CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212725Orig1s000
212726Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Original New Drug Application
Application Number(s)	212725
Priority or Standard	Priority
Submit Date(s)	December 18, 2018
Received Date(s)	December 18, 2018
PDUFA Goal Date	August 18, 2019
Division/Office	DOP2/OHOP
Review Completion Date	August 14, 2019
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
Dosing Regimen	600 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	Patients with metastatic non-small cell lung cancer (NSCLC) that is *ROS1*-positive
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OPE= Office of Pharmacovigilance and Epidemiology
OSE= Office of Surveillance and Epidemiology
OSI= Office of Scientific Investigations
OSIS= Office of Study Integrity and Surveillance
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DNP=Division of Neurological Products
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor

1 Executive Summary

1.1. Product Introduction

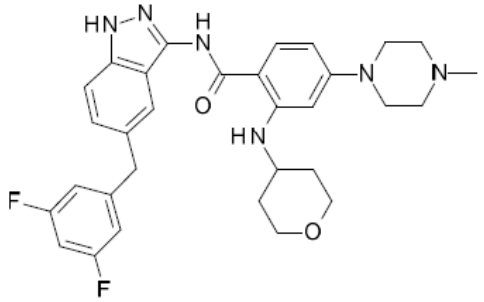
On December 18, 2018, Genentech Inc. (Genentech) submitted original New Drug Application (NDA) 212725 under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) seeking approval of entrectinib (Rozlytrek) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is *ROS1*-positive. On the same day, Genentech submitted original NDA 212726 seeking approval of entrectinib for the treatment of adult and pediatric patients with (b) (4) metastatic solid tumors harboring an *NTRK* gene fusion (please see the separate multidisciplinary review for additional details regarding NDA 212726).

Entrectinib (RO7102112; also known as RXDX-101 and NMS-1191372) is an inhibitor of ROS proto-oncogene 1 receptor tyrosine kinase (encoded by the *ROS1* gene), tropomyosin receptor kinases A, B, and C (TRKA, TRKB and TRKC; encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively), and anaplastic lymphoma kinase (ALK; encoded by the *ALK* gene). Gene rearrangements (fusions) in each of the genes encoding these target kinases have the potential to be oncogenic drivers, tend to be mutually exclusive, and have been observed at low incidence in a variety of tumor types. Entrectinib is being developed as an anti-cancer agent for the treatment of patients with tumors that harbor *NTRK1/2/3, ROS1*, or *ALK* gene fusion.

The molecular formula for entrectinib is: $C_{31}H_{34}F_2N_6O_2$ and the molecular weight is 560.64 daltons. The chemical name is N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzamide.

Entrectinib has the following chemical structure:

Figure 1: Organic Structure of Entrectinib



Source: NDA submission Nonclinical Overview Module 2.4

Entrectinib is a new molecular entity; entrectinib has not been previously marketed in the U.S. and has not been approved for any indication by FDA. Entrectinib was approved in Japan on

June 18, 2019 for the treatment of adult and pediatric patients with *NTRK* fusion-positive, advanced recurrent solid tumors.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for regular approval. The recommendation for regular approval is based on the results from a pooled subgroup of 51 patients with metastatic *ROS1* fusion-positive (*ROS1*-positive) non-small cell lung cancer (NSCLC) who received entrectinib at various doses and schedules (90% received entrectinib 600 mg once daily) in one of three multicenter, single-arm, open-label, dose escalation and/or activity-estimating clinical trials (ALKA, STARTRK-1 and STARTRK-2). This pooled subgroup (referred to hereafter as the primary efficacy set) comprises the first 51 consecutively enrolled patients with *ROS1*-positive NSCLC who had not received prior treatment with a ROS1 tyrosine kinase inhibitor (TKI) and had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1), ECOG performance status (PS) of ≤2, and had ≥12 months of follow-up from first post-treatment tumor assessment.

The pooled analysis demonstrated a large, clinically meaningful, and durable overall response rate (ORR) per blinded independent central review (BICR) assessment in patients with metastatic *ROS1*-positive NSCLC treated with entrectinib. Confirmed ORR per BICR was 78% (95% CI: 65%, 89%), and the Kaplan-Meier estimated median duration of response (DOR) was 15.7 months (95% CI: 11.4, 34.8), with 70%, 55%, and 30% of the 40 responders having observed DOR of at least 9, 12, and 18 months, respectively. Since only 30% of patients had an observed DOR of ≥18 months and follow-up is short, the estimated median DOR may not be a reliable estimate of the true median DOR; therefore, the estimated median DOR will not be included in product labeling. Durable responses were observed across study sites and in subgroups of patients who had received no prior systemic therapy for metastatic disease and in patients who had received prior systemic therapy, other than *ROS1* TKI, for metastatic disease. The ORR and the proportion of responders with DOR ≥12 months reported here for entrectinib are similar to that observed with crizotinib, which was approved for the treatment of patients with metastatic *ROS1*-positive NSCLC based on demonstration of a large magnitude of ORR that were durable in 50 patients with metastatic *ROS1*-positive NSCLC. The lower limit of the 95% CI for ORR with entrectinib (65%) in the primary efficacy set, the majority of whom had received prior platinum-based systemic chemotherapy for the treatment of metastatic disease, excludes the ORR observed in clinical trials of other therapies approved for the first-line treatment of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy plus anti-PD-(L)1 antibody, ORR 48% to 58%).

Assessment of the anti-tumor activity of entrectinib in the CNS was pre-specified in the plan for analysis of the pooled dataset, specifically as descriptive analyses of intracranial ORR (IC-ORR) and IC-DOR as secondary endpoints. The primary efficacy set included 7 patients with measurable CNS metastases at baseline per BICR who had not received radiation to the brain within 2 months of first dose of entrectinib; 5 of these patients had confirmed IC response. Given the limited number of patients, the point estimate for these results needs to be

interpreted with caution; however, the results do support a conclusion that entrectinib has anti-tumor activity in the CNS in patients with *ROS1*-positive NSCLC with brain metastases. Anti-tumor activity in the CNS was not assessed in the study supporting the approval of crizotinib.

The rarity of *ROS1*-positive NSCLC renders the conduct of a randomized trial not feasible. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with entrectinib is sufficient to establish clinical benefit in the genetically defined (*ROS1*-positive), rare subgroup of patients with metastatic NSCLC.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Metastatic NSCLC is a life-threatening condition with poor survival. The 5-year survival for this population is less than 5%. The incidence of *ROS1* gene fusions in metastatic NSCLC is 1-2%. Crizotinib is the only kinase inhibitor currently approved in the US for the treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive and is the preferred first-line treatment for this patient population, per the NCCN clinical practice guidelines. Crizotinib was approved in the US based on observation of a high ORR and prolonged DOR in 50 patients with *ROS1*-positive NSCLC treated in a multicenter, single arm study. ORR according to RECIST v1.0 assessed by independent radiology review was 66% (95% CI: 51, 79), and the median DOR was 18.3 months (95% CI: 12.7, not reached). The approval of the companion diagnostic for crizotinib occurred after initial approval of crizotinib for the ROS1 indication. Following progression on crizotinib, treatment options for patients with *ROS1*-positive NSCLC include regimens used for first-line systemic therapy an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy and/or anti-PD-(L)1 antibody). The highest ORRs, 48% and 58%, have been reported for platinum-based chemotherapy plus pembrolizumab (regardless of histology) and platinum-based chemotherapy plus atezolizumab and bevacizumab (non-squamous NSCLC), respectively.

Entrectinib is an inhibitor of ROS proto-oncogene 1 receptor tyrosine kinase (encoded by the *ROS1* gene), tropomyosin receptor kinases A, B, and C (TRKA, TRKB and TRKC; encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively), and anaplastic lymphoma kinase (ALK; encoded by the *ALK* gene). The proposed dosing regimen is 600 mg orally once daily with or without food until disease progression or unacceptable toxicity. Genentech's proposed indication for entrectinib is for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is *ROS1*-positive.

The primary efficacy data supporting this NDA are from a pooled subgroup of 51 patients who received treatment with entrectinib at various doses and schedules (90% received entrectinib 600 mg once daily) in one of three multicenter, single-arm, open-label, dose escalation and/or activity-estimating clinical trials (ALKA, STARTRK-1 and STARTRK-2). This pooled subgroup (referred to hereafter as the primary efficacy set) comprises the first 51 consecutively enrolled patients with *ROS1* fusion-positive (*ROS1*-positive), metastatic non-small cell lung cancer (NSCLC) who had not received prior treatment with a ROS1 tyrosine kinase inhibitor (TKI) and had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1), ECOG performance status (PS) of ≤2, and ≥12 months of follow-up from first post-treatment tumor assessment.

The pooled analysis demonstrated a large, clinically meaningful, and durable overall response rate (ORR) per blinded independent central

review (BICR) assessment in patients with metastatic *ROS1*-positive NSCLC treated with entrectinib. Confirmed ORR per BICR was 78% (95% CI: 65%, 89%), and the estimated median duration of response (DOR) was 15.7 months (95% CI: 11.4, 34.8), with 70%, 55%, and 30% of the 40 responders having observed DOR of at least 9, 12, and 18 months, respectively. Since only 30% of patients had an observed DOR of ≥18 months and follow-up is short, the estimated median DOR may not be a reliable estimate of the true median DOR; therefore, the estimated median DOR will not be included in product labeling. Durable responses were observed across study sites and in subgroups of patients who had received no prior systemic therapy for metastatic disease and in patients who had received prior systemic therapy, other than *ROS1* TKI, for metastatic disease. The ORR and the proportion of responders with DOR ≥12 months reported here for entrectinib is similar to that observed with crizotinib, which was approved for the treatment of patients with metastatic *ROS1*-positive NSCLC based on demonstration of a large magnitude of ORR that were durable in 50 patients with metastatic *ROS1*-positive NSCLC. The lower limit of the 95% CI for ORR with entrectinib (64%) in the primary efficacy set, the majority of whom had received prior systemic therapy for the treatment of metastatic disease, excludes the ORR observed in clinical trials of other therapies approved for the first-line treatment of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy plus anti-PD-(L)1 antibody, ORR 48% to 58%).

Assessment of the anti-tumor activity of entrectinib in the CNS was pre-specified in the plan for analysis of the pooled dataset, specifically as descriptive analyses of intracranial ORR (IC-ORR) and IC-DOR as secondary endpoints. The primary efficacy set included 7 patients with measurable CNS metastases at baseline per BICR who had not received radiation to the brain within 2 months of first dose of entrectinib; 5 of these patients had confirmed IC response. Given the limited number of patients, the point estimate for these results needs to be interpreted with caution; however, the results do support a conclusion that entrectinib has anti-tumor activity in the CNS in patients with *ROS1*-positive NSCLC with brain metastases. Anti-tumor activity in the CNS was not assessed in the study supporting the approval of crizotinib.

Safety data supporting these applications reflected exposure to entrectinib in 355 patients, in which 48% of patients were exposed for greater than 6 months and 24% patients were exposed for greater than 12 months. The safety of entrectinib was evaluated in a pooled group of pediatric and adult patients enrolled in one of four multicenter, single-arm, open-label clinical trials: ALKA (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267), and STARTRK-NG (NCT02650401). All patients had an unresectable or metastatic solid tumor and no satisfactory alternative treatment options or disease progression following treatment. The population characteristics were: median age 55 years (range: 4 to 86 years); 5% (n = 17) were 18 years or younger; 55% were female; and 66% were White, 23% were Asian, and 5% were Black; 3% were Hispanic/Latino. The most common tumors (≥ 5%) were lung (56%), sarcoma (8%), and colon (5%). *ROS1* gene fusions were present in 42% and *NTRK* gene fusions were present in 20%. Most adults (75%) received entrectinib 600 mg orally daily. The dose ranged from 100 mg daily to 2600 mg daily in adults and 250 mg/m^2 to 750 mg/m^2 in pediatric patients.

Although assessment of a causal relationship between entrectinib and adverse events (AEs) was somewhat limited in the context of the single

arm design of trials providing safety data, AEs observed in patients treated with entrectinib were consistent with the mechanism of action (multiple kinase inhibition) and toxicities observed in preclinical studies with entrectinib. The most common adverse reactions (≥ 20%) in order of decreasing frequency were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders. The most common laboratory abnormalities ((≥ 20%) worsening from baseline were increased creatinine, anemia, hyperuricemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), hypernatremia, hypocalcemia, hypophosphatemia, neutropenia, increased lipase, hypoalbuminemia, increased amylase, hyperkalemia, and increased alkaline phosphatase.

The primary serious risks of entrectinib are congestive heart failure (CHF), central nervous system (CNS) adverse reactions, skeletal fractures, hyperuricemia, hepatotoxicity, QT prolongation, and vision disorders. These adverse reactions largely appear manageable and reversible with dose modification or discontinuation of entrectinib and are adequately addressed in product labeling. Genentech has committed to post-marketing requirement (PMRs) for the conduct of additional studies to further characterize the risks of congestive heart failure and skeletal fractures with entrectinib and identify ways to mitigate these risks.

A broad spectrum of CNS adverse reactions can occur in patients receiving entrectinib, including impairment in cognitive function or mood, dizziness, and sleep disturbances. These CNS effects appear to be a class effect of TRK inhibitors and were observed in preclinical models.

Among the 355 patients (338 adult and 17 pediatric patients) who received entrectinib across clinical trials, congestive heart failure (CHF) occurred in 3.4% of patients, including Grade 3 (2.3%). In clinical trials, baseline cardiac function and routine cardiac monitoring other than electrocardiograms (ECGs) were not conducted and eligibility criteria excluded patients with symptomatic CHF, myocardial infarction, unstable angina, and coronary artery bypass graft within 3 months of study entry. Genentech is required to conduct a study as a postmarketing requirement to further assess the contribution of entrectinib to cardiac risk and characterize cardiac adverse reactions and risk mitigation strategies.

Entrectinib also increases the risk of skeletal fractures. In an expanded safety population (n=368) of 338 adult patients and 30 pediatric patients who received entrectinib across clinical trials, 5% of adult patients and 23% of pediatric patients experienced fractures. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients, all fractures occurred in patients with minimal or no trauma. Genentech was required to conduct a study as a postmarketing requirement to further assess the risk of fractures with entrectinib and identify ways to mitigate this risk.

Among 355 patients who received entrectinib across clinical trials, 32 patients (9%) experienced symptomatic hyperuricemia. Grade 4

hyperuricemia occurred in 1.7% of patients. Increased AST of any grade occurred in 42% of patients and increased ALT of any grade occurred in 36%. Grade 3 to 4 increased AST or ALT occurred in 2.5% and 2.8% of patients, respectively; the incidence may be underestimated as 4.5% of patients had no post-treatment liver function tests.

Among the 355 patients who received entrectinib across the clinical trials, 2.8% of patients with at least one post-baseline ECG assessment experienced QTc interval prolongation of >60 ms after starting entrectinib and 1.7% had a QTc interval >500 ms. In the QT substudy of STARTRK-2, of 113 patients receiving entrectinib 600 mg daily, there was no large increase in QTc change (i.e., 20 ms) from baseline. Based on QT-IRT review, the data did not support an exposure-response analysis because the exposure range was narrow and the PK/ECG sampling schedule could not be used to evaluate possible PK/PD hysteresis. There is unclear significance of sporadic outliers in an uncontrolled study when the limited QT assessment does not support a large drug-effect. Due to the nature of single arm data, however, prolongation of QT could not be excluded; therefore, the package insert will include language in Warnings and Precautions that patients should be monitored who already have or who are at significant risk of developing QTc interval prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation.

