than 2 years of age

Median [range]			Peds >1 month to 1 year 250 mg/m^2 dose			Peds 1 year to <2 year 300 mg/m^2 dose		
			observed (n=8)	predicted	pred/obs	observed (n=4)	predicted	pred/obs
Entrectinib	C_{max} (nM)	DAY1	804	3244	4.0	956	2738	2.9
		SS	1008	3451	3.4	1330	2957	2.2
	AUC (nM*h)	DAY1	9417	34733	3.7	11900	30641	2.6
		SS	11000	38140	3.5	18000	31555	1.8
M5	C_{max} (nM)	DAY1	1175	587	0.5	615	487	0.8
		SS	1400	696	0.5	862	586	0.7
	AUC (nM*h)	DAY1	18833	8417	0.4	10400	7060	0.7
		SS	22750	10004	0.4	15300	8259	0.5

Source: entrectinib-250mgm2qd-30days-0-1-yr.xlsx and entrectinib-300mgm2qd-30days-1-2-yr.xlsx in the response-fda-ir-pbpk-20230831 (seq0022). Observed data are the results of population PK analysis.

Figure 17 Predicted and observed plasma concentration-time profiles of entrectinib after multiple oral administration of entrectinib at steady-state in pediatrics less than 2 years of age



PK profiles of entrectinib over time after oral administration of entrectinib at the designated doses in pediatric subjects (**A** at >1-month to <1-year-old and **B** at 1-2- year- old) were simulated using the updated models of entrectinib and M5. Observations are represented as colored circles. Green lines are simulated median plasma concentrations profiles of 100 virtual subjects (n=10×10 trials; female proportionality: 0.5). Gray lines represent the respective 95th/5th percentiles.
Source: entrectinib-250mgm2qd-30days-0-1-yr.xlsx and entrectinib-300mgm2qd-30days-1-2-yr.xlsx in the response-fda-ir-pbpk-20230831 (seq0022)

4. Can PBPK analyses be used to estimate the effects of strong and moderate CYP3A inhibitors on the exposure of entrectinib and M5 in pediatric patients older than 2 years?

The PBPK models of entrectinib and M5 can be used to evaluate the effects of strong and moderate CYP3A inhibitors on the exposure of entrectinib in pediatric patients older than 2 years, based on their performance in simulating the effects of itraconazole and rifampin on

entrectinib and M5 in adults and the exposure of entrectinib and M5 PK in patients older than 2 years. Moderate CYP3A inhibitors erythromycin and fluconazole were predicted to increase the combined exposure of entrectinib and M5 by 2- to 3-fold **(Table 44),** which were similar to that predicted in adults (data not shown). The predicted exposure of entrectinib and M5 were within the observed efficacious exposure in adults. Strong CYP3A inhibitors modeled using the itraconazole PBPK model were predicted to increase approximately 6- to 7-fold of the combined exposure of entrectinib and M5, which was similar to the predicted effect of itraconazole in adults. Except for the 2- to 4-year-old, the combined AUC values of entrectinib and M5 at the steady state in pediatric patients following administration of entrectinib at the reduced doses with itraconazole approximated the steady state exposure of entrectinib and M5 in adults following administration of entrectinib 600 mg once daily, which is also the maximal tolerated exposure observed in adult patients (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%20212726Orig1s000MultidisciplineR.pdf). For the 2- to 4-year-old, the combined exposure of entrectinib and M5 was within the efficacious exposure in adults when the AUCs of entrectinib and M5 were normalized to the 24-hour dosing interval. Therefore, these simulation results support the proposed dose reduction scheme (**Table 35**) in the proposed label.

It should be noted that the ability of these PBPK models to predict the effect of CYP3A inhibitors is also dependent on whether the inhibitor models could predict the inhibitor concentrations in different age groups. At the reviewer's request (FDA-IR dated August 9th, 2023), the applicant compared the simulated plasma concentration-time profiles and PK parameters of the strong CYP3A inhibitor itraconazole, and moderate CYP3A inhibitors fluconazole and erythromycin with that reported in the literature (PMID: 17517842*,* 9527794*,* 8070441*, and* 7313575). The PBPK models of erythromycin and fluconazole could reasonably capture the erythromycin PK profiles in patients aged 0.5 – 6 years old (**Figure 18**) and fluconazole PK parameters in patients aged 2 -16 years old (Table 45). However, the PBPK models of itraconazole and its hydroxyl metabolite significantly overpredicted their plasma exposure in patients aged 2-12 years old. Compared to the observed, the predicted AUC and C_{max} were overpredicted up to 11- and 6-fold, respectively, for itraconazole and up to 7.4- and 5-fold, respectively, for its major metabolite hydroxyl itraconazole (Table 45). The observed concentrations of itraconazole and hydroxyl itraconazole approximated the 5th percentile of the predicted concentrations (**Figure 18**). At these concentrations observed in patients < 12 years old, assuming that the effects of itraconazole on entrectinib and M5 were equivalent to the 5th percentile of the predicted effects of itraconazole on entrectinib, itraconazole was predicted to increase entrectinib exposure around 3-fold and increase M5 exposure 1- to 1.5-fold. If the proposed 6- to 8-fold dose reduction for strong CYP3A inhibitors is applied when itraconazole is co-administered, the exposure of entrectinib and M5 in pediatric patients would be below the efficacious exposure unless dose adjustment is made to the itraconazole dose.