Vision disorders can occur in patients receiving entrectinib. In preclinical studies in rats, microscopic findings of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium were and are considered entrectinib-related. There are no specific findings that suggested vision disturbances had a neurological etiology and vision disorders have been seen in other drugs that affect the ALK pathway, including crizotinib. The spectrum of visual impairment reported were blurred vision, photophobia, diplopia, visual impairment, photopsia, vitreous floaters, vitreous detachment, vitreous adhesions, blindness, corneal erosion, and retinal hemorrhage. The majority of vision disturbances were of low-grade severity and patients were able to continue entrectinib.

The adverse reaction profile is acceptable when assessed in the context of clinical benefit observed (ORR of 78% with at least half of the responses durable for ≥12 months) and the life-threatening nature of metastatic NSCLC (5-year survival <5%). Although entrectinib can cause severe/serious toxicities, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. Entrectinib will be prescribed by oncologists who know how to monitor for, identify and manage such toxicities. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use by either the clinical review team or the Division of Medication Error and Prevention Analysis (DMEPA).

This application is seeking approval of entrectinib for the treatment of *ROS1*-positive NSCLC without contemporaneous approval of a companion diagnostic. The tests used in the three studies were heterogeneous. Given the efficacy of entrectinib in patients with *ROS1* gene

fusion-positive unresectable or metastatic NSCLC, the low prevalence of this subset of NSCLC and the availability of non-companion diagnostic testing for *ROS1* fusions in NSCLC, the clinical review team determined that it is in the best interest of U.S. patients to approve entrectinib before one or more companion diagnostic assays are ready for PMA submission. Since a PMA for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, approved labeling will state that there is no FDA-approved for detection of *ROS1* rearrangement(s) in NSCLC for selecting patients for treatment with entrectinib. Genentech has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect *ROS1* rearrangements for identifying patients who may benefit from entrectinib.

In the opinion of the review team, the submitted evidence meets the statutory evidentiary standard for regular approval. The rarity of *ROS1*-positive NSCLC renders the conduct of a randomized trial not feasible. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with entrectinib is sufficient to establish clinical benefit in the genetically defined, rare subgroup of patients with *ROS1*-positive metastatic NSCLC. Based on these results, the potential for clinical benefit outweighs the risks of entrectinib identified during review of this NDA. The review team's regulatory recommendation is to grant entrectinib regular approval for the following indication: "For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive".

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer-related deaths worldwide and in the US. • Non-small cell lung cancer accounts for 80% -85% of lung cancer patients and adenocarcinoma is the most common histological subtype. The majority of patients present with locally advanced or metastatic disease at the time of diagnosis, which is generally considered incurable. • The incidence of *ROS1* gene fusions in metastatic NSCLC is 1-2%.	Metastatic *ROS1*-positive NSCLC is a life-threatening condition with poor survival.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The 5-year survival for patients with metastatic NSCLC is less than 5%; there is no randomized trial data available regarding survival specifically for patients with *ROS1*-positive metastatic NSCLC.	
Current Treatment Options	• Crizotinib is a kinase inhibitor approved in the US for the treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive and is the preferred first-line treatment for this patient population. Crizotinib was approved in the US based on observation of a high ORR and prolonged DOR in 50 patients with *ROS1*-positive NSCLC treated in a multicenter, single arm study. ORR according to RECIST v1.0 assessed by independent radiology review was 66% (95% CI: 51, 79), and the median DOR was 18.3 months (95% CI: 12.7, not reached; proportion of responders with DOR ≥12 months 64%). • Following progression on crizotinib, treatment options for patients with ROS1-positive NSCLC include regimens used for first-line systemic therapy of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy and/or anti-PD-(L)1 antibody). The highest ORRs, 48% and 58%, have been reported for platinum-based chemotherapy plus pembrolizumab (regardless of histology) and platinum-based chemotherapy plus atezolizumab and bevacizumab (non-squamous NSCLC), respectively.	Crizotinib is the only kinase inhibitor currently approved in the US for the treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive and is the preferred first-line treatment for this patient population. Recommended treatment following progression on crizotinib is with combination therapy (i.e., chemotherapy and/or anti-PD-(L)1 antibody) which are approved as first-line treatment for patients with metastatic NSCLC regardless of the presence of *ROS1* rearrangement, associated with ORR of 48% to 58% at most.
Benefit	• The primary efficacy data supporting this NDA are from a pooled subgroup of 51 patients who received treatment with entrectinib at various doses and schedules (90% received entrectinib 600 mg once daily) in one of three multicenter, single-arm, open-label, dose escalation and/or activity-estimating clinical trials (ALKA, STARTRK-1 and STARTRK-2). This pooled subgroup (referred to hereafter as the primary efficacy set) comprises the first 51 consecutively enrolled patients with *ROS1* fusion-positive (*ROS1*-	The rarity of ROS1-positive NSCLC renders the conduct of a randomized trial not feasible. The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with entrectinib is sufficient to establish clinical benefit in the genetically defined, rare

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	positive), metastatic non-small cell lung cancer (NSCLC) who had not received prior treatment with a ROS1 tyrosine kinase inhibitor (TKI) and had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (v1.1), ECOG performance status (PS) of ≤2, and ≥12 months of follow-up from first post-treatment tumor assessment. • Confirmed ORR per BICR was 78% (95% CI: 65%, 89%), and the estimated median duration of response (DOR) was 15.7 months (95% CI: 11.4, 34.8), with 70%, 55%, and 30% of the 40 responders having observed DOR of at least 9, 12, and 18 months, respectively. • Assessment of the anti-tumor activity of entrectinib in the CNS was pre-specified in the plan for analysis of the pooled dataset, specifically as descriptive analyses of intracranial ORR (IC-ORR) and IC-DOR as secondary endpoints. The primary efficacy set included 7 patients with measurable CNS metastases at baseline per BICR who had not received radiation to the brain within 2 months of first dose of entrectinib, and 5 of these patients had confirmed IC response. Given the limited number of patients, the point estimate for these results needs to be interpreted with caution. • This application is seeking approval of entrectinib for the treatment of *ROS1*-positive NSCLC without contemporaneous approval of a companion diagnostic. The tests used in the three studies were heterogeneous.	subgroup of patients with ROS1-positive metastatic NSCLC. The magnitude of the ORR was sufficiently large to overcome the uncertainty inherently related to results from a pooled efficacy analysis of data from three single arm trials. While the point estimate of the results of the descriptive analyses of IC-ORR and IC-DOR need to be interpreted with caution given the limited number of patients, the results do support a conclusion that entrectinib has anti-tumor activity in the CNS in patients with *ROS1*-positive NSCLC with brain metastases. Given the efficacy of entrectinib in patients with *ROS1* gene fusion-positive unresectable or metastatic NSCLC, the low prevalence of this subset of NSCLC and the availability of non-companion diagnostic testing for *ROS1* fusions in NSCLC, the clinical review team determined that it is in the best interest of U.S. patients to approve entrectinib before one or more companion diagnostic assays are ready for PMA submission. Since a PMA for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, approved labeling will state that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		there is no FDA-approved for detection of *ROS1* rearrangement(s) in NSCLC for selecting patients for treatment with entrectinib. Genentech has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect *ROS1* rearrangements for identifying patients who may benefit from entrectinib.
Risk and Risk Management	• The safety population included 355 patients, including 49% of patients exposed for greater than 6 months and 24% of patients exposed for greater than 1 year. • Central nervous system (CNS) toxicity, congestive heart failure (CHF), skeletal fractures, QT prolongation, and vision disorders are the primary safety risks identified for entrectinib. Hyperuricemia and transaminase elevations, although generally mild, can also occur. Uric acid should be monitored in patients receiving entrectinib. • The most common adverse reactions (≥ 20%) in order of decreasing frequency were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, pain, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders. • Serious adverse reactions including fatal events occurred in 39% of patients. The most frequent serious adverse reactions (≥2%) were pneumonia, dyspnea, pleural effusion, sepsis, pulmonary embolism respiratory failure, and pyrexia.	While entrectinib can cause severe/serious toxicities, these safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. Entrectinib will be prescribed by oncologists who know how to monitor, identify, and manage such toxicities. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Grade 3 or 4 adverse reactions occurred in 60% of patients; the most common were lung infection, increased weight, dyspnea, fatigue/asthenia, cognitive disorders, syncope, pulmonary embolism, hypoxia, pleural effusion, hypotension, diarrhea, and urinary tract infection.	

1.4. 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			
			X	Patient reported outcome (PRO)	Section 8.2.3 Efficacy Results – Secondary and Other Important Endpoints Section 19.5 Additional Clinical Outcome Assessment Analyses
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

Cross-Disciplinary Team Leader
Erin Larkins, MD

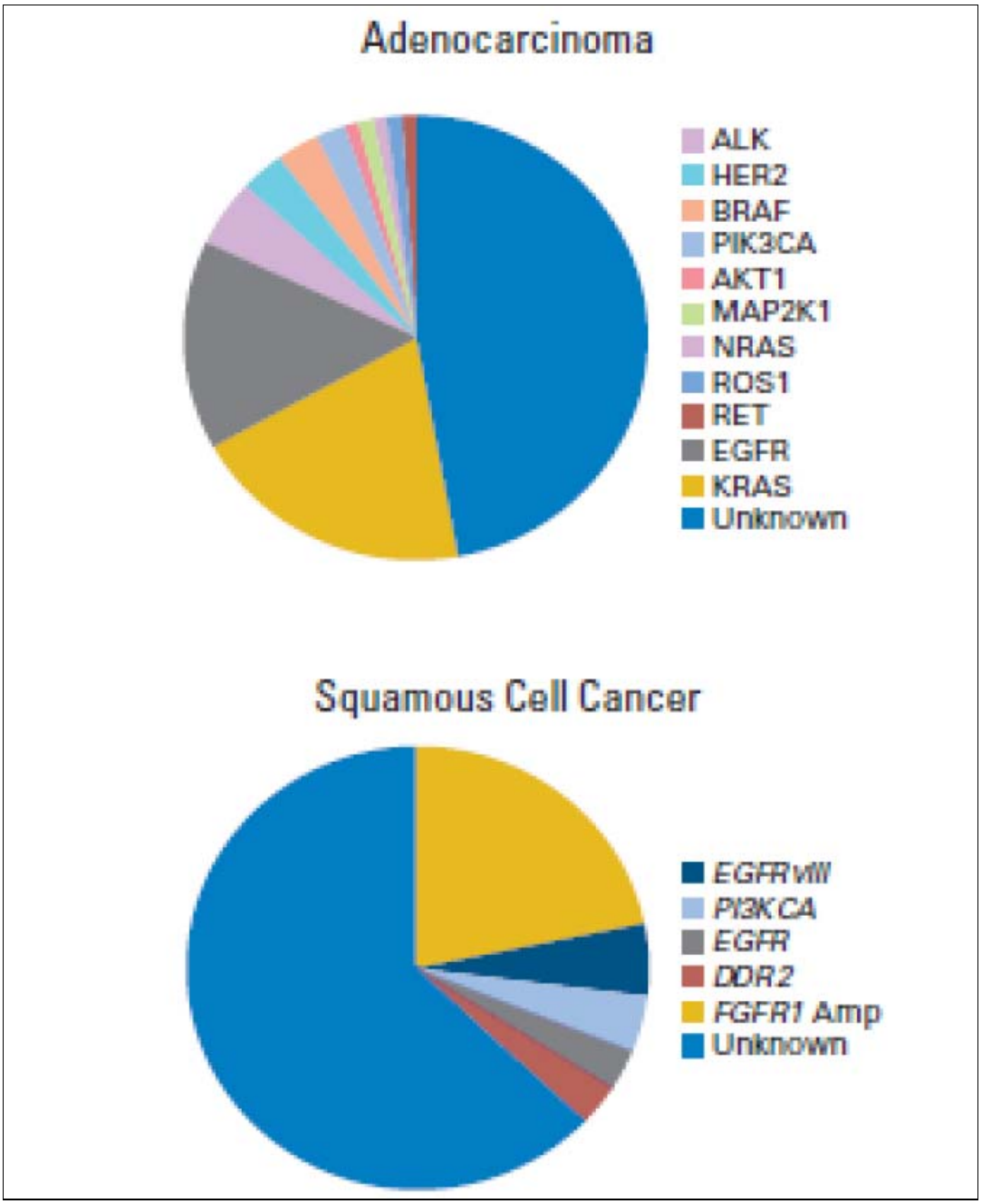
2 Therapeutic Context

2.1. Analysis of Condition

Lung cancer is the leading cause of cancer-related deaths worldwide and in the US, with an estimated 234,030 new cases of lung and bronchial cancers and 154,050 deaths due to lung cancer estimated to occur in 2018[1,2]. NSCLC accounts for 80% of lung cancers and adenocarcinoma is the most common histological subtype[3]. The majority of patients present with locally advanced or metastatic disease at the time of diagnosis, which is generally considered incurable. The anticipated 5-year survival for patients with clinical stage IIIB NSCLC is approximately 26% and is less than 5% for patients who present with clinical stage IV disease[4].

Prior to the integration of immunotherapy and targeted therapy into the treatment of these patients, platinum-based combination chemotherapy was the preferred front-line therapy for metastatic NSCLC. The median OS for patients receiving platinum-based combination chemotherapy ranges from 8 to 12 months[5]. With the advent of targeted therapeutic approaches, a number of novel agents such as monoclonal antibodies, antibody directed conjugates and small molecule kinase inhibitors have been developed to target specific molecular aberrations.[5,6] Those patients whose tumors harbor driver mutations such as epidermal growth factor receptor (*EGFR*) activating mutations, *ALK* rearrangements and *ROS1* fusions, found in approximately 10% , 3% and 1-2% of patients with NSCLC (Figure 2), respectively, are sensitive to specific oral targeted therapies.[7] EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib and afatinib, osimertinib are FDA-approved for patients with sensitizing *EGFR* mutations (present in about 20% of patients with adeno NSCLC).[8,9,10,11] Crizotinib, ceritinib, alectinib and lorlatinib are FDA-approved for patients with NSCLC whose tumors harbor *ALK* rearrangements (present in about 5% of adenocarcinoma NSCLC).[12,13,14,15] Crizotinib is the only drug FDA-approved specifically for the treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive.[12]

Figure 2: Proportion of Specific Molecular Alterations in Adenocarcinoma and Squamous Cell NSCLC[7]