Table 44 Predicted Exposure of entrectinib and M5 following ora administration of multiple-dose entrectinib with strong or moderate CYP3A inhibitors for 2 weeks in pediatrics

Inhibitor Dose	Age Groups	(b) (4) doses in the inhibited state	Predicted $AUC_{,ped}$ or $AUC_{i,ped}$			$AUC_{i,ped}$/ AUC_{ped}	$AUC_{i,ped}$/$AUC_{ss,adults}$
			Ent	M5	Ent+M5	Ent+M5	Ent+M5
Itraconazole (5 mg/kg)	2-4 yr	50 mg q2d	13318	3346	16669		
		50 mg q2d+Inh	108399	16246	130060	6.8	1.8
	4-7 yr	50 mg q2d	10573	2666	13239		
		50 mg q2d+Inh	72469	9877	82346	6.2	1.1
		50 mg qd	10612	2709	13305		
		50 mg qd+Inh	95135	12116	111026	6.5	1.6
	7-10 yr	50 mg qd	8754	2182	10923		
		50 mg qd+Inh	79058	8673	92657	6.6	1.3
		100 mg q2d	15510	3908	19424		
		100 mg q2d+inh	146371	15459	168059	6.6	2.4
	10-12 yr	50 mg qd	7493	1877	9370		
		50 mg qd+Inh	53664	6122	59786	6.4	0.8
		100 mg qd	13610	3450	17010		
		100 mg qd+Inh	127284	11644	134640	6.9	1.9
	12-18 yr	100 mg qd	11055	2758	13814		
		100 mg qd+Inh	93739	7770	100153	6.1	1.4
Erythromycin (7.5 mg/kg)	2-4 yr	50 mg qd	19299	4874	16600		
		50 mg qd+Inh	61775	15075	52560	3.0	0.7
	4-7 yr	50 mg qd	10612	2709	13301		
		50 mg qd+Inh	33593	8286	41880	2.9	0.6
	7-10 yr	100 mg qd	15462	3895	19357		
		100 mg qd+Inh	48017	11815	59832	2.9	0.8
	10-12 yr	200 mg qd	21703	5582	27305		
		200 mg qd+Inh	72899	17920	91064	2.9	1.3
	12-18 yr	200 mg qd	19299	4874	24177		
		200 mg qd+Inh	61775	15075	76932	2.8	1.1
Fluconazole (3 mg/kg)	2-4 yr	50 mg qd	13275	3328	16600		
		50 mg qd+Inh	31297	7108	38787	2.2	0.5
	4-7 yr	50 mg qd	10612	2707	13288		
		50 mg qd+Inh	26021	6166	32162	2.2	0.5
	7-10 yr	100 mg qd	15462	3897	19356		
		100 mg qd+Inh	37618	8900	46496	2.3	0.7
	10-12 yr	200 mg qd	21703	5576	27318		
		200 mg qd+Inh	54540	13105	67661	2.3	1.0
	12-18 yr	200 mg qd	19299	4803	24157		
		200 mg qd+Inh	46384	10728	57118	2.3	0.8

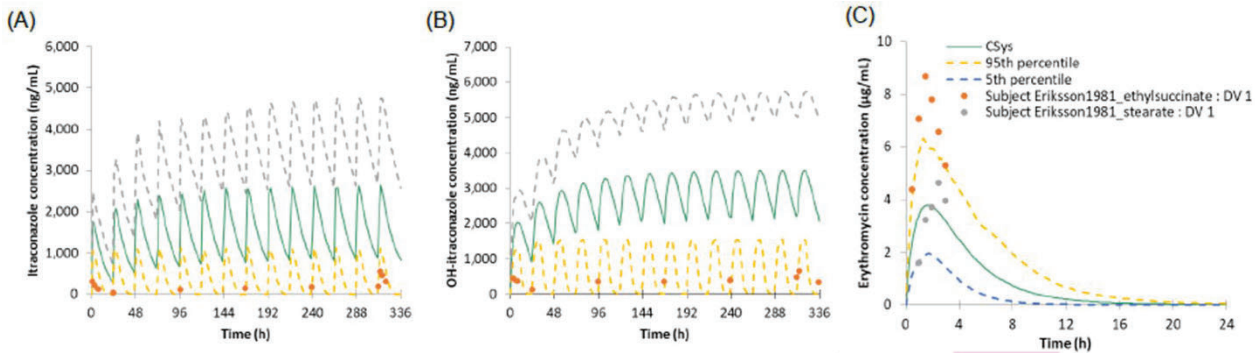
$AUC_{ss,adults}$ = combined steady-state AUC of entrectinib and M5 in adult following entrectinib 600 mg QD under the fed state = maximal tolerated exposure; AUC_{ped} and $AUC_{i,ped}$, $AUC_{0\text{-}24h}$ in the absence and presence of an inhibitor; AUC0-48h was reported for entrectinib given in alternate day. qd, once daily; q2d, every other day; yr, years old; +inh, in the presence of an inhibitor; Ent, entrectinib
Source: Tables 7- 9 in the PBPK report 1119857, Table 10 in the response-fda-ir-pbpk-20230831 (seq0022), and reviewer's analysis

Table 45 Simulated and observed PK parameters of the CYP3A inhibitors in pediatric subjects

Dose		Day	Parameter	>2 to 6 yr		>6 to 12 yr		>12 to 16 yr	
				Observed	Predicted	Observed	Predicted	Observed	Predicted
				n=9	n=100	n=7	n=100	n=11	n=100
Itraconazole: 2.5 mg/kg/day i.v.	Itraconazole	1	AUC(0-24) (ng·h/mL)	9510 (11316)	9756 (3426)	3765 (1711)	10983 (3551)	2669 (1076)	12668 (3684)
	OH-itraconazole	1	AUC(0-24) (ng·h/mL)	4249 (4103)	15589 (4840)	4166 (2036)	16568 (4559)	3133 (1789)	17473 (4562)
				>2 to 5 yr		>5 to 12 yr			
				Observed	Predicted	Observed	Predicted		
				n=7	n=100	n=11	n=100		
Itraconazole: 5 mg/kg/day p.o.	Itraconazole	1	AUC(0-24) (ng·h/mL)	2740 (1080)	21014 (8156)	2010 (1580)	22093 (8455)		
			Cmax (ng/mL)	314 (105)	1747 (427)	298 (292)	1824 (432)		
		14	AUC(0-24) (ng·h/mL)	7330 (5420)	37355 (26519)	8770 (5050)	39413 (31927)		
			Cmax (ng/mL)	534 (431)	2551 (1176)	631 (358)	2678 (1380)		
	OH-itraconazole	1	AUC(0-24) (ng·h/mL)	6730 (1950)	34790 (10184)	4920 (4390)	36293 (10774)		
			Cmax (ng/mL)	493 (106)	2106 (462)	447 (365)	2167 (484)		
		14	AUC(0-24) (ng·h/mL)	13400 (9110)	68868 (39667)	13450 (7190)	70896 (38315)		
			Cmax (ng/mL)	687 (419)	3472 (1405)	699 (234)	3558 (1370)		
				>2 to 12 yr		≥12 to 16 yr			
				Observed	Predicted	Observed	Predicted		
				[1]	n=100	[1]	n=100		
Fluconazole: 3 mg/kg/day i.v.	Fluconazole	1	AUCinf (μg·h/mL)	No data	125	No data	156		
Fluconazole: 8 mg/kg/day i.v.				218.2 (77.1)	334	230.9 (94.2)	415		
Fluconazole: 3 mg/kg/day p.o.				62.8 (15.8)	124 (23.2)	52.8 [2]	153 (23.6)		
Fluconazole: 8 mg/kg/day p.o.				354 (223.6)	330 (61.8)	354.4 (127.9)	409 (63.0)		

PK parameters are represented as mean with standard deviation (SD) in parentheses. The identical female proportionality in the clinical study populations was used for the respective simulation (itraconazole); otherwise a default value (0.5) was used (fluconazole).
1) Not reported. A total of 113 pediatric patients were enrolled in the study.
2) AUC(0-t)
Observed data from PMID17517842, 9527794 and 8070441.
Source: Table 8 in the response-fda-ir-pbpk-20230831 (seq0022)

Figure 18 Simulated and observed mean plasma concentration-time profiles of itraconazole and erythromycin following oral administration in pediatrics



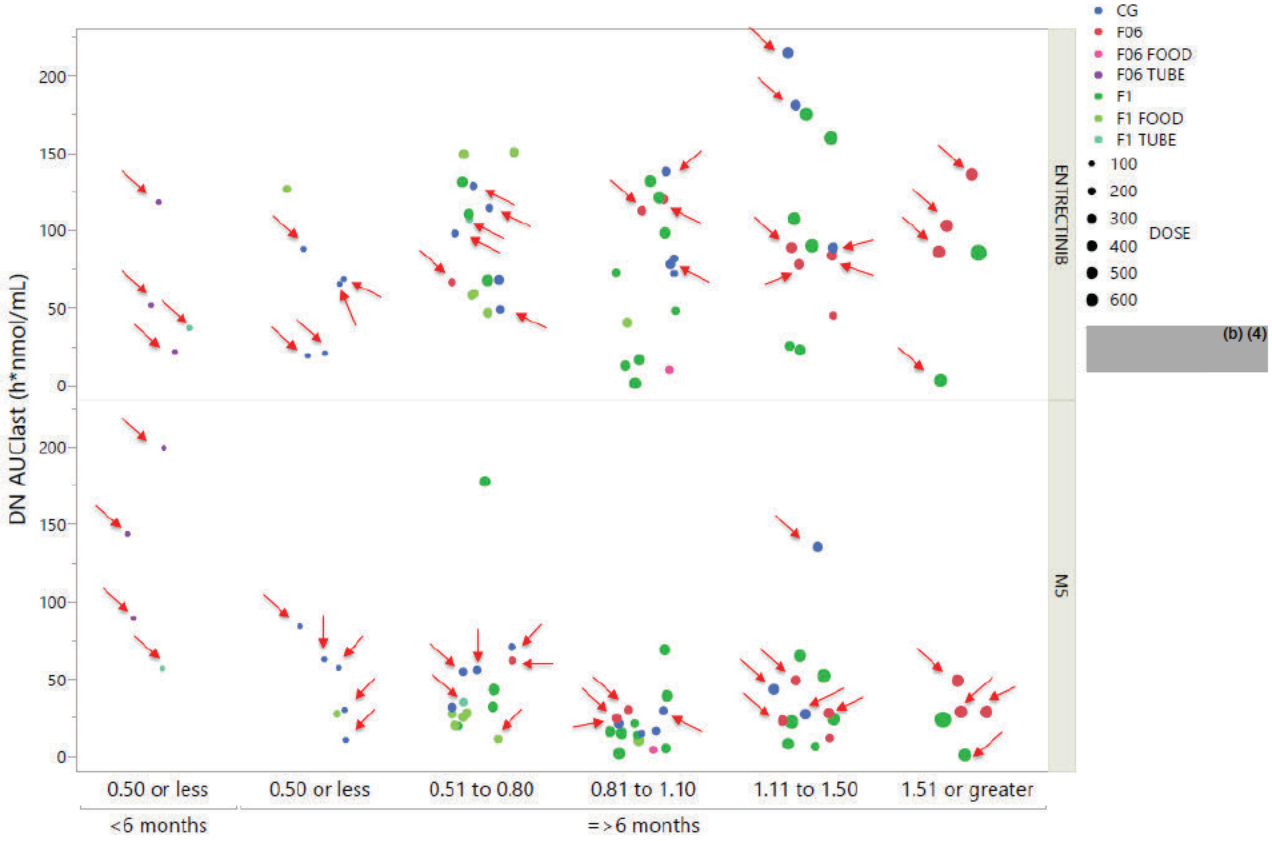
PK profiles of itraconazole (A), hydroxyitraconazole (B) and erythromycin (C) over time after oral administration of itraconazole at 5 mg/kg/day for 14 days (A, B) in the subjects at 5-12 years old and erythromycin at 20 mg/kg (single dose, C) in the subjects at 0.5-6 years old were simulated. Observations are represented as colored circles. Green lines are simulated mean plasma concentrations profiles of 100 virtual subjects Broken lines represent the respective 95th/5th percentiles. Observed data from PMID9527794 and 7313575.
Source: Figure 3 in the response-fda-ir-pbpk-20230831 (seq0022)