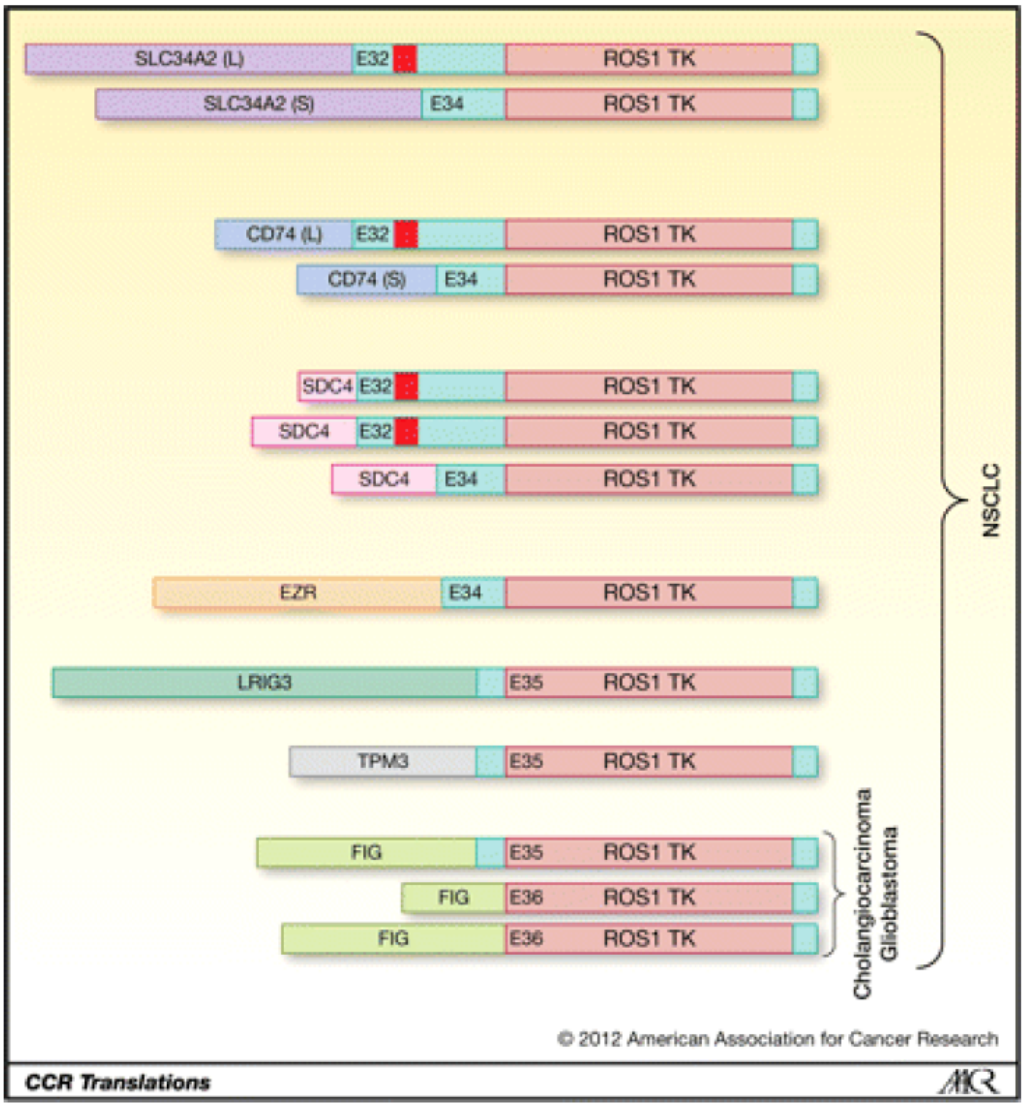


The *ROS1* oncogene encodes an orphan receptor tyrosine kinase (related to ALK) which is not usually expressed in normal lung tissue and its true wild-type function is unknown. The *ROS1* oncogene is activated by chromosomal rearrangements specifically seen in certain tumor types such as NSCLC, cholangiocarcinoma and a variety of other cancers[16]. Rearrangements within the *ROS1* gene leads to fusion of a portion of ROS1 with 1 of 12 different partner proteins.[17] The resulting ROS1 fusion kinase is thought to directly or indirectly regulate downstream pathways

such as RAS-MAPK, PI3K-AKT, and STAT3.[18] Unlike ALK, which becomes activated by dimerization of the partner gene, it is unknown how the ROS1 receptor is activated and the contribution of the partner fusion gene.

Unlike *ALK*-positive NSCLC where the most common partner fusion genes are *EML4*, many fusion partners have been identified in *ROS1* NSCLC including *FIG, SLC34A2, CD74, TPM3, SDC4, EZR, LRIG3, KDELR2*, and *CCDC6*. Figure 3 shows the *ROS1* fusions identified to date, but it is likely more will be identified in the future. Most of the rearrangements identified are inter-chromosomal except for FIG which is a deletion.[19]

Figure 3: *ROS1* Fusion Partners in NSCLC[19]



Interestingly, *ROS1* fusions have been identified at an even greater frequency in cholangiocarcinoma along with ovarian, gastric, and colorectal cancers.[20] There have been

three main studies which describe the incidence of *ROS1* rearrangements in patients with NSCLC. The three different studies (3,000 total patient cases) have found the incidence to be between 0.9% and 1.7%.[21] Additionally, *ROS1* rearrangements in NSCLC mostly occur in adenocarcinoma. Similar to patients with *ALK*-positive NSCLC, more patients with *ROS1*-positive NSCLC are younger and never smokers compared to the general population of patients with NSCLC. At the genetic level, *ALK* and *ROS1* rearrangements rarely occur in the same tumor and each define a unique molecular subgroup of NSCLC.

2.2. Analysis of Current Treatment Options

Crizotinib is the only kinase inhibitor currently approved in the US for the treatment of patients with metastatic NSCLC whose tumors are *ROS1*-positive. Crizotinib was approved in the US based on observation of a high ORR and prolonged DOR in 50 patients with *ROS1*-positive NSCLC treated in a multicenter, single arm study. ORR according to RECIST v1.0 assessed by independent radiology review was 66% (95% CI: 51, 79), and the median DOR was 18.3 months (95% CI: 12.7, not reached). The approval of the companion diagnostic for crizotinib, the Oncomine Dx assay by Thermo Fisher, occurred after initial approval of crizotinib for the ROS1 indication.[22]

Table 1: Currently Available Treatments for First-Line Treatment of Metastatic *ROS1*-Positive NSCLC

Product (s) Name	Approval Year	Indication	Efficacy Information
Crizotinib[12,22]	2016	*ROS1*-positive metastatic NSCLC	**Single arm, multicenter trial** **ORR by IRR:** 66% (95% CI 51, 79) **Median DOR**: 18.3 months (12.7, NR) **Responders with DOR ≥6 months:** 85% **Responders with DOR ≥12 months:** 64%
Available treatments for patients with NSCLC regardless of presence of ***ROS1*** rearrangement			
Pembrolizumab + pemetrexed and platinum chemotherapy (KN-189)[23]	2017 (AA) 2018 (RA)	metastatic non-squamous NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations	**Control: pemetrexed + platinum chemotherapy** **Median OS:** NR vs 11.3 months, HR 0.49 **Median PFS** 8.8 vs 4.9 months, HR 0.52 **ORR**: 48% (43, 53) vs 19% (14, 25) **Median DOR**: 11.2 vs 7.8 months
Pembrolizumab + carboplatin and paclitaxel or paclitaxel protein-bound (KN-407)[23]	2018	metastatic squamous NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations	**Control: placebo + carboplatin + paclitaxel or paclitaxel protein-bound** **Median OS:** 15.9 vs 11.3 months, HR 0.64 **Median PFS:** 6.4 vs 4.8 months. HR 0.56 **ORR**: 58% (48, 68) vs 35% (26, 45) **Median DOR**: 7.2 vs 4.9 months
Pembrolizumab as a single agent (KN-042)[23]	2019*	advanced NSCLC expressing PD-L1 (Tumor Proportion Score [TPS] ≥1%), with no *EGFR* or *ALK* genomic tumor aberrations	**Control: carboplatin + pemetrexed or paclitaxel** **Median OS** 16.7 vs 12.1 months, HR 0.81 **Median PFS:** 5.4 vs 6.5 months, HR 1.07 **ORR:** 27% (24, 31) vs 27% (23, 30) **Responders with DOR ≥12 months:** 47% vs 16% **Responders with DOR ≥18 months**: 26% vs 6%
Atezoluzimab + bevacizumab, paclitaxel, and carboplatin (IMpower150)[24]	2018	metastatic non-squamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations	**Control: bevacizumab + paclitaxel + carboplatin** **Median OS:** 19.2 vs. 14.7 months, HR 0.78 **Median PFS:** 8.5 vs. 7.0 months, HR 0.71 **ORR:** 55% (49, 60) vs. 42% (37, 48) **Median DOR:** 10.8 vs 6.5 months

*AA in 2016 and RA in 2017 for metastatic NSCLC expressing PD-L1 (TPS ≥50%), with no *EGFR* or *ALK* genomic tumor aberrations
AA, accelerated approval; IRR, independent radiology review; RA, regular approval

The toxicity profile of platinum-based combination chemotherapy is well characterized, with common toxicities including myelosuppression, fatigue, nausea, and vomiting. The primary toxicities of concern for pembrolizumab and atezolizumab are immune-related adverse reactions.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Entrectinib is a new molecular entity (NME) that is not currently marketed in the U.S. and has not been approved for any indication by FDA.

3.2. Summary of Presubmission/Submission Regulatory Activity

Following receipt of final written responses for a Type B pre-IND meeting on December 4, 2013, regarding the design of the first-in-human trial of entrectinib (STARTRK-1) under IND 120500, the original IND was submitted on February 27, 2014. The regulatory history prior to submission of NDA 212725 is summarized in Table 2.

Table 2: Regulatory History

Date	Regulatory History
February 3, 2014	Final written response issued in response to a pre-IND meeting request (IND 120500) seeking feedback on the design of the first-in-human trial of entrectinib (STARTRK-1).
February 27, 2014	Ignyta, Inc. (Ignyta) submitted IND 120500.
February 3, 2015	Entrectinib received orphan drug designation for treatment of *TrkA*-positive, *TrkB*-positive, *TrkC*-positive, *ROS1*-positive or *ALK*-positive NSCLC under IND 120500.
February 17, 2015	Meeting minutes issued for a Type B meeting under IND 120500, held on January 29, 2015, to discuss the overall design of two proposed studies: • STARTRK-2, proposed as a multicenter, single-arm study of entrectinib in any line in patients with crizotinib-naïve ROS1 or TrkA/B/C rearranged advanced NSCLC • STARTRK-3, proposed as a randomized, multicenter study comparing entrectinib versus docetaxel as second-line treatment for patients with ROS1 or TrkA/B/C rearranged advanced NSCLC
October 21, 2015	Meeting minutes issued for a Type B EOP1 meeting under IND 120500, held on September 22, 2015, to discuss STARTRK-2, entitled "An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements," and to discuss Ignyta's overall clinical development plan.

Date	Regulatory History
November 10, 2016	Ignyta Trailblaze Pharos Assay received Expedited Access Pathway (EAP) designation from FDA (under IND 120500).
May 3, 2017	Ignyta submitted IND 135124 to serve as the IND for the development program for entrectinib for *ROS1* fusion-positive NSCLC.
May 23, 2017	Preliminary Breakthrough Therapy Designation Request (BTDR) Advice teleconference was held in response to a May 5, 2017 Request for Preliminary BTDR Advice for *ROS1*-positive NSCLC. FDA stated that the data provided did not meet criteria for BTD.
July 26, 2017	Final written responses were issued in response to a Type C meeting request seeking feedback on the acceptability of the proposed integrated efficacy and safety analyses to support a planned NDA for the proposed indication of the treatment of patients with *ROS1* fusion-positive, (b) (4) metastatic NSCLC. FDA stated patients included in the efficacy analysis population should have a minimum of 12 months follow up from the onset of response.
December 11, 2017	BTDR was submitted for entrectinib for the treatment of *ROS1* fusion-positive locally advanced or metastatic NSCLC. An informal teleconference was held between FDA and Ignyta on December 15, 2017 to discuss the data proposed to support the BTDR. FDA stated that the data were not consistent with preliminary clinical evidence indicating that entrectinib may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapy.
December 18, 2017	Ignyta withdrew the December 11, 2017 BTDR submission.
June 12, 2018	Ignyta transferred sponsorship of IND 135124, and all rights and responsibilities related to the IND application to Genentech.
June 25, 2018	Preliminary BTDR Advice teleconference in response to an April 27, 2018 Request for Preliminary BTDR Advice for *ROS1*-positive NSCLC. FDA stated that the data provided did not meet criteria for BTD.

Date	Regulatory History
Nov 6, 2018	Meeting minutes were issued for a Type B pre-NDA meeting, held on October 18, 2018, for the *ROS1*-positive NSCLC indication. Following FDA's recommendation from the July 26, 2017 Type C meeting that patients included in the efficacy analysis population should have a minimum of 12 months follow-up from the onset of first response, Genentech proposed a primary analysis population comprising 53 patients with measurable disease at baseline and a minimum follow-up of 12 months from the onset of response. Agreement was reached that results and data would also be included in the NDA for patients with non-measurable disease and for patients with <12 months follow-up past onset of response.
Nov 26, 2018	Meeting minutes were issued for a CMC only meeting, held on November 7, 2018, to discuss the data to be presented in the future NDAs, including that to support the selection of the solid form for launch of entrectinib, and to capture agreements regarding the contents of a complete application under the PDUFA VI Program for the two NDAs to be submitted for entrectinib.
December 18, 2018	NDA 212725 was submitted (NDA 212726 for *NTRK* fusion-positive solid tumors was submitted on the same day).
February 13, 2019	FDA issued a Priority Review Designation letter.
March 1, 2019	FDA issued a Filing Communication outlining the filing review issues identified.
March 13, 2019	Meeting minutes were issued for the Mid-cycle communication meeting, held on March 18, 2019. Issues discussed included the financial disclosure information, the efficacy evaluable population, and postmarketing requirements (PMRs) and postmarketing commitments (PMCs).
May 13, 2019	The proposed proprietary name, ROZLYTREK, was conditionally accepted.
July 15, 2019	Meeting minutes were issued for the Late cycle meeting, held June 17, 2019. Key review issues discussed included substantive review issues related the new safety data submitted on two pediatric patients with femoral neck fractures. Issues related to ROZLYTREK labeling, and PMRs and PMCs were also discussed.

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

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigations (OSI) to perform an audit of 4 clinical trial sites (Site #19011: Dr. Alexander Drilon and Site #19022: Dr. Robert Doebele, Site #14001, Dr Byoung Chul Cho, and Site #013, Dr. Jeeyun Lee), and the contract research organization (CRO) that performed blinded central review of imaging (b) (4) to identify any issues that could affect the quality and interpretation of the data submitted with these applications regarding the clinical trials, ALKA, STARTRK-1/RXDX-101-01, STARTRK-2/RXDX-101-02, STARTRK-NG/RXDX-101-103. DOP2, in consultation with OSI, selected these clinical sites for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, and patterns of serious adverse event (SAE) reporting. Specifically, the sites were selected based on high enrollment and treatment efficacy, and the fact that they had not been inspected by FDA recently. The final compliance classification for these inspections is No Action Indicated (NAI). OSI concluded that the data submitted by Genentech to support NDA 212726 appear reliable based on information from the inspections.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) did not identify any product quality issues that would preclude approval of entrectinib capsules under NDA 212726 or NDA 212725.

Entrectinib is a small molecule new molecular entity with the molecular formula of C31H34F2N6O2 and the molecular weight of 560.64 Daltons.

Entrectinib is an achiral, white to (b) (4) pale pink crystalline powder (b) (4). Entrectinib is a free base with the melting point between 198.2 to 200.7°C. Entrectinib is non-hygroscopic and shows an exponential increase in aqueous solubility in acidic media compared to neutral conditions, which is indicative of a potential food effect. However, the pivotal clinical formulation (F2A) and the proposed to-be-marketed commercial formulation (F06) include an (b) (4). The clinical study, RXDX- 101-15 established BA/BE between F2A and F06 formulations and the absence of food effect on in vivo exposure with F06 formulation, which is reviewed by clinical pharmacology review team.

Entrectinib is considered as a Biopharmaceutics Classification System (BCS) Class 2 compound with low solubility and low-moderate permeability. Entrectinib exhibits polymorphisms with Form A being selected for development and for use in the commercial drug product.