22.4.19. Observed PK Analysis

22.4.20. STARTRK-NG

This ongoing study includes dose escalation and dose expansion phases in pediatric patients >1 month old. In the dose escalation phase, 15 pediatric patients with relapsed or refractory extracranial solid tumors were enrolled. The starting dose was 250 mg/m^2 (~63% of the adult BSA based RP2D of 400 mg/m^2). Up to 4 dose levels were evaluated. F1 capsules were administered orally with food, once a day (QD), in repeated 4-week cycles in the dose escalation phase The dose expansion included 53 pediatric patients (>1 month old) with primary brain tumors with NTRK1/2/3, ROS or ALK molecular alterations, including gene fusions (Cohort A), primary brain tumors harboring NTRK1/2/3 or ROS1 gene fusions (Cohort B), neuroblastoma (Cohort C), extracranial solid tumors harboring NTRK1/2/3 or ROS1 gene fusions (Cohort D), and exploratory cohort for patients unable to swallow capsules (Cohort E). Expansion Cohorts A, C, and E were subsequently closed. In expansion cohorts, patients received the RP2D (550 mg/m2, using the F1 capsule formulation) from Phase 1 and 300 mg/m^2 of the F06 capsule and coated granule capsules (F15/F17) as assessed by modeling and simulation. Initially, patients who were unable to swallow capsules received the contents of F1 capsules mixed in with liquid or soft food appropriate for their age administered orally with food or via enteral feeding tube. Later, patients unable to swallow capsules were switched to coated granules that were administered orally mixed with soft food. The coated granules were adminstered without regards to additional food. Also, F06 capsule were administered as intact capsules for patients able to swallow capsules, or F06 capsule as suspension were administered either orally for patients unable to swallow soft food or via nasogastric tube for patients who required enteral administration. The F06 capsules were adminstered without regards to food. Detailed information with regard to meal status and the type of meal administered for individual patients were not captured, meal times for patients receiving F06 capsules were not consistently captured and meal times for patients receiving coated granules (in addition to soft foods) were not captured. Also, the information on the soft foods used to administer coated granules was not formally collected.
The dose normalized entrectinib and M5 exposures were comparable across the different age groups and BSA exposure categories based on BSA-based doses of 550 mg/m^2 (for F1 capsule formulation) and 300 mg/m^2 (for F06 Capsule and coated granule formulations) (see Figure C).

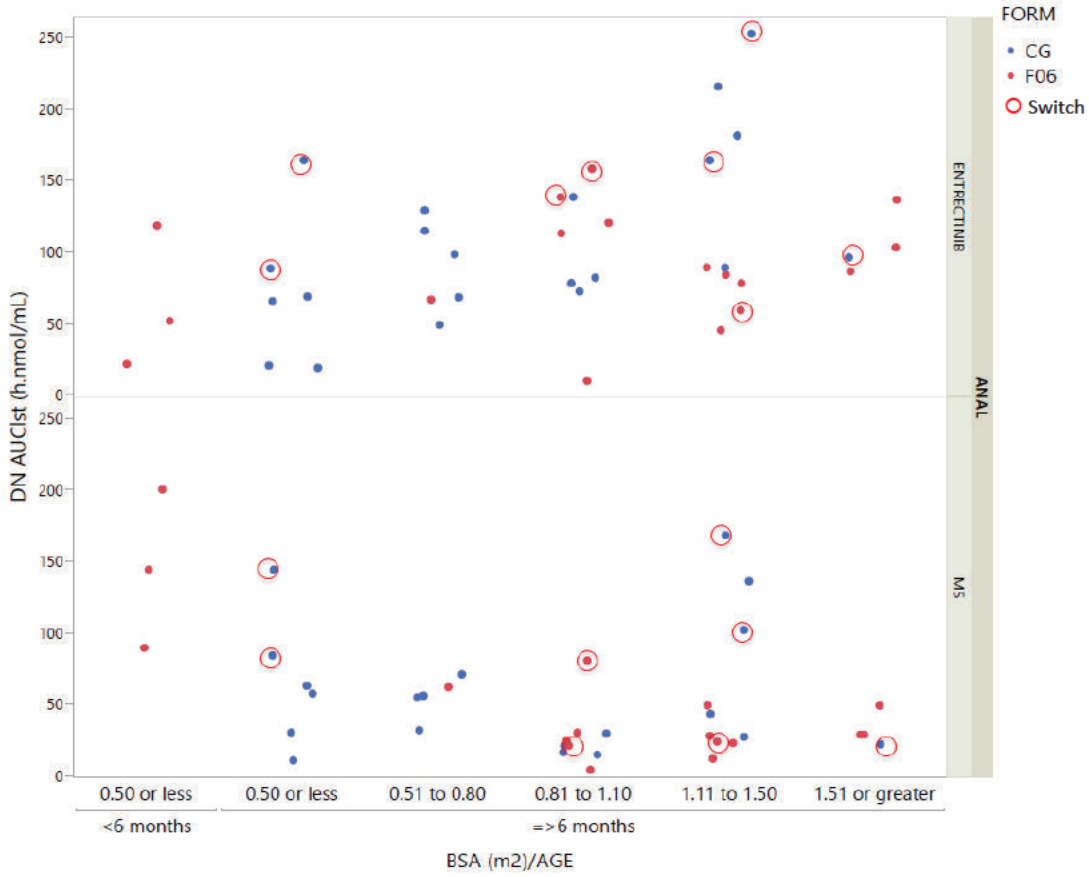
Figure C: Dose-Normalized Exposures at steady state of Patients Administered Different Formulations and Administration Methods Subgrouped by Age Group, Body Surface area (BSA) categories, and Dose in Study STRTRK-NG



DN AUClast represents dose normalized AUC over the last measurable time point at steady state (Cycle 2 or greater). Arrows represent the proposed doses for the different age groups and BSA categories as detailed in Table 4 and Table 5.
Source: Reviewer generated

During the study, at least 8 pediatric patients had formulations switched from either F06 capsule to coated granules or from coated granules to F06 capsules. As indicated in Figure D, the dose normalized steady state exposures in patients after the switch was comparable to those in other patients who were administered coated granules or F06 capsules.

Figure D: Dose-Normalized Exposure at Steady State of Patients Administered Capsule and Coated Granule Formulations and Patients who Switched Between the Two Formulations in Study STRTRK-NG



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22.4.21. Relative Bioavailability Studies

GP41341: This was 2 part single dose study in healthy subjects.
Part 1 was a three-treatment, three-period, three-sequence, three-way crossover design comparing single dose (600 mg) of two multi-particulate entrecatinib coated granule formulations (F15 and F16: 240 mg x 2.5) against F06 capsule formulation (200 mg x 3) as reference in 15 healthy subjects. Study treatments were administered orally within 30 minutes of consumption of a standardized light "pediatric" breakfast (250 Kcal, 25% from fat). The washout period between entrectinib doses was at least 14 days. At the time of administration, the contents of coated granules were mixed with one tablespoon (15 mL) of yoghurt and swallowed with 240 mL of water. Blood samples for the measurement of entrectinib were obtained for up to 96 hours post-dose.

Table E: Statistical Analysis of Pharmacokinetic Parameters of Entrectinib – Part 1

Formulations Compared	PK Parameters	GMR (90% CI)	90% CI

		Entrectinib	M5
Coated Granules (F15) vs. Capsules (F06)	Cmax (nmol/mL)	1.03 (95, 112)	1.10 (97, 126)
	AUClast (h*nmol/mL)	0.98 (90, 108)	1.01 (92, 112)
GMR: geometic mean ratio, CI: confidence interval Source: CSR GP41341			

Part 2 was a randomized, open-label, two-treatment, two-period, two-sequence, two-way crossover design. In each treatment period, subjects received a single 200 mg oral dose of two entrectinib F06 capsule formulations under fasted conditions. This part is not relevant to the current submission and therefore, the results are not presented.

GP44192: This was a two-part, open-label, comparative, single-dose, randomized, five-treatment, three-way crossover, relative bioavailability study of entrectinib administered at 600 mg in healthy subjects.
Part 1 was a randomized, open-label, three-treatment, three-period, three-sequence, three-way crossover design to be conducted in 13-16 subjects. Subjects were randomly assigned to one of three treatment sequences (ABC, BCA, or CAB) in a 1:1:1 allocation ratio to receive the following treatments:
Treatment A: Nasogastric administration of 600 mg entrectinib F06 capsule as 30 mL of 20 mg/mL suspension in water on Day 1 following an 8-hour fast;
Treatment B: Oral administration of 600 mg entrectinib F06 capsule as 30 mL of 20 mg/mL suspension in milk on Day 1 following an 8-hour fast;
Treatment C: Oral administration of 600 mg entrectinib F06 capsule as 3 × 200 mg hard capsules with ~240 mL of water on Day 1 following an 8-hour fast.
The washout period between entrectinib doses was at least 14 days. Blood samples for the measurement of entrectinib were obtained for up to 96 hours post-dose. The statistical summary of the comparisons are provided in Table F.