The proposed commercial drug product is an immediate-release hard Hypromellose (HPMC) capsule containing 100 mg and 200 mg of entrectinib for oral administration.

- Entrectinib 100 mg capsule is a size 2, 2-piece capsule with yellow opaque body and cap with ENT 100 imprinted in blue on the body and is packaged in (b) (4) HDPE bottle with 30 capsule counts.
- Entrectinib 200 mg capsule is a size 0, 2-piece capsule with orange opaque body and cap with ENT 200 imprinted in blue on the body and is packaged in (b) (4) HDPE bottle with 90 capsule counts.

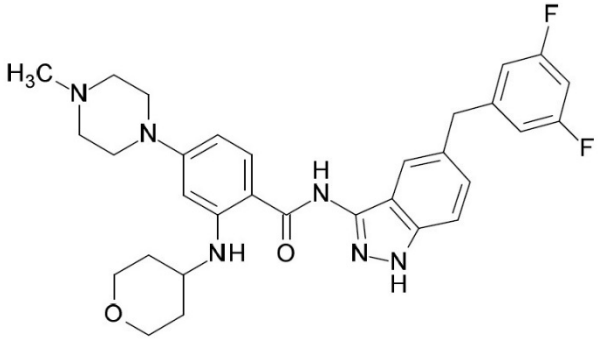
(b) (4)

The drug products are packaged in HDPE bottle with (b) (4) (b) (4) caps.

Drug Substance

The entrectinib drug substance (DS) has the following chemical name, structural formula, molecular formula, and molecular weight.

Figure 4: Entrectinib Structure and Chemical Name



Chemical Name: *N*-{5-[(3,5-difluorophenyl)methyl]-1*H*-indazol-3-yl}-4-(4- methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide
Mol. Formula: $C_{31}H_{34}F_2N_6O_2$ Mol. Wt.: 560.64 g/mol

The drug substance is manufactured (b) (4) (b) (4) (b) (4). The CMC review team determined that the proposed starting materials are acceptable and that the control strategy (b) (4) appears to ensure the impurity profile of the drug substance.

The drug substance (DS) specification for entrectinib includes the following critical quality attributes (CQAs): appearance and color by visual inspection, identification by HPLC, IR, and

XRPD (b) (4) impurities (organic impurities by HPLC and residual solvents by HS-GC), assay by HPLC, particle size by laser diffractometry, (b) (4) by ICP-MS per USP <232>, and residue on ignition per USP <281>.

Specified and unspecified impurities are controlled to the ICH Q3A qualification and identification thresholds, respectively. A total of seven compounds were identified as genotoxic or potentially genotoxic in accordance with the classification scheme outlined in ICH M7. All other compounds that underwent the assessment belong to Class 5 after being tested in silico negative using two orthogonal methods, or after Ames-negative testing following a positive in silico result in at least one of the two in silico methods. A thorough analysis of the clinical batches and of purging studies found only negligible amounts of the genotoxic impurities. Therefore, no specific controls are included in the drug substance specification for potential or known genotoxic impurities except for benzene.

(b) (4)

The NDA submission included batch analyses data for 28 DS batches including the development, clinical, toxicology, stability, and commercial batches. The CMC review team determined that the batch analyses data conformed to the proposed DS specification for commercial, primary stability, and late clinical batches. Twelve months of primary stability data were available for four DS batches. In addition, up to 24 months of supportive stability data were also provided. The container closure system used for these batches was representative of the proposed commercial packaging to support the proposed retest period of (b) (4) months while store at no more than (b) (4) in the proposed container closure system (b) (4) Forced degradation study showed that entrectinib is not sensitive to the combination of elevated temperature, thermal, light, and humidity conditions. It is however, unstable under acidic, basic, and oxidative conditions.

Twelve months stability data on four primary stability batches supports an initial retest period of (b) (4) months for entrectinib DS while (b) (4) in the proposed container closure system.

Drug Product [Entrectinib Capsules, 100 and 200 mg]

The proposed commercial drug product (DP) is an immediate-release hard Hypromellose (HPMC) capsule containing 100 mg and 200 mg of entrectinib for oral administration.
The two strengths are visually distinguishable by size, color, and script. The excipients are all compendial or composed of compendial components. Excipient of animal origin (lactose) is supported by BSE/TSE compliance statements. These excipients have all been used in approved drug products at levels greater than proposed in the current product.

There are no overages in the drug product.

The proposed commercial formulation is an immediate-release hard capsule for oral administration manufactured with standard excipients using conventional equipment and manufacturing process. The intended market formulation (F06) is designed to be equivalent to the clinical formulation (F2A) and enable a robust commercial-scale manufacturing process using compendial excipients. Bioequivalence between the market (F06) and pivotal (F2A) formulations was demonstrated.

The drug product commercial manufacturing process (b) (4) (b) (4). The composition of the 100 mg and 200 mg capsule (b) (4) use the same commercial manufacturing process. (b) (4) (b) (4) (b) (4). The proposed commercial batch size for the 200 mg and 100 mg doses is (b) (4) for both strengths. (b) (4) (b) (4) (b) (4)

Genentech provided 12 months primary stability data at 30oC/65%RH and 6 months primary stability data at 40oC/75%RH for three primary batches of each entrectinib capsules, 100 mg and 200 mg, manufactured at the intended commercial manufacturing site (Mayne Pharma) and packed at Mayne Pharma. Genentech also provided 6 months supportive site-specific stability data at 30oC/75%RH and 6 months stability data at 40oC/75%RH for three batches of each entrectinib capsules, 100 mg and 200 mg, manufactured at the intended commercial bulk manufacturing site (b) (4) and packed at the commercial packaging site (Roche Kaiseraugst).

All batches were tested for stability indicating parameters (description of capsule and capsule content, content per capsule of entrectinib, degradation products, (b) (4) dissolution, and microbial limits). All stability data show that there is no apparent change of quality attributes on long-term (30°C/65% RH or 30°C/75% RH) or accelerated stability (40°C/75% RH). On the basis of 12 months long-term stability data for the registration stability batches, a 24-month shelf life is granted when the product is stored below 30°C (86°F).

Both photo-stability and in-use stability to simulate the actual use of the product were also provided with no significant changes/trends noted. Thus, no stated in-use period is necessary in the labeling.

The Quality review team recommended that the drug product be granted a 24-month shelf life when stored below 30°C (86 °F)

Pursuant to 21 CFR 25.31(b), Genentech submitted a request for Categorical Exclusion from the requirement to prepare an environmental assessment for entrectinib. OPQ granted the request for a waiver from an environmental analysis since this product is indicated for an orphan population and quantities entering the aquatic environment will be exceptionally low (below 1 part per billion). No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

Facility Evaluation

The Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

(b) (4)

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug product manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

(b) (4)

- F. Hoffmann-La Roche Ltd. (FEI #: 3002807200) in Basel, Switzerland
- F. Hoffmann-La Roche Ltd. (FEI #: 3003973536) in Kaiseraugst, Switzerland

Biopharmaceutics Evaluation

Biopharmaceutics review evaluated 1) the proposed dissolution method, 2) the proposed dissolution acceptance criterion, 3) the need for bridging the different formulations and packaging site throughout the product development stage, and 4) the biowaiver request for the 100 mg F06 to-be-market drug product.

The dissolution profile data for various testing parameters and discriminating ability of the proposed dissolution method below was determined to be acceptable as a quality control tool for batch release and stability testing of the 100 mg and 200 mg entrectinib capsules.

The proposed acceptance criterion of "Q (b) (4) % in 60 minutes" for batch release and on stability for the proposed drug product based on the bio-batch, clinical, and stability batches was also determined to be acceptable.

The comparative dissolution profiles using the proposed dissolution method and f2 similarity analysis with f2 value (50.51) > 50 indicates that three registration batches of the 100 mg and

200 mg F06 drug product manufactured (b) (4) and packaged (b) (4) and Roche Kaiseraugst are similar and provide a bridge between the two packaging sites.

The biowaiver request for the 100 mg F06 drug product was granted based on 1) the compositional proportionality between the 100 mg and 200 mg strength drug product with respect to entrectinib, the active pharmaceutical ingredient (API) and excipients; 2) bioequivalence between the 200 mg F06 and F2A drug products in the bioequivalence (BE) study RXDX-101-15; 3) linear pharmacokinetics of the F06 drug product between the dose ranges of 100 mg - 600 mg under fasted condition based on the bioavailability study RXDX-101-12; and 4) similarity in the dissolution profile data for the 100 mg and 200 mg F06 drug product.

4.3. Clinical Microbiology

The application was reviewed by OPQ's Division of Microbial assessment. The reviewers did not identify any issues that would preclude approval of entrectinib capsules under NDA 212726 or NDA 212725. CMC microbiology reviewers determined that the microbiology controls for the entrectinib solid dosage form was adequate. Due to the controls on raw materials, dry manufacturing process, and manufacturing site inspection history, microbial limits testing was deemed unnecessary.

4.4. Devices and Companion Diagnostic Issues

This application is seeking approval of entrectinib for the treatment of *ROS1*-positive NSCLC without contemporaneous approval of a companion diagnostic. The tests used in the three studies were heterogeneous. Genentech has been working with Foundation Medicine (FM1), who is developing a next generation sequencing (NGS) platform which will detect multiple types of driver mutations in NSCLC and intends for this to eventually serve as the companion diagnostic test for entrectinib. FM1's current target date for submission of a premarket application (PMA) for such a companion diagnostic is end of Q4 2019. Center for Devices and Radiologic Health (CDRH) was consulted by the review team and was involved in discussions with the Genentech regarding the plans to develop a companion diagnostic for the proposed indication.

Among the 51 patients with *ROS1*-positive NSCLC included in the primary efficacy analysis population, 27 patients (53%) were enrolled based on genomic alterations in tumor samples determined by RNA-based NGS, seven (14%) by DNA-based NGS, two (4%) by DNA and RNA-based NGS, and 15 (29%) by fluorescence in situ hybridization (FISH). The fusion partner was unknown in 12 patients enrolled by FISH; for the three other patients enrolled based on FISH results, tumor tissue was retested with RNA-based NGS and the fusion partner was identified. No tissue is available for retesting of any samples.

Given the efficacy of entrectinib in patients with *ROS1* gene fusion-positive unresectable or metastatic NSCLC, the low prevalence of this subset of NSCLC (1-2% of all NSCLC) and the availability of non-companion diagnostic testing for *ROS1* fusions in NSCLC, the clinical review

team determined that it is in the best interest of U.S. patients to approve entrectinib before one or more companion diagnostic assays are ready for PMA submission. Since a PMA for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, approved labeling will state that there is no FDA-approved for detection of *ROS1* rearrangement(s) in NSCLC for selecting patients for treatment with entrectinib. Genentech has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect *ROS1* rearrangements for identifying patients who may benefit from entrectinib.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Entrectinib (RXDX-101) is a small molecule drug with an established pharmacological class of kinase inhibitor. In biochemical assays, entrectinib inhibited wild-type tropomyosin receptor kinases (TRK) A, B, and C, ROS proto-oncogene1 (ROS1), and anaplastic lymphoma kinase (ALK) proteins at inhibitory concentrations (IC_{50}) between 0.057 and 3.55 nM, with M5, the major human metabolite of entrectinib, having activity at similar inhibitory concentrations ranging from 0.007 to 6.97 nM. These concentrations are clinically achievable based on a maximum concentration (Cmax) of 3130 nM in patients treated at the once daily oral dose of 600 mg and >99% protein binding (~30 nM free entrectinib). In a second biochemical assay, entrectinib inhibited ALK, TRKA, and ROS1, as well as JAK2, ACK1, and JAK1 at IC_{50} values ranging from 0.019 to 0.164 µM.

TrkA, TrkB, and TrkC are encoded by the neurotrophic tyrosine receptor kinase [NTRK] genes *NTRK1, NTRK2,* and *NTRK3,* respectively. ROS1 is encoded by the gene *ROS1* and ALK is encoded by the gene *ALK*. *NTRK*, *ROS1*, and *ALK* gene fusions resulting from chromosomal rearrangements can generate novel fusion oncoproteins that act as dominant drivers of tumorigenesis. Activation of the endogenous proteins occurs upon binding of ligands to the extracellular domains of the receptors, leading to receptor dimerization, phosphorylation, and signaling via the Ras/MEK/ERK, PI3K/AKT, and PLC-γ pathways; fusion proteins from gene rearrangements often lead to constitutive activation of the resulting proteins in the absence of ligand binding. Genentech conducted additional studies investigating the activity entrectinib and M5 against TRKs, ROS1, and ALK. In cellular anti-proliferation assays, entrectinib and M5 had IC_{50} values of less than 1 µM against 14 cell lines: five with *NTRK* fusions, four with *ROS1* fusions, and five with *ALK* dysregulation. The IC_{50} values for entrectinib inhibition of proliferation in cells overexpressing *NTRK* or *ROS1* fusions ranged from 0.37 to 20.1 nM. Evaluation of the mechanism of action in cells with TRK, ROS1, or ALK fusion proteins indicated that both entrectinib and M5 led to inhibition of downstream signaling pathways and induced cellular apoptosis.

Entrectinib showed in vivo antitumor activity in *NTRK*, *ROS1*, and *ALK* fusion-driven xenograft tumor models, leading to tumor growth inhibition (TGI) and tumor regressions in multiple tumor types expressing these fusions, including non-small cell lung carcinoma (NSCLC). Entrectinib was also able to inhibit tumor growth of *NTR*K and *ALK* fusion lines in intracranial implantation models, suggesting that therapeutic concentrations of entrectinib can reach the brain, and consistent with the finding that both entrectinib and M5 had significant distribution to the brain in rats (up to 60% of the plasma concentration following a single IV infusion) and dogs (approximately equal to the plasma concentrations in the one-month toxicology study).

Genentech evaluated the safety of entrectinib in toxicology studies of up to 13 weeks' duration in rats and dogs. In both species, in the one-month studies at doses that resulted in exposures ≥ human exposures at the 600 mg dose (~48 µM*hr), there was evidence of central nervous system (CNS) toxicity characterized by abnormal gait and lack of coordination, decreased activity, tremors, depression, decreased grip strength and impaired righting reflex. Based on the roles of the TRK proteins in multiple aspects of neurologic function, CNS effects are consistent with the expected pharmacological activity of entrectinib and occur clinically as well. In addition, in a secondary pharmacology screening assay, entrectinib had potential activity against other receptors that could contribute to CNS effects. As Genentech conducted these preliminary assessments at concentrations that are significantly higher than those that are clinically relevant, FDA requested a PMR for a follow-up assays to determine the potential for contribution of other targets to the toxicity of entrectinib. There was also evidence of anemia in both species accompanied by increased spleen weight and reticulocytes and, in the rat, extramedullary hematopoiesis. Anemia occurs clinically as well.

In the rat, the skin was a major target organ, with early deaths in the 13-week study attributable to skin lesions (sores/ulcerative dermatitis) at doses ≥15 mg/kg/day (approximately 0.3 times the human exposure by AUC at the 600 mg dose). Trk-deficient mice exhibit defective nociception (Smeyne et al., 1994), suggesting that there is a potential pharmacologically-mediated decrease in sensitivity to bodily damage that may contribute to the poor skin condition in rats. Increased neutrophils, likely associated with skin infections, also occurred. In addition, there was evidence of very mild phototoxicity with entrectinib in both in vitro and in vivo assays. Rash is a common finding clinically. In the in vivo phototoxicity assay, Genentech reported entrectinib-related findings of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium at 200 mg/kg, consistent with corneal opacity that occurred in 1-month studies in rats at exposures similar to the clinical dose. Ocular disturbances are a common clinical finding with entrectinib. Finally, consistent with literature reporting hyperphagia and obesity in mice that express reduced amounts of TrkB (Xu et al, 2003) and in a human with a missense mutation in *NTRK2*, the gene encoding TrkB (Yeo et al., 2004), in the 13-week study, entrectinib-treated male rats demonstrated increased food consumption.

In the 13-week dog study, there were no treatment-related deaths. The gastrointestinal tract was a target organ with clinical signs included discolored/liquid/mucoid feces and weight loss accompanied by dosing holidays and a need for canned food supplementation at the high dose level of 30 mg/kg (~0.16 times the human exposure at the 600 mg dose), as well as hypophosphatemia. Diarrhea, nausea, and hypophosphatemia occur frequently in entrectinib-treated patients. In the same study, multiple animals at dose levels ≥7.5mg/kg/day (~ 0.04 times the human exposure at the 600 mg dose) experienced footpad injuries and related skin complications (sores, scabs, swollen/discolored areas). In addition, animals at the 30 mg/kg dose level exhibited a trend towards QTc prolongation. QTc prolongation occurred more clearly in the 4-week repeat-dose study and single-dose study in dogs treated with 120 mg/kg entrectinib (3.2 times the human exposure by AUC at the 600 mg dose). These findings were

consistent with in vitro effects of entrectinib on hERG inhibition (IC_{50} of 0.6 µM) and clinical reports of QTc prolongation.

Although not typically recommended for drugs intended for the treatment of children with advanced cancer, Genentech also performed a study to evaluate the effect of entrectinib administration in juvenile rats. Animals received entrectinib at doses of 4, 8, or 16 mg/kg/day (approximately 0.06, 0.14, and 0.18 times the human exposure by AUC at the 600 mg dose at the end of the dosing period) between postnatal days 7-97, corresponding to the neonatal through young adult stages. Three preterm deaths associated with CNS toxicity occurred at the high dose. Two deaths (1 high dose, 1 low dose) were associated with kidney toxicity and one death (high dose) was accompanied by skin toxicity. Entrectinib caused dose-dependent delays in development including decreases in the rate of weight gain in all male dose groups and the high-dose females, growth rate (as measured by femur length), and delays in sexual maturation (statistically significant for all dose groups in both sexes). In juvenile animals, CNS-related toxicity was clear and included clinical signs of abnormal gait, tremors, decreased activity, convulsions, hunched posture, repetitive behavior, partly closed eyes, and piloerection. In addition, in high-dose animals there were decreases in forelimb and hindlimb grip strength as well as deficits in spatial learning and memory. The impairment in memory is consistent with known effects of TrkA signaling deficiencies in humans associated with the rare recessive disorder, congenital insensitivity to pain and anhidrosis (Indo et al., 1996). Other clinical signs included dehydration (seen in humans), skin scabs, and thin/lost fur. Consistent with studies in adult rats, dogs, and humans, entrectinib resulted in decreases in red blood cells, hemoglobin, and hematocrit, accompanied by increased spleen size and extramedullary hematopoiesis.

Genentech did not conduct carcinogenicity or fertility studies with entrectinib and, consistent with ICH S9, these studies were not warranted for the development of a drug intended for the treatment of patients with advanced cancer. Genentech did include a histopathological assessment of reproductive organs in all general toxicology studies and, with the exception of decreased prostate weight, there were no clear signs of effects on fertility. Entrectinib was aneugenic, but not mutagenic in in vitro genotoxicity studies.

To address the potential reproductive effects of entrectinib, Genentech conducted an embryo-fetal development study in rats. Administration of entrectinib to pregnant rats during the period of organogenesis (Gestation Days 6-17) did not result in maternal mortality or evidence of embryolethality; however, entrectinib did cause dose-dependent reductions in gravid uterine and fetal weight. The fetal weight decrements were statistically significant at doses ≥ 12.5 mg/kg (~0.2 times the human exposure at the 600 mg dose), the lowest tested dose. Fetal malformations occurred primarily at the high dose level of 200 mg/kg (~2.7 times the human exposure at the 600 mg dose) and included body closure defects (omphalocele and gastroschisis), micromelia, adactyly, limb hyperextension, and filamentous tail. Reduced skeletal ossification occurred frequently at doses ≥50 mg/kg (~ 0.9 times the human exposure at the 600 mg dose).

Beyond the animal findings in the embryo-fetal development study, there are additional concerns about the use of entrectinib during pregnancy due to the established role of Trk proteins in neuronal development (Tucker et al., 2001; Smeyne et al., 1994). Published reports of congenital somatic mutations in TRK proteins or their ligands suggest a relationship between deficient Trk signaling and development of schizophrenia, mood disorders, obesity, and peripheral sensory and motor disorders (Krantz 2015; Otnaess et al., 2009; Knable 1999; Lewis et al., 2005; Indo et al., 1996; Yeo et al., 2004). While embryo-fetal development studies can detect malformations in brain structure, they are not designed to assess motor development or psychiatric function and though a pre- and postnatal development study may be capable of evaluating some of these endpoints, they are not typically required for a drug intended to treat patients with advanced cancer. The clear CNS findings at low clinical exposure multiples in the juvenile animal study do, however, suggest an increased risk for entrectinib-mediated neurological effects during development. Given the published literature on the importance of Trk signaling in neural development, including human syndromes, the limitations of the embryo-fetal development studies to assess the toxicities of particular concern following disruption of this pathway, and the available animal data, there is a potential for significant neurocognitive effects in children exposed to entrectinib during prenatal development. The combination of the clear teratogenic findings in animals and the potential for neurological risks suggested by the mechanism of action and literature reports warrants a warning in the label for embryo-fetal risk. In addition, consistent with current recommendations for genotoxic compounds with embryo-fetal risk, the label also includes recommendations for contraception of 3 (b) (4) months for males (b) (4). Based on the half-life of entrectinib the label also includes a recommendation not to breastfeed for one week after the last dose of ROZLYTREK.

There are no outstanding issues from a nonclinical perspective that would prevent approval of entrectinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is *ROS1*-positive, and for the treatment of adult and adolescent patients with (b) (4) (b) (4) metastatic solid tumors that are neurotrophic tyrosine receptor kinase (*NTRK*) fusion-positive who have either progressed (b) (4) (b) (4).

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

Genentech evaluated the selectivity of entrectinib (RXDX-01-0177, RXDX-101, NMS-01191372) using a HotSpot Kinase profiling assay (Study #1087232). Briefly, Genentech screened for entrectinib activity against a panel of 7 kinases using serial dilutions of entrectinib and ^{33}P-ATP

(0.01 µCi/µL) and calculated IC_{50}s based on the amount of radioactive substrate on ion exchange filters. Entrectinib inhibited TRK A, B and C, ROS1, and ALK at concentrations that were clinically relevant based on a Cmax at the 600 mg clinical dose of 3130 nM and considering the >99% level of entrectinib protein binding (~31 nM free entrectinib). Using a similar assay, Genentech showed that M5, the major human metabolite of entrectinib had similar inhibitory activity against TRK targets, ROS1, and ALK compared to entrectinib (Study #1087249, Table 3).

Table 3: Entrectinib and M5 IC_{50} Values for TRKs, ROS1, and ALK

Target	RXDX-101* IC_{50} (nM)	RXDX-101[a] IC_{50} (nM)	M5[a] IC_{50} (nM)
TRKA	1.66	3.55	6.97
TRKB	0.0567	0.008	0.05
TRKC	0.107	0.007	0.007
ROS1	0.181	0.05	0.25
ALK	1.58	0.996	1.94
JAK2	-	5.38	14.15

*Study report 1087232. [a]Study report 1087249, data represents mean from two separate experiments.

In a second kinase screening selectivity assay (Study #1087233), Genentech assessed entrectinib selectivity against 51 kinases. Entrectinib inhibited ALK, TRKA, ROS1, JAK2, ACK1, and JAK1 at IC_{50} values ranging from 0.019 to 0.164 µM (Table 4). Other kinases with an IC_{50} values less than 1 µM included AUR2, FAK, BRK, JAK3, IGFR1, FLT3, IR, and RET.

Table 4: Entrectinib IC_{50} Values Against Selective Kinases

Target	IC_{50} (µM)	Target	IC_{50} (µM)	Target	IC_{50} (µM)	Target	IC_{50} (µM)	Target	IC_{50} (µM)
TRKA	0.002	AUR2	0.220	FLT3	0.299	LCK	1.519	VEGFR2	4.058
ROS1	0.007	FAK	0.227	IR	0.366	KIT	1.725	PKCβ	4.061
ALK	0.019	BRK	0.241	RET	0.540	MELK	2.926	EphA2	4.964
JAK2	0.038	JAK3	0.277	FGFR1	1.033	AUR1	2.986	Syk	5.021
ACK1	0.068	IGFR1	0.294	VEGFR3	1.244	C-ABL	3.647	CDK2/CYCA	5.773
JAK1	0.164	-	-	-	-	-	-	-	-

Additional screening using a SelectScreen™ profiling service against 293 kinases (Study # 1089804) demonstrated that 100 nM of entrectinib inhibited 6 kinases greater than 95%, including ALK, ROS1, TXK, TRKA, TRKB, and TRKC, and 2 kinases greater than 80% (CSF1R and JAK2), 4 kinases greater than 60% (ITK, LTK, MuSK, and TYK2).

In Studies #1087234 and 1090429, Genentech evaluated the anti-proliferative activity of entrectinib and the M5 metabolite in panels of up to 308 cell lines (269 adult and 39 pediatric). Briefly, investigators seeded cells into 384 well plates with serial dilutions of entrectinib or M5 for 72 hours then determined cell proliferation using the CellTiterGlo assay by measuring ATP concentration (#1087234) or the Vi-CELL analyzer (#1090429) and calculated IC_{50} values. The panels consisted of tumor cell lines derived from leukemia/lymphoma, lung, colorectal, breast, kidney adenocarcinoma, melanoma, multiple myeloma, ovarian, glioblastoma, pancreatic

adenocarcinoma, prostatic carcinoma, cervical adenocarcinoma, astrocytoma, osteosarcoma, neuroblastoma, bladder carcinoma, and gliosarcoma tumors as well as non-tumoral cell lines. In the first assay, entrectinib had the highest anti-proliferative activity against cell lines known to bear constitutively active forms of ALK such as anaplastic large cell lymphoma (ALCL) lines Karpas-299 (IC_{50} = 0.031 µM), SR-786 (IC_{50} = 0.081 µM), SU-DH-1 (IC_{50} = 0.020 µM), and SUP-M2 (IC_{50} = 0.041 µM). Entrectinib also inhibited the growth of the NSCLC line NCI-H2228, which bears the *EML4-ALK* gene rearrangement, with an IC_{50} of 0.068 µM, and of KM12, a colorectal cancer cell line with the *TPM3-TrkA* gene rearrangement, with an IC_{50} of 0.017 µM. In the second study, both entrectinib and M5 had IC_{50} values of < 1 µM in 15 cell lines, including five cell lines with *NTRK* fusions, four with *ROS1* fusions, and five with *ALK* dysregulation (Table 5).

Table 5: Anti-Proliferative Activity of Entrectinib and M5 Against Cell Lines Harboring Specific *NTRK*, *ROS1*, and *ALK* Fusion

Fusion	Cell line	Cancer type	Specific fusion	Entrectinib IC_{50} (nM)	M5 IC_{50} (nM)
NTRK	IMS-M2	AML	ETV6-NTRK3	12	15
	M0-91	AML	ETV6-NTRK3	17	9
	CUTO-3	NSCLC	MPRIP-NTRK1	94	122
	KM12	CRC	TPM3-NTRK1	77	113
	G111	Glioma	EML4-TRK3	276	157
ROS1	CUTO-27	NSCLC	CD74-ROS1	201	135
	CUTO-28	NSCLC	TPM3-ROS1	215	244
	HCC1493	Breast carcinoma	CD74-ROS1	230	199
	HCC-78	NSCLC	CD74-ROS1	524	621
ALK	SU-DHL-1	T-cell ALCL	NPM-ALK	188	147
	DEL	T-cell ALCL	NPM-ALK	204	294
	NB-1	Neuroblastoma	ALK amplification	240	138
	KARPAS-299	T-cell ALCL	NPM-ALK	257	197
	NCI-H2228	NSCLC	EML4-ALK	669	798
Other	MV-4-11	BBML	FLT3-ITD	431	243

ALCL=anaplastic large-cell lymphoma; AML=acute myeloid leukemia; CRC=colorectal cancer; NSCLC=non-small cell lung cancer; BBML=biphenotypic B myelomonocytic leukemia

Genentech further assessed the in vitro anti-proliferative activity of entrectinib against cells bearing *NTRK* fusion genes by transducing mouse Pro B Ba/F3 cells with *NTRK* fusion cDNAs using a lentiviral system (Study #1087236). Investigators incubated *NTRK* fusion expressing Ba/F3 cells with serial dilutions of entrectinib and measured proliferation using the CellTiterGlo assay. Mouse Ba/F3 cells normally require IL3 for proliferation; however, cells with *NTRK* fusions proliferate independent of IL3. Entrectinib inhibited *NTRK* fusion-dependent growth with IC_{50} values ranging from 0.37 to 5.39 nM (Table 6). Ba/F3 cells without *NTRK* fusions served as controls and did not proliferate without IL3 present; the entrectinib IC_{50} for control cells incubated in IL3 was greater than 1000 nM.

Table 6: Anti-Proliferative Activity of Entrectinib Against *NTRK* Fusion Expressing Ba/F3 Cells

NTRK fusion	IL3 independent Proliferation	IC_{50} (nM)	NTRK fusion	IL3 independent Proliferation	IC_{50} (nM)
Ba/F3 control	No	>1000	PLEKHA6-NTRK1	Yes	1.05
TPM3-NTRK1	Yes	2.52	VCL-NTRK2	Yes	5.39
LMNA-NTRK1	Yes	1.28	AFAP1-NTRK2	Yes	2.85
ETV6-NTRK1	Yes	2.50	TRIP13-NTRK2	Yes	0.70
BCAN-NTRK1	Yes	0.51	ETV6-NTRK2	Yes	4.12
SQSTM1-NTRK1	Yes	0.85	ETV6(e5)-NTRK3(e15)	Yes	4.47
SCYL3-NTRK1	Yes	1.42	ETV6(4)-NTRK3(e14)	Yes	0.37

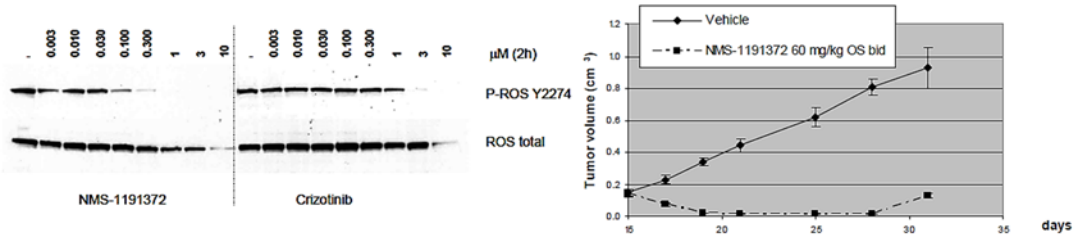
In Study #1087687, investigators evaluated the anti-proliferative activity of entrectinib and other available ROS1 inhibitors against the NSCLC line CUTO-28, which harbors a *TPM3-ROS1* fusion. Entrectinib inhibited the proliferation of CUTO-28 cells with IC_{50} values that were similar to several other inhibitors known to target ROS1 including crizotinib, ceritinib, and lorlatinib (Table 7).