Table F: Statistical Analysis of Pharmacokinetic Parameters of Entrectinib– Part 1

Comparisons (600 mg dose) (fasted conditions)	**n**	**PK Parameters**	**GMR (90% CI)**	
			Entrectinib	**M5**
F06: NG vs. Capsules	13-16	Cmax	0.99 (85, 116)	0.98 (79, 122)
		AUCinf	1.04 (87, 125)	1.03 (89, 120)
F06: Oral Susp (20 mg/mL in milk) vs. Capsules	13-16	Cmax	1.24 (106, 145)	1.48 (119, 184)
		AUCinf	1.13 (94, 135)	1.32 (112, 154)
F06: Oral Susp (20 mg/mL in water) vs. Capsules	13-15	Cmax	0.81 (72, 93)	0.73 (55, 98)
		AUCinf	0.91 (82, 101)	0.88 (70, 110)
GMR: geometic mean ratio, CI: confidence interval Source: CSR GP44192				

Part 2 was a randomized, open-label, three-treatment, three-period, two-sequence, two-way crossover design to be conducted in 16 subjects. Subjects were randomly assigned to one of two treatment sequences (CD or DC) in a 1:1 allocation ratio for Periods 1 and 2. In Period 3, all subjects partook in a fixed treatment (Treatment E).
Treatment C: Oral administration of 600 mg entrectinib (F06) as 3 × 200 mg hard capsules with ~240 mL of water on Day 1 following an 8-hour fast;
Treatment D: Oral administration of 600 mg entrectinib (F06) as 30 mL of 20 mg/mL suspension in water on Day 1 following an 8-hour fast;
Treatment E: Oral administration of 30 mg lansoprazole orally disintegrating delayed release tablet (1 × 30 mg) at 24-hour (±1 hour) intervals on Days 1 to 4. On Day 5, 30 mg lansoprazole orally disintegrating delayed release tablet (1 ×30 mg) was co-administered with oral dosing of 600 mg entrectinib (F06) as 30 mL of 20 mg/mL suspension in water following an 8-hour fast.

The washout period between entrectinib doses was at least 14 days. Blood samples for the measurement of entrectinib were obtained for up to 96 hours post-dose. The statistical summary of the comparisons are provided in Table G.

Table G: Statistical Analysis of Pharmacokinetic Parameters of Entrectinib– Part 2

Comparisons (600 mg dose) (fasted conditions)	**n**	**PK parameters**	**GMR (90% CI)**	
			Entrectinib	**M5**
F06: Oral Susp (20 mg/mL in water) vs. Capsules	15	Cmax	0.81 (72, 93)	0.73 (55, 98)
		AUCinf	0.91 (82, 101)	0.88 (70, 110)
F06: Oral Susp (20 mg/mL in water) + PPI vs. Capsules	15	Cmax	0.94 (87, 102)	0.67 (53, 84)
		AUCinf	1.14 (103, 125)	0.93 (79, 110)
F06 Oral Susp (20 mg/mL in water): +PPI vs. Alone	15	Cmax	1.17 (104, 132)	0.93 (79, 110)
		AUCinf	125 (108, 144)	1.08 (95, 122)

GMR: geometic mean ratio, CI: confidence interval
Given that all subjects in Period 3 received the same treatment "E", the statistical model used for "E" vs "C" and "E" vs "D" comparisons only included treatment as fixed effect and subject as random effect (and cannot include treatment sequence or period as fixed effects; otherwise there would be confounding).
Source: CSR GP44192

The logistic regression model linking the entrectinib average concentration to the probability of bone fracture indicated that the risk for the increase in entrectinib AUC following administration of F06 oral suspension in milk (Table F) is expected to increases in the probability of bone fracture between F06 oral suspension in milk and F06 capsule between 0.4 % and 1.6 % across the 3 age/BSA categories (Table H).

Table H: Comparison of the probability of bone fractures between administration of F06 capsule and F06 oral suspension in milk

Category	Dose	Probability of bone fracture (%)			
		F06 capsule		F06 oral suspension in milk	
		Average	95 %CI	Average	95 %CI
1 – 6 months	250 mg/m^2	11.9	4.89 – 26.4	12.3	5.13 – 26.6
6 months – 0.5 m^2	100 mg	13.1 (*)	5.82 – 27.1(*)	13.7	6.25 –27.4
0.51 – 0.80 m^2	200 mg	18.3 (*)	10.3 – 30.5 (*)	19.9	11.7 –31.7

P5: 5th percentile, P95: 95th percentile, CI: confidence interval.
*: the simulated numbers differ slightly from the numbers provided in table 30 of the population PK report due to stochasticity of the simulations

Source: Table 4, Applicant's Response to Information Request, SDN 21

22.4.22. Bioanalysis

Bioanalytical Method Validation

A LC-MS/MS assay for the measurement of entrectinib in human plasma was initially developed and validated. During the course of the initial study sample analysis, M5 metabolite was identified and a new LC-MS/MS bioanalytical method for the determination of entrectinib and M5 was developed and validated in human plasma at [(b) (4)] (hereafter referred to as Original Method). A modified LC-MS/MS method was later developed and validated for the simultaneous measurement of both entrectinib and M5 in human plasma (Report 1087331) at [(b) (4)] (hereafter referred to as [(b) (4)] assay). This method was used to analyze study samples from STARTRK-NG, GP41341 and GP44192. Subsequently another LC-MS/MS method was established and validated for the simultaneous measurement of both entrectinib and M5 in human plasma (Report 1087327) at Ignyta (hereafter referred to as Ignyta assay). The second part of STARTRK-1, and subsequent clinical studies, were analyzed using this method. [(b) (4)] assay involved protein precipitation extraction followed by LC/MS/MS detection of entrectinib and M5. Ignyta assay used a similar extraction and detection procedure (with some variations) as [(b) (4)] to analyze entrectinib and M5 in human plasma. Since the [(b) (4)] method is related to the current submission, only the method validation for the [(b) (4)] assay is presented here (Table I).

Table I: Method validation parameters for [(b) (4)] Assay for Entrectinib and M5 in human plasma

Validation Parameters	Report 1087331	
Analyte	Entrectinib	M5

Detection	Protein precipitation extraction followed by LC/MS/MS detection			
Anticoagulant	Sodium heparin			
Range	2-2000 ng/mL			
Internal Standard	D8-entrectinib		D8-M5	
Calibrators Concentrations	2, 4, 20, 50, 200, 500, 1800, 2000 ng/mL			
Regression model and weighting	Linear			
Quality Controls	6, 150, 1500 ng/mL			
Precision at LLOQ (%CV)	11%		15%	
Accuracy at LLOQ	14%		16%	
Inter/Intra-assay Precision (%CV)	≤8% / ≤7%		≤7% / ≤7%	
Inter/Intra-assay Accuracy (% accuracy)	-9.83 to -2.00% / 0.667 to 2.00%		-8.67 to 0.00% / -6.00 to -2.00%	
Selectivity **Matrix factor** **Precision at Low QC** **Accuracy at Low QC**	 1.00 No interference in 6 of 6 matrix blanks and with concomitant drugs 3% 7%		 1.04 No interference in 6 of 6 matrix blanks and with concomitant drugs 1% 7%	
Dilution Linearity 10x	**3.3-fold**	**10-fold**	**3.3-fold**	**10-fold**
% Accuracy **% Precision**	≤15% <11%	3% 11%	<18% <9%	3% 12%
Stock stability [%Bias (%CV)]	316 days at RT: 1% (5%)			
Extract stability	117 hours at 5°C			
Reinjection Satbility	117 hours at 5°C			
Short-term Stability	13 hours in Ice**			
Long-term Stability [%Accuracy (%CV)]	533 days at -80°C** 179 days at -20°C		417 days at -80°C** 42 days at -20°C	
Freeze-Thaw Stability [%Accuracy (%CV)]	4 cycles at -20°C: 5 cycles at -80°C* :		4 cycles at -20°C: 5 cycles at -80°C* :	
Assayed in Clinical Studies	STARTRK-NG, GP41341, GP44192 (in the current submission)			
Cross-Validation† **QC (%, Accuracy)** **Incurred Samples (% Pass rate)**	 ≤19% vs. <16% (Original vs. (b) (4)) 97% (Ignyta vs. (b) (4)); 60% (Original vs. Ignyta)‡; 40% (Original vs. (b) (4) ‡		 ≤34% vs. <18% (Original vs. (b) (4)) 83% (Ignyta vs. (b) (4)); 73% (Original vs. Ignyta)‡; 47% (Original vs. (b) (4))‡	

- *Report 1097193
- **Report 1101993

†Cross Validation Report 1087689

‡ study analyzed using the original method was not used for popPK analysis.

In-Study Analyses (related to the current submission)

The validated (b) (4) method was used to analyze samples from pediatric studies and relative bioavailbailty studies GP41341 and GP44192. Since greater than 90% of pediatric PK samples were collected and analyzed from STARTRK-NG, the discussion of sample analysis in pediatric patients is limited to Study STARTRK-NG.
In Studies STARTRK-NG, GP41341 and GP44192, precision and accuracy were <10% (Table J, Table K and Table L). Majority (≥80%) of the analytical runs in the studies were successful. The incurred sample reanalysis (ISR) analyses in the studies were within the acceptable limits, with >80% of ISR samples reproducible. The study sample concentrations reported were analyzed within the validated storage and handling conditions. About 2% of the study samples in Study STARTRK-NG were analyzed outside of established long-term frozen stability period for M5 (417 days), however, M5 results for these samples were not reported.

Table J: In-study Method Performance Parameters for Entrectinib and M5 in Human Plasma in Study STARTEK-NG

Parameters	STARTRK-NG (Report 1117085)	
	Entrectinib	M5
Calibrators Concentrations	2, 4, 20, 50, 200, 500, 1800, 2000 ng/mL	
Regression model and weighting	Linear	
Quality Controls	6, 85, 150, 600, 1500 ng/mL	
Range	2-2000 ng/mL	
Inter-assay Precision (%CV)	<8%	<9%
Inter-assay Accuracy	- 2.67 to 1.33%	- 2.17 to 2.67%
Diluted QCs [%Accuracy (%CV)]	0% (<6%)	1.33-4% (<7%)
Analytical run pass rate	88%	86%
Reanalyses	9%, mainly as original values were >ULOQ.	5%, mainly due to reference standard issues ins original analysis.
Incurred Sample Reanalysis (ISR)	117 of 1223 (10%) samples were reanalyzed for ISR	
Pass rate (%)	80% were within 20% of original values	80% were within 20% of original values
Sample storage	Samples were analyzed within 528 days after collection. Of total patient samples analyzed in Study STARTRK-NG, ~2% of the study samples were analyzed outside of established stability for M5 (417 days); therefore, M5 results for these samples were not reported.	