Table 7: Comparison of Anti-Proliferative Activity of Entrectinib to Other Available ROS1 Inhibitors in a *TPM3-ROS1* Fusion Expressing NSCLC Line

Compound	IC_{50} (nM)	Compound	IC_{50} (nM)	Compound	IC_{50} (nM)
Entrectinib	20.1	Cabozantinib	34.8	Ensartinib	>1000
Ceritinib	176.9	Altiratinib	113.2	TAE684	18
Crizotinib	36.6	Brigatinib	81.5	Dovitinib	>1000
Lorlatinib	1.1	TPX-0005	10.5	Belizatinib	98.1

In the Ba/F3 ROS1-dependent *TEL-ROS1* cell line, entrectinib inhibited in vitro cellular proliferation with an IC_{50} of 5 nM. Western blot analysis showed that a 2-hour incubation with entrectinib decreased phosphorylated ROS, with complete inhibition observed at 1 µM, compared to 10 µM for crizotinib. Adult SCID mice bearing subcutaneous Ba/F3 *TEL-ROS1* tumors (left flank) treated with 60 mg/kg entrectinib starting on Day 15 for 10 consecutive days showed tumor growth inhibition (TGI) of 98% (Figure 5).

Figure 5: Entrectinib Decreased Phosphorylated ROS in Ba/F3 TEL-ROS1 Cells (Left) and Showed Anti-Tumor Activity in Mice Bearing Ba/F3 TEL-ROS1 Tumors (Right)



(Figure excerpted from Study #1087258)

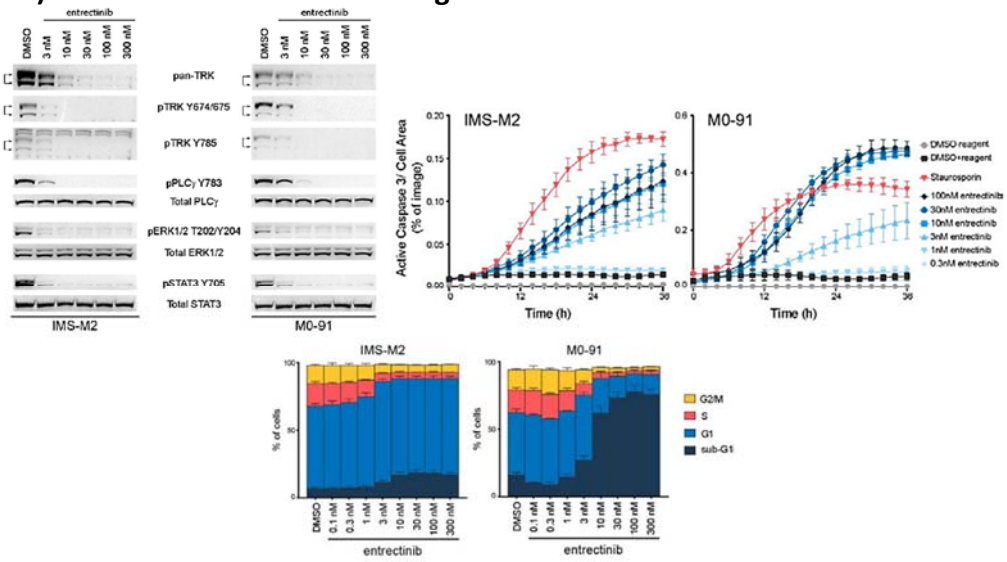
In a CellTiterGlo assay, entrectinib had anti-proliferative activity against two acute myeloid leukemia (AML) cell lines harboring *ETV6-TRK3* fusions (IMS-M2 and M0-91) at 6 to 190-fold lower concentrations compared to larotrectinib, crizotinib, and TSR-011 (Table 8). In addition, entrectinib inhibited phosphorylation of the ETV6-TRK3 fusion protein and known downstream TRKC targets, induced apoptotic cell death as measure by Caspase 3 activity, and induced cell cycle arrest in the G1 phase in a dose dependent manner (Figure 6).

Table 8: Entrectinib Had Greater Anti-Proliferative Activity Compared to Crizotinib, Larotrectinib, and TSR-011 Against AML Cells Bearing ETV6-TRK3 Fusions

IC_{50} (nM)	Entrectinib	Crizotinib	Larotrectinib	TSR-011
IMS-M2	0.47	60.9	3.06	27.7
M0-91	0.65	121.9	4.1	51.7
Kasumi-1	>1000	>1000	>1000	>1000

IMS-M2 and M0-91 carry the ETV6-NTRK3 fusion.
Kasumi-1 AML cells carry the RUNX1-RUNK1T1 translocation.

Figure 6: Entrectinib Inhibits Phosphorylation of TRKC and Its Downstream Targets (Upper Left) and Led to Dose-Dependent Increases in Caspase 3 (Upper Right) and Cell Cycle Arrest in G1 (Bottom) in Two AML Cell Lines Bearing the ETV6-TRK3 Fusion

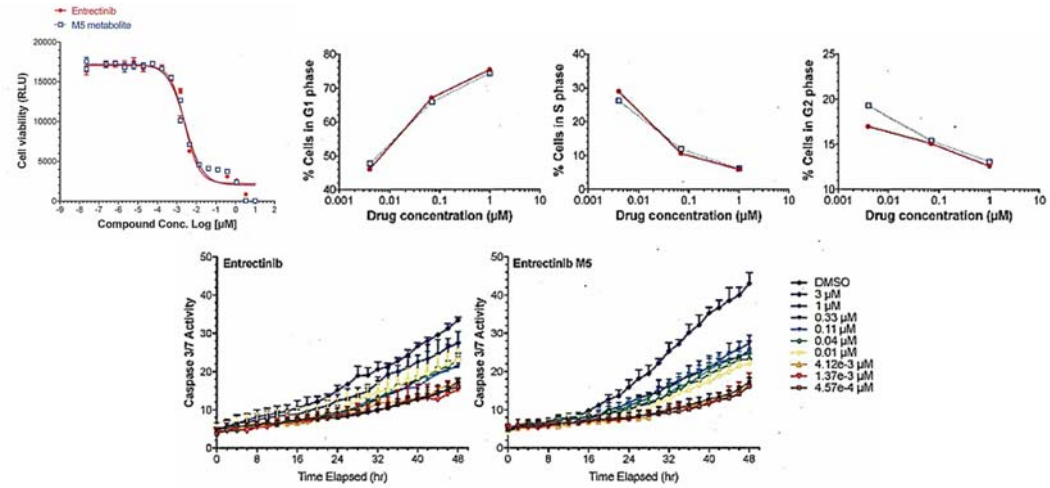


(Figure excerpted from Study #1087247)

Study #1089907 investigated the anti-proliferative, cell cycle, and apoptotic activity of entrectinib and its major metabolite M5 against the human colorectal carcinoma cell line KM12, which contains the *TPM3-NTRK1* fusion. Investigators treated KM12 cells with serial dilutions of entrectinib or M5 then assessed cell cycle and caspase 3/7 activity. The EC_{50} values for induction of cell death for entrectinib and M5 were 2.76 and 2.63 nM, respectively. Both compounds increased the percentage of cells in the G1 phase of the cell cycle with a

compensatory decrease in the number in the S and G2 phases, consistent with inhibition of the cell cycle. Additionally, both entrectinib and M5 increased the percentage of cells positive for caspase 3/7 activity, indicating that both enhanced apoptosis in the KM12 cell line. Entrectinib also reduced phosphorylation of TRKA and its downstream targets PLCγ, AKT, and MAPK in a second study (Study #1087242).

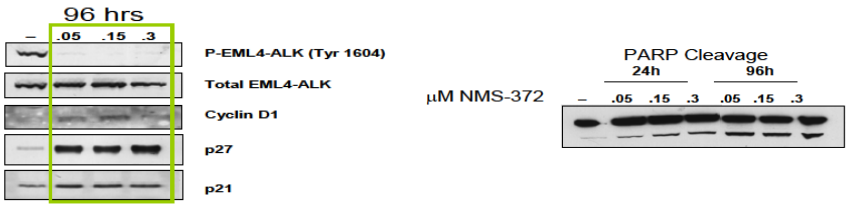
Figure 7: Entrectinib Showed Anti-Proliferative Activity, Led to Cell Cycle Arrest in G1, and Increased Caspase 3/7 Activity in a Dose-Dependent Manner in CRC Cells Bearing the *TPM3-NTRK1* Fusion



(Figure excerpted from Study #1089907)

Entrectinib inhibited proliferation of NCI-H2228 (*EML4-ALK* fusion) cells in vitro after 72 hours of incubation with an IC_{50} of 68 nM in Study #1087265. A 96-hour treatment inhibited ALK phosphorylation with concomitant induction of markers of G1 block such as cyclin D1, p27, and p21. Following 24 and 96 hours of treatment, there was a time-dependent accumulation in the GI phase of the cell cycle (data not shown) and cleavage of PARP as a marker of apoptosis (Figure 8).

Figure 8: Entrectinib Inhibited ALK Phosphorylation and Induced Markers of G1 Block (Right) and Led to PARP Cleavage (Left) in NSCLC Cells With the *EML4-ALK* Fusion



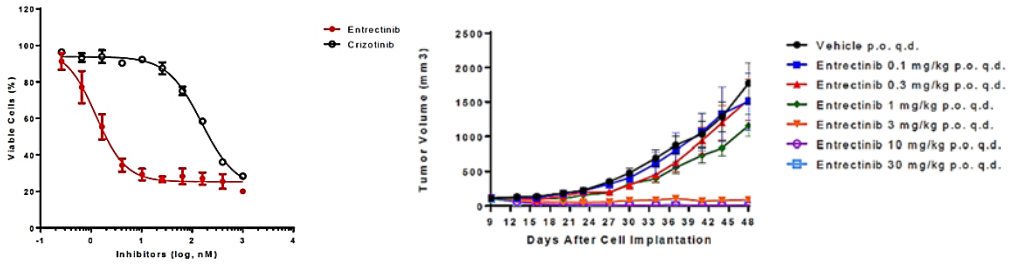
(Figure excerpted from Study #1087265)

B. <u>In Vivo Studies</u>

NTRK fusions

In Study #1087237 Genentech evaluated the in vitro and in vivo anti-proliferative and anti-tumor activity of entrectinib in the NSCLC line CUTO-3 which contains the *MPRIP-NTRK1* fusion gene. Using the CellTiterGlo assay to measure in vitro cellular proliferation, Genentech compared entrectinib and crizotinib and showed that entrectinib inhibited proliferation of CUTO-3 cells at concentrations 100 times lower than crizotinib, with IC_{50}s of 1.6 and 153.5 nM, respectively (Figure 9; left panel). In vivo, CUTO-3 cells were implanted subcutaneously in the right flank of adult athymic nu/nu female mice, and treated with vehicle or 0.1, 0.3, 1, 3, 10, or 30 mg/kg of entrectinib orally once daily after tumors reached approximately 130 mm^3. Entrectinib showed dose-dependent tumor growth inhibition (TGI), with 3 mg/kg having a 100% TGI and 10 and 30 mg/kg reducing tumor volume below measurable limits resulting in TGI for both of greater than 100% (Figure 9; right panel).

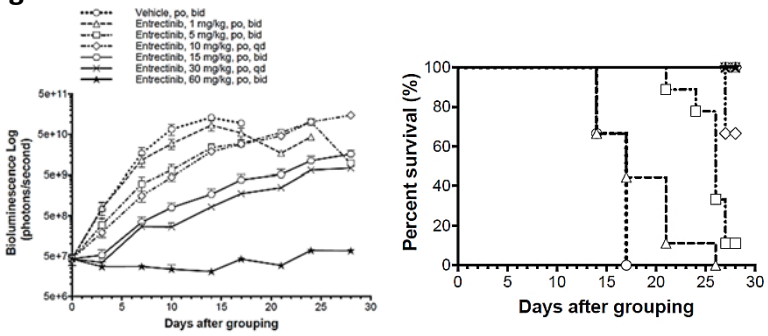
Figure 9: Entrectinib Had Greater Anti-Proliferative Activity Against NSCLC Cells Bearing the *MPRIP-NTRK1* Fusion Compared to Crizotinib (Left) and Showed Dose-Dependent Anti-Tumor Activity in a Xenograft Mouse Model (Right)



(Figure excerpted from Study #1087237)

Entrectinib showed dose-dependent anti-tumor activity in an intracranial mouse model using a luciferase labeled colorectal carcinoma cell line, KM12-luc, that contains the *TPM3-NTRK1* fusion, suggesting blood brain barrier penetration by entrectinib. In Study #1090134, investigators injected adult female Balb/c mice with 3 x 10^4 KM12-luc cells into the right lobe of the brain and allowed tumors to grow for 5 days before measuring baseline bioluminescence and beginning dosing on Day 6 with entrectinib at dose levels of 0, 1, 5, 15, or 60 mg/kg twice daily (BID) for 28 days or 10 and 30 mg/kg three times daily (TID) for 28 days. Treatment with entrectinib did not affect body weight. Entrectinib decreased the bioluminescence with 60 mg/kg having the greatest effect, decreasing the amount of tumor bioluminescence and increasing survival up to 30 days compared to 7-12 for vehicle treated mice (Figure 10).

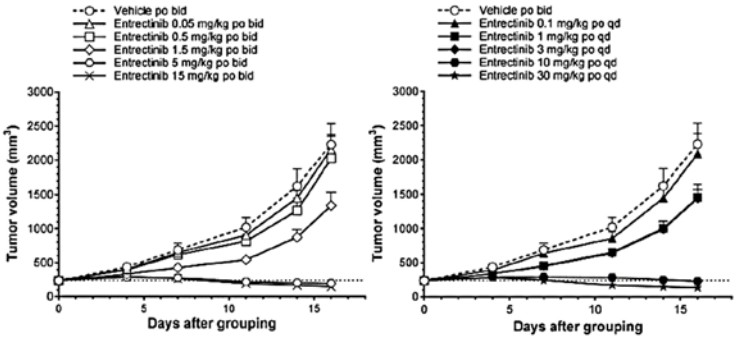
Figure 10: Entrectinib Had Anti-Tumor Activity and Increased Survival in a Mouse Intracranial Tumor Model Using CRC Cells With a *TPM3-NTRK1* Fusion



(Figure excerpted from Study #1090134)

In Studies 1090136 and 1087241, adult female and male Balb/c nude mice were subcutaneously injected with 5 x 10^6 KM12-luc labeled or unlabeled cells into the right or left flank. Females received entrectinib orally starting on Day 15 at doses of 0, 0.05, 0.5, 1.5, 5, or 15 mg/kg BID or 0.1, 1, 3, 10, or 30 once daily (QD) for 15 days. BID doses of ≥5 mg/kg and QD doses of ≥10 mg/kg led to tumor regression (Figure 11). Males received entrectinib at doses of 0, 15, 30, or 60 mg/kg BID starting on Day 8 for 10 consecutive days and showed TGI ranging from 87-94% compared to vehicle controls (data not shown).

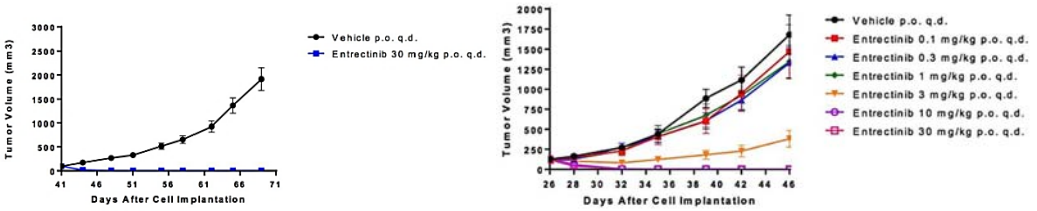
Figure 11: Entrectinib Had Anti-Tumor Activity Against Subcutaneous CRC Tumors Bearing the *TPM3-NTRK1* Fusion



(Figure excerpted from Study #1090136)

In Study #1087257, mice bearing patient derived xenograft (PDX) sarcoma, G002, harboring the *TPM3-NTRK1* fusion, treated with 30 mg/kg entrectinib orally once daily for 28 days had TGI of greater than 100% for all days measured. In a dose range activity study (#1087246) G002 bearing mice treated with entrectinib orally once daily at doses ranging from 0.1 and 30 mg/kg indicated that doses greater than 1 mg/kg resulted in significant tumor inhibition and regression, with doses starting at 3 mg/kg having a TGI of 84% or greater (Figure 12).

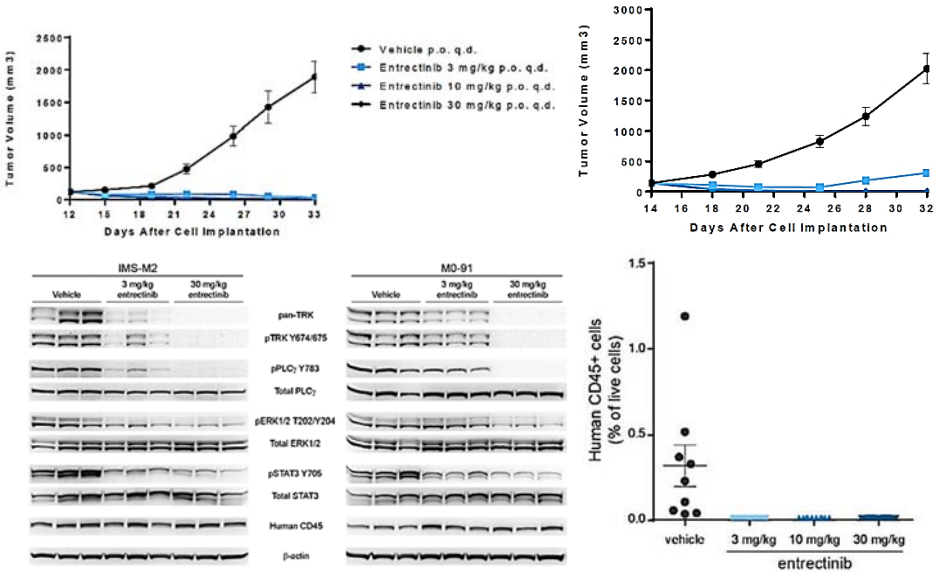
Figure 12: Entrectinib Had Dose-Dependent Anti-Tumor Activity Against a PDX Sarcoma Bearing the *TPM3-NTRK1* Fusion



(Figures excerpted from Studies #1087257 and 1087246)

In Studies #1087247 and #1087243, Genentech evaluated the antitumor activity of entrectinib against 2 acute myeloid leukemia (AML) cell lines (IMS-M2 and M0-91) driven by the *ETV6-NTRK3* fusion gene. Investigators subcutaneously injected $1x10^6$ tumor cells into the right flank of adult female CB.17 SCID mice and allowed tumor volume to reach 120-140 mm^3 before initiation of entrectinib at daily oral doses of 0, 3, 10, or 30 mg/kg for a total of 21 days. Entrectinib decreased tumor growth by 100% in IMS-M2 and M0-91 tumors at the 10 and 30 mg/kg dose levels. A single dose of 3 or 30 mg/kg resulted in dose-dependent decreases in phosphorylated TRKC in harvested tumors, plus decreased phosphorylation of downstream targets PLCγ, ERK1/2, and STAT3. Evaluation of the effect of entrectinib on leukemic cells in sites such as bone marrow, where leukemic cells spontaneously migrate, showed that entrectinib eliminated bone marrow resident tumor cells as measure by flow cytometry separation of human CD45+ cells (Figure 13).

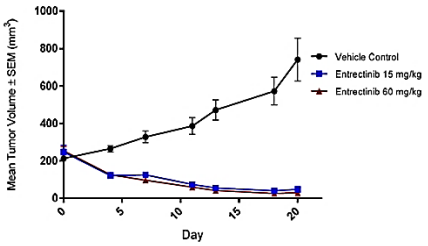
Figure 13: Entrectinib Had Anti-Tumor Activity (Top), Decreased Phosphorylated TRKC (Bottom Left), and Decreased Leukemic Cells in Bone Marrow in an *ETV6-NTRK3* Fusion Bearing AML Xenografts (Bottom Right)



(Figures excerpted from Studies #1087247 and 1087243)

In Study #1087238 assessing a patient derived xenograft (PDX) model of human head and neck cancer, CTG-0798 harboring the *ETV6-NTRK3* fusion, mice treated with entrectinib at 15 and 60 mg/kg PO, BID for 21 days had significant tumor regressions of 146 and 149% TGI at the 15 and 60 mg/kg doses, respectively (Figure 14).

Figure 14: Entrectinib Showed Anti-Tumor Activity Against a PDX HNSCC Harboring the *ETV6-NTRK3* Fusion



(Figure excerpted from Study #1087238)

<u>ALK fusions</u>

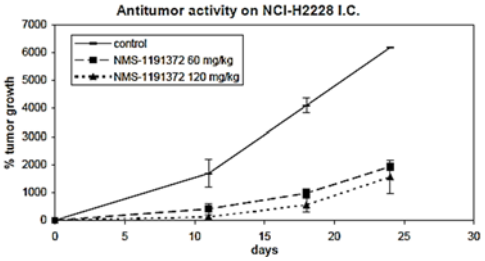
In Studies #1087263 and #1087265, Genentech evaluated the antitumor activity and mechanism of action of entrectinib using subcutaneously and intracranially implanted NCI-H2228 (NSCLC line containing the *EML4-ALK* fusion) tumors. Briefly, adult male Balb Nu/Nu mice were subcutaneously injected with 1 x 10^7 cells into the left flank and treated with entrectinib orally at 15, 30, or 60 mg/kg BID or 30, 60, or 90 mg/kg QD for 10 days starting on Day 14. For intracranial tumors, mice were injected with 2 x 10^6 cells intracranially and treated with entrectinib at 60 and 120 mg/kg BID for 10 days starting on Day 18. Entrectinib led to tumor growth inhibition ranging from 87-99% at all dose levels and schedules (Table 9) in the subcutaneous tumor model. The 30 and 60 mg/kg BID doses led to 2/7 and 3/7 mice being tumor free; the QD doses did not include any tumor free mice at the end of the study. In the intracranial tumor model, both doses of entrectinib led to significant inhibition of tumor growth compared to vehicle controls (Figure 15). Entrectinib at any dose or schedule had little to no effect on body weight (<3% change in BW compared to controls).

Table 9: Anti-Tumor Activity of Different Doses and Schedules of Entrectinib in a Subcutaneous NSCLC Xenograft Bearing the *EML4-ALK* Fusion

Treatment	TGI%	Treatment	TGI%
15 mg/kg BID	87 (Day 34)	30 mg/kg PO	96 (Day 24-27)
30 mg/kg BID	98 (Day 43)	60 mg/kg PO	98 (Day 27-53)
60 mg/kg BID	98 (Day 31-52)	90 mg/kg PO	98 (Day 27-53)
60 mg/kg BID[a]	99 (Day 43-71)	-	-

BID - twice daily oral dosing. PO - once daily oral dosing. Treatment started on Day 14 post inoculation and continued for 10 consecutive days. TGI% is compared to vehicle controls from individual experiments.
[a]TGI confirmed in separate experiment.

Figure 15: Entrectinib Had Anti-Tumor Activity in the Intracranial Model of NSLCL Bearing the *EML4-ALK* Fusion



(Figure excerpted from Study #1087263)

Similar results were obtained in a subcutaneous xenograft study (Study 1907262) using Karpas-299 human Anaplastic Large Cell Lymphoma (ALCL) cells containing the ALK gene fusion *NPM-ALK*. The oral BID dose of 60 mg/kg given for 5 consecutive days or 20 consecutive days led to 4/7 and 3/7 animals with no observable tumors by the end of the experiment. Entrectinib had no effect on body weight. In single dose multi-dose level experiment, investigators harvested Karpas-299 tumors from mice at several time points then analyzed tumors for phosphorylation of ALK and STAT3 by Western blot. The 60 mg/kg dose inhibited NPM-ALK and STAT3 phosphorylation starting 3 hours post dose and maintained for 18 hours with 50% inhibition still evident after 24 hours for both (Figure 16). Similar data were obtained in Study #1087264 utilizing in vitro incubation of NPM-ALK fusion protein containing cell lines SR-786, SUP-M2, and SU-DHL-1, with entrectinib (data not shown).

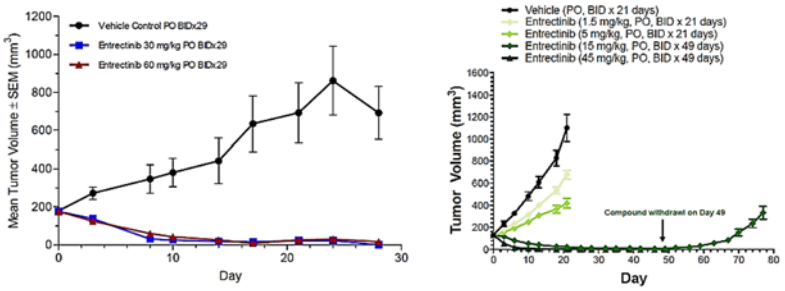
Figure 16: Entrectinib Decreased Phosphorylated AK and STAT3 in ALCL Xenograft Tumors Containing the *NPM-ALK* Fusion

(Figure excerpted from Study #1087262)

<u>ROS1 fusions</u>

In Study #1087260, entrectinib given at 30 or 60 mg/kg orally BID for 29 days to CTG-0848 (NSCLC PDX model bearing *CD75-ROS1* fusion) tumor bearing mice resulted in tumor regression of 134 and 131%, respectively. In a separate study of another *ROS1* fusion model (Study 1087259), entrectinib at doses of 0, 1.5, 5, 15 and 45 mg/kg orally BID for 21 or 49 resulted in dose-dependent inhibition of tumor growth in mice bearing LU-01-0414 NSCLC PDX (*SCD4-ROS1* fusion), with 15 and 45 mg/kg having a TGI of 111 and 113%, respectively.

Figure 17: Entrectinib Had Anti-Tumor Activity in a PDX NSCLC Model Bearing the *CD75-ROS1* Fusion



(Figures excerpted from Studies #1087260 and 1087259)

Secondary Pharmacology

Genentech screened off-target activity of entrectinib and its active metabolite M5 against a panel of 89 targets (receptors, ion channels, and transporters) in Studies 1089509, 1089510, 1089511, and 1089512. These studies indicated that at the concentration of 10 µM, either entrectinib or M5 activity had greater than 50% inhibition or activation for multiple targets.

Receptors: Adrenergic receptors α1A, 2A, 2C; cannabinoid receptor CB2; dopamine receptors D1, D2s, D3, D5; opioid receptors δ (DOP), κ (KOP), µ (MOP), glucocorticoid receptor GR; sigma 2 receptor; orexin receptor OX1; histamine receptors H1, H2; muscarinic receptors M1, 4, 5; peroxisome proliferator-activated receptor PPARγ, serotonin receptors 5-HT1B, 2A, 2B, 5a, 6, 7; somatostatin receptor sst4, COX2 receptor: *Channels:* L-type Ca^{2+} channels (dihydropyridine, verapamil, diltiazem, phenylalkylamine, and benzothiazepine sites); hERG potassium channel; sodium channel (site 2): *Transporters:* norepinephrine, serotonin, dopamine, and choline transporters. Less than 1% of entrectinib or M5 is protein bound, leaving free-compound C_{max} values at steady state of approximately 0.031 and 0.013 µM, respectively, 323x and 769x lower, respectively, compared to the 10 µM used in these assays. This study was, therefore, inadequate on its own to determine whether entrectinib is likely to affect any of these potential targets at clinically achievable concentrations.

Safety Pharmacology

In non-GLP Study #1087271, HEK293 cells stably expressing human hERG potassium channel were incubated with entrectinib (0.05, 0.5, 1.5, 15 µM) or 0.12% DMSO (negative control) followed by measurement of potassium current using the patch-clamp technique. No positive control was used in the study. The negative control behaved as expected. Entrectinib dose-dependently inhibited the hERG potassium current with an IC_{50} value of 0.6 µM, suggesting some potential for interference of cardiac repolarization and risk of QT prolongation in humans taking entrectinib. In Study #1087275, the M5 metabolite demonstrated an IC_{50} value of greater than 10 µM for inhibition of hERG potassium channel current. The positive control Cisapride (0.05 µM) inhibited hERG potassium channel current by 64%, as expected.

In GLP-compliant Study #1087273, radiotelemetry-instrumented male (n=2) and female (n=2) beagle dogs received single oral doses of entrectinib at 60 and 120 mg/kg with a 1-week washout between doses to assess the effects of entrectinib on cardiovascular parameters. Arterial pressure, ECG, and body temperature were recorded from one hour before to 24 hours post dose, and cardiovascular data (systolic, diastolic, and mean arterial pressure, heart rate, ECG intervals, body temperature) were obtained from 60 minutes before treatment to 7 hours post treatment. A prolongation in QTc occurred at the dose of 120 mg/kg from 15-105 minutes (7-14 msec) and again from 270-360 (10 msec) post dose. Oral administration of entrectinib to male and female beagle dogs at doses of 60 and 120 mg/kg did not have any effect on other cardiovascular measurement intervals or body temperature.

In GLP-compliant study #1087274, Genentech assessed entrectinib for the potential to induce respiratory toxicity by administering a single oral dose at 0, 50, 100, or 200 mg/kg to female Sprague-Dawley rats followed by measurement of respiratory parameters (tidal volume, minute volume, respiratory rate, peak inspiratory flow, peak expiratory flow, inspiration time, expiration time, relaxation time, Penh (an index of bronchoconstriction)) from 30 minutes before to 4 hours after treatment. The study included only female rats due to higher systemic exposure in females compared to males. Oral administration of entrectinib at doses up to 200 mg/kg did not have any physiologically relevant effects on respiratory parameters.