Table K: In-study Method Performance Parameters for Entrectinib and M5 in Human Plasma in Study GP41341

Parameters	GP41341 (Report 11020283)	
	Entrectinib	M5
Range	2 – 2000 ng/mL	
Calibrators Concentrations	2, 4, 20, 50, 200, 500, 1800, 2000 ng/mL	
Regression model and weighting	Linear	

Parameters	GP41341 (Report 11020283)	
Quality Controls	6, 85, 150, 600, 1500 ng/mL	
Inter-assay Precision (%CV)	<7%	<8%
Inter-assay Accuracy	- 6.67 to -1.33%	- 6.50 to 0.667%
Analytical run pass rate	83%	91%
Reanalyses	One study sample was reanalyzed.	
Incurred Sample Reanalysis (ISR)	116 samples reanalyzed (10% of total) for ISR	
Pass rate (%)	83% were within 20% of original values	91% were within 20% of original values
Sample storage	Samples were analyzed within 46 days after collection	

Table L: In-study Method Performance Parameters for Entrectinib and M5 in Human Plasma in Study GP44192

Parameters	GP44192 (Report RO7102122)	
	Entrectinib	M5
Range	2-2000 ng/mL	
Calibrators Concentrations	2, 4, 20, 50, 200, 500, 1800, 2000 ng/mL	
Regression model and weighting	Linear	
Quality Controls	6, 85, 150, 600, 1500 ng/mL	
Inter-assay Precision (%CV)	<8%	<6%
Inter-assay Accuracy	- 1.33 to 4.01%	0.667 to 4.33%
Diluted QCs [%Accuracy (%CV)]		
Analytical run pass rate	81%	81%
Reanalyses	3 (0.22%) of study samples were reanalyzed.	--
Incurred Sample Reanalysis (ISR)	120 samples reanalyzed (10% of total) for ISR	
Pass rate (%)	84% were within 20% of original values	93% were within 20% of original values
Sample storage	Samples were analyzed within 100 days after collection	

An Office of Study Integrity and Surveillance (OSIS) inspection of (b) (4) was requested. OSIS determined that an inspection was not needed due to earlier inspection history of this facility. Earlier inspection did not not find any major issues at (b) (4) that would affect the reliability of bioanalytical data from the audited studies.

22.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

No additional safety analyses were conducted

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Stephanie Aungst, Ph.D.	CDER/OOD/DHOT	Sections: 6	**Select one:** X Authored X Approved
	Signature: Stephanie L. Aungst -S Digitally signed by Stephanie L. Aungst -S Date: 2023.10.16 15:08:39 -04'00'			
Nonclinical Supervisor	Claudia P. Miller, Ph.D.	CDER/OOD/DHOT	Sections: 6	**Select one:** X Authored X Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2023.10.16 15:12:32 -04'00'			
Clinical Pharmacology Reviewer	Sriram Subramaniam, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** x Authored ___Approved
	Signature: Sriram Subramaniam -S Digitally signed by Sriram Subramaniam -S Date: 2023.10.16 16:38:58 -04'00'			
Clinical Pharmacology Master Pharmacokine ticist	Jeanne Fourie Zirkelbach, Ph.D.	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: 2023.10.16 16:32:10 -04'00'			
Division of Pharmacometrics (DPM) Reviewer	Ye Xiong, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** X Authored ___ Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2023.10.16 16:41:43 -04'00'			
Division of Pharmacometrics (DPM) Team Leader	Youwei Bi, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** X Authored X Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2023.10.16 16:46:01 -04'00'			

Division of Pharmacometrics (DPM) PBPK Reviewer	Ying-Hong Wang, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored ___ Approved
	Signature: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2023.10.16 17:47:34 -04'00'			
Division of Pharmacometrics (DPM) PBPK Team Leader	Yuching Yang, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored x Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2023.10.17 09:03:01 -04'00'			
Clinical Pharmacology Deputy Division Director	Stacy Shord, Pharm.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** Authored x Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S Date: 2023.10.17 09:05:57 -04'00'			
Clinical Reviewer	Marjilla Seddiq, M.D.	CDER/OOD/DO2	Sections: 1, 2, 4,5,7,10,11,12,13,15,16, 22	**Select one:** _x_ Authored ___ Approved
	Signature: Marjilla Seddiq -S Digitally signed by Marjilla Seddiq -S Date: 2023.10.17 09:07:46 -04'00'			
Clinical Team Leader	Amy Barone, M.D.	CDER/OOD/DO2	Sections: see CTDL	**Select one:** x Authored x Approved
	Signature: see CDTL signature			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Xiaoxue Li, Ph.D.	CDER/OTS/DBV	Sections: 1,2,8	**Select one:** _X_ Authored _X_ Approved
	Signature: see Statistical Team Leader signature Xiaoxue Li -S Digitally signed by Xiaoxue Li -S Date: 2023.10.17 09:14:18 -04'00'			
Deputy Division Director (OB/DBV)	Pallavi Mishra-Kalyani Ph.D.	CDER/OTS/DBV	Sections: 1,2,8	**Select one:** ___ Authored _X_ Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2023.10.17 09:19:19 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OOD	Section: 11	**Select one:** x Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2023.10.17 09:33:33 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Amy Barone, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** x Authored x Approved
	Signature: See Electronic Signature in DARRTS			
Division Deputy Director	Nicole Drezner, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored X Approved
	Signature: See Electronic Signature in DARRTS			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY K BARONE
10/17/2023 09:38:26 PM

NICOLE L DREZNER
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