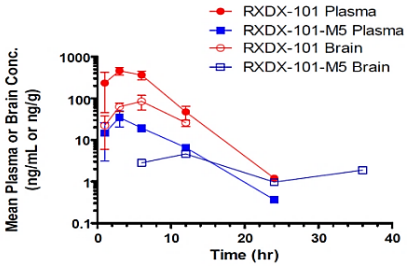
5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Protein Binding</td></tr>
<tr><td>Study#1087282: Determination of plasma protein binding. Cross species comparison</td><td>No significant differences in protein binding of RXDX-101 occurred between any species tested.
<table>
<tr><th>Species</th><th>Mean % binding 5 µM</th><th>Mean % binding 50 µM</th></tr>
<tr><td>Mouse</td><td>97.4</td><td>98.4</td></tr>
<tr><td>Rat</td><td>99.4</td><td>99.3</td></tr>
<tr><td>Dog</td><td>98.8</td><td>100</td></tr>
<tr><td>Monkey</td><td>98.4</td><td>99.2</td></tr>
<tr><td>Human</td><td>99.5</td><td>99.4</td></tr>
</table></td></tr>
<tr><td>Study #1087285: Evaluation of the plasma protein binding of RXDX-101*M5 in mouse, rat, dog, monkey, and human plasma by equilibrium dialysis</td><td>No significant differences in protein binding of metabolite M5 occurred across any species tested, with similar fractions of protein binding occurring at all M5 concentrations tested (0.5, 2.5, 10 µM).
<table>
<tr><th>Species</th><th>Mean % binding</th></tr>
<tr><td>Mouse</td><td>99.7-99.8</td></tr>
<tr><td>Rat</td><td>99.8-100</td></tr>
<tr><td>Dog</td><td>99.7-99.8</td></tr>
<tr><td>Monkey</td><td>99.6-99.7</td></tr>
<tr><td>Human</td><td>99.9-100</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Study #1087277:
Evaluation of the pharmacokinetics following single IV and oral administration and evaluation of brain levels following single IV administration to male Sprague Dawley rats
and
Study# 1087278:
Evaluation of bioavailability of NMS-1191372 following single IV and oral administration to beagle dog</td><td>A single-dose PK study in the rat using an intravenous (IV) dose of 10 mg/kg and oral doses of 10 and 30 mg/kg showed a dose-dependent bioavailability for oral administration. Brain concentration in rats treated intravenously was 5% of the plasma concentration.
<table>
<tr><th rowspan="2">Administration Route
Parameter</th><th>IV</th><th colspan="2">Oral</th></tr>
<tr><th>10 mg/kg</th><th>10 mg/kg</th><th>30 mg/kg</th></tr>
<tr><td>Cmax (µM)</td><td>11</td><td>0.461</td><td>1.433</td></tr>
<tr><td>AUC (µM*hr)</td><td>15.1</td><td>3.95</td><td>19.2</td></tr>
<tr><td>F% (AUC)</td><td>-</td><td>33</td><td>48</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>3.8</td><td>-</td><td>3.9</td></tr>
</table>
<table>
<tr><th>Parameter</th><th>IV 10 mg/kg</th></tr>
<tr><td>Brain concentration (µM)</td><td>0.591</td></tr>
<tr><td>Plasma concentration (µM)</td><td>11.17</td></tr>
<tr><td>Blood to plasma ratio</td><td>0.053</td></tr>
</table>
A single-dose PK study in the dog using an IV dose of 10 mg/kg and oral doses of 10 and 60 mg/kg showed a dose-dependent bioavailability for oral administration.
<table>
<tr><th rowspan="2">Administration Route
Parameter</th><th>IV</th><th colspan="2">Oral</th></tr>
<tr><th>10 mg/kg</th><th>10 mg/kg</th><th>60 mg/kg</th></tr>
<tr><td>Cmax (µM)</td><td>8.55</td><td>0.595</td><td>2.7</td></tr>
<tr><td>AUC (µM*hr)</td><td>17.1</td><td>5.35</td><td>48.5</td></tr>
<tr><td>F% (AUC)</td><td>-</td><td>31.2</td><td>48</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>11.9</td><td>15.2</td><td>8.99</td></tr>
</table></td></tr>
<tr><td>Study #1087302:
Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to rats
<i>and</i>
Study #1087301:
Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to dogs</td><td>RXDX-101 accounted for 29-40% (oral 20 mg/kg) or 45-53% (IV 2 mg/kg) of the total circulating plasma radioactivity in rats and 13.8% (oral) and 7.48% (IV) in dogs.

M5 accounted for 0.6-0.9% (oral or IV) of the total circulating plasma radioactivity in rats and 27% (oral) and 4.5% (IV) in dogs.

Oral bioavailability was 38% in the rat and 74% in the dog.</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Study #1090366:
Entrectinib (RO7102122) and M5 (RO7278378)</td><td>Rats received a single intravenous (IV) dose of 6 mg/kg entrectinib followed by a 6-hour continuous infusion of 1.2 mg/kg entrectinib.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>concentrations in plasma, CSF, and brain after single intravenous bolus dose followed by IV infusion in rats</td><td>
<table>
<tr><th rowspan="2">Parameter Mean</th><th>Entrectinib</th><th>M5</th></tr>
<tr><th>6 hrs pSOI</th><th>6 hrs pSOI</th></tr>
<tr><td>Plasma (nM)</td><td>1400</td><td>84.8</td></tr>
<tr><td>Brain (nM)</td><td>843</td><td>37.3</td></tr>
<tr><td>CSF (nM)</td><td>0.813</td><td><0.178</td></tr>
<tr><td>Brain/Plasma</td><td>0.598</td><td>0.435</td></tr>
<tr><td>CSF/Free plasma</td><td>0.227</td><td>0.180</td></tr>
<tr><td>M5/Parent plasma</td><td>0.0604</td><td>-</td></tr>
<tr><td>M5/Parent brain</td><td>0.0446</td><td>-</td></tr>
</table>
pSOI – post start of infusion
</td></tr>
<tr><td>Study #1087283: Plasma and brain pharmacokinetics of RXDX-101 and RXDX-101-M5 in SD rats following single oral dose of RXDX101</td><td>Mean plasma and brain concentrations of RXDX-101 and its metabolite M5 following a single oral dose of 20 mg/kg RXDX-101


(Figure excerpted from Study #1087283)</td></tr>
<tr><td>Study# 1087284: Quantitative whole-body autoradiography of male rats after oral administration of [14C] RXDX-101</td><td>Quantitative whole-body radiography to determine tissue distribution in the male Long Evans and Sprague Dawley rats following administration of a single 20 mg/kg oral dose of [^{14}C] RXDX-101 (111 µCi/kg) evaluated for up to 168 hours was comparable between the two species, with the exception of distribution to ocular melanin in the pigmented Long Evans rats.

The highest mean Cmax values were observed in lungs, pituitary gland, liver, uveal tract, adrenal glands, bile, and urine. Tissues with the lowest mean Cmax values observed were bone, testes, abdominal fat, epididymis, and seminal vesicles.

[^{14}C]RXDX-101 distribution did not occur in the central nervous system.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td>Study # 1087479: Metabolic profiles of entrectinib in mouse, rat, dog, monkey, and human liver microsomes</td><td>Following a 60-minute incubation of [^{14}C] entrectinib in mouse, rat, dog, monkey, and human liver microsomes, approximately 33 to 79% entrectinib remained.

No metabolite was human specific, with M5 and M7 present in microsomes from all species.
<table>
<tr><th>Species</th><th>M1</th><th>M2</th><th>M3[a]</th><th>M5</th><th>M7</th><th>M13[a]</th><th>Others[b]</th><th>Entrectinib</th><th>Total</th></tr>
<tr><td>Mouse</td><td>ND</td><td>ND</td><td>ND</td><td>14.1</td><td>6.53</td><td>ND</td><td>ND</td><td>79.3</td><td>100</td></tr>
<tr><td>Rat</td><td>ND</td><td>ND</td><td>ND</td><td>17.8</td><td>8.96</td><td>ND</td><td>2.30</td><td>70.9</td><td>100</td></tr>
<tr><td>Dog</td><td>ND</td><td>ND</td><td>ND</td><td>29.9</td><td>36.5</td><td>ND</td><td>ND</td><td>33.6</td><td>100</td></tr>
<tr><td>Monkey</td><td>5.05</td><td>ND</td><td>5.40</td><td>40.4</td><td>3.77</td><td>10.6</td><td>2.20</td><td>32.6</td><td>100</td></tr>
<tr><td>Human</td><td>7.48</td><td>8.05</td><td>1.97</td><td>28.4</td><td>1.69</td><td>5.74</td><td>0.108</td><td>46.5</td><td>100</td></tr>
</table>
[a] Overlapped in the radioactive chromatogram, relative percentage was based on the mass response from selective ion monitoring; [b] Others refer to unassigned minor radioactive peaks

One metabolite, M5, was a major human metabolite (i.e. comprised</td></tr>
</table>

Type of Study	Major Findings
	≥10% of parental AUC), and was detected in mice, rats, dogs, and monkeys with M5-to-parent AUC ratios of 0.05 (rat) and 2 (dog) in repeat-dose toxicology studies in adult animals with quantitative toxicological coverage obtained in the dog. The M5-to-parent AUC ratio in juvenile rats was similar to that observed in adult rats. There were no other major human metabolites.
Excretion	
Study #1087302: Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to rats *and* Study #1087301: Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to dogs	RXDX-101 elimination occurred primarily through fecal excretion (rat 97-101%; dog 78-84%) after IV (dog 1 mg/kg; rat 2 mg/kg) or oral (dog 10 mg/kg; rat 20 mg/kg) administration. Elimination was completed by 48 hours in rats regardless of route of administration, and 48 hours (oral) and 72 hours (IV) in dogs. **Route of administration: Oral / IV** **Route of excretion: Feces / Urine** Rat: 97.6% / 0.77% / 100.8% / 1.5% Dog: 84.6% / 0.4% / 78% / 0.6%

5.5. Toxicology

5.5.1. General Toxicology

Study title / Study number: RXDX-101: 13-Week Toxicity and Toxicokinetic Study in Rats with an 8-Week Recovery Phase / 1087349

Key Study Findings

- Preterm deaths were attributable to sores/ulcerative dermatitis in mid-dose and high-dose males and females.
- Key target organs were the skin, bone marrow, and spleen.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

<u>Methods</u>

Dose and frequency of dosing: Group 1: 0 mg/kg/day
Group 2: 7.5 mg/kg/day
Group 3: 15 mg/kg/day
Group 4: 30 mg/kg/day

	(once daily for 13 weeks)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 % (w/v) methylcellulose in reverse osmosis-purified water
Species/Strain:	Rat / Sprague-Dawley
Number/Sex/Group:	Main: Groups 1-4: 10/sex Recovery: Groups 1, 3, and 4 only: 5/sex
Age:	6-7 weeks at initiation of dosing
Satellite groups/unique design:	Toxicokinetic: Group 1: 3/sex; Groups 2-4: 9/sex
Deviation from study protocol affecting interpretation of results:	None that affected interpretation of results

Observations and Results: Changes from Control

Parameters	Major Findings
Mortality	3 HD males, 1 HD female, and 1 MD female were sacrificed in moribund condition due to skin toxicity (sores/ulcerative dermatitis) generally after Day 70; cause of death undetermined for 1 MD male.
Toxicity Mitigation (Dosing Suspensions, Veterinary Treatments)	HD and MD animals frequently required dosing holidays of between 1 and 3 weeks because of significant skin lesions and, in some cases, resulting infections (treated with antibiotics).
Clinical Signs	Skin abnormalities occurred and persisted to a reduced degree in the recovery period.

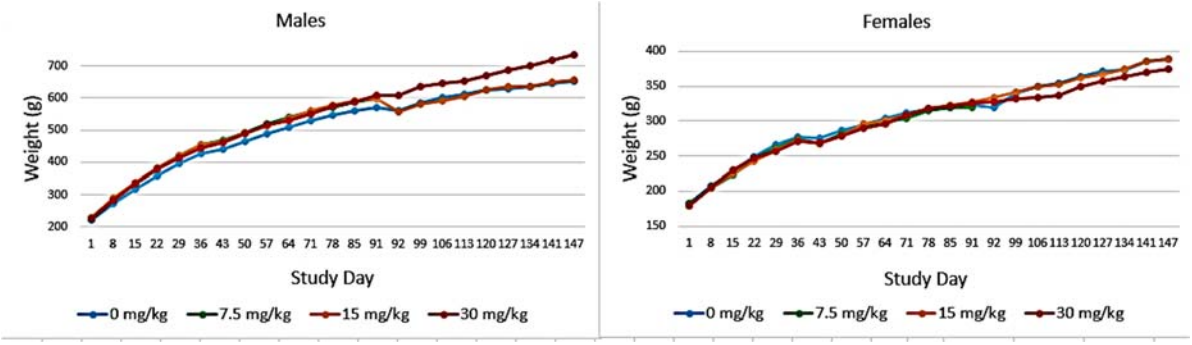
Skin-Related Clinical Signs (13-Week Study; Rats)

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Sore; scab; discolored/broken skin	6	0	35, 1R	67, 5R	0	7	28, 1R	38, 1R
Alopecia/thinning/discolored haircoat	8, 5R	3	18	17, 5R	3, 6R	8	20, 4R	10, 2R

R: Recovery groups (0, 15, and 30 mg/kg only)

Body Weights and Feed Consumption	• Main group males had modest increases in body weight gain compared to controls that correlated with increased food consumption. • No clear changes in female weight.

Mean Body Weights (13-Week Study; Rats)



Note: Day 92 is the start of the recovery period (0, 15, and 30 mg/kg; 5 animals/sex/group)

Ophthalmoscopy	Unremarkable

Hematology and Coagulation	In males and females, changes consistent with anemia occurred; these correlated with increased spleen weight and extramedullary hematopoiesis. In males and females, dose-dependent increases in white blood cells and neutrophils, and an increase in serum globulin, likely correlated with inflammation associated with skin lesions.

Hematology and Coagulation: % Change from Concurrent Control (13-Week Study; Rats)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
RBC	End of dosing	-0.7%	-6.3%	-8.6%	-1.4%	-6.8%	-13.2%
	End of recov.		0.7%	-10.2%		-0.8%	-0.1%
RETIC	End of dosing	16.7%	44.1%	56.1%	17.8%	36.1%	119.9%
	End of recov.		16.9%	25.0%		4.3%	22.0%
PLT	End of dosing	7.1%	15.6%	27.6%	-0.1%	0.6%	15.7%
	End of recov.		0.7%	6.9%		5.4%	15.3%
WBC	End of dosing	2.7%	11.8%	38.7%	5.6%	10.5%	34.0%
	End of recov.		3.6%	29.6%		-15.2%	26.5%
NEUT	End of dosing	29.2%	72.0%	127.4%	14.3%	59.3%	168.1%
	End of recov.		11.8%	37.3%		-0.8%	19.4%
FIB	End of dosing	1.5%	4.4%	2.9%	-4.5%	-5.1%	3.5%
	End of recov.		7.0%	1.5%		-7.3%	-5.6%

End of dosing: Day 92; end of 13-week dosing period
End of recov: Day 57 of the recovery period; end of the 8-week recovery period, which only included the 0, 15, and 30 mg/kg groups

Clinical Chemistry

Clinical Chemistry: % Change from Concurrent Control (13-Week Study; Rats)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
GLOB	Day 42	8.7%	8.7%	8.7%	9.5%	19.0%	14.3%
	End of dosing	3.6%	3.6%	3.6%	7.7%	7.7%	11.5%
	End of recov.		8.0%	4.0%		0%	0%
CHOL	End of dosing	-7.7%	-11.0%	-14.3%	-5.3%	-9.7%	-19.5%
	End of recov.		1.1%	13.7%		3.3%	-17.1%
TRIG	End of dosing	34.9%	7.0%	34.9%	-8.7%	10.9%	15.2%
	End of recov.		-0.9%	36.8%		66.7%	62.2%
PHOS	Day 42	8.0%	11.4%	8.0%	4.1%	5.4%	10.8%
	End of dosing	-1.3%	5.3%	4.0%	-3.0%	-1.5%	4.5%
	End of recov.		5.0%	6.7%		7.0%	16.3%

End of dosing: Day 92; end of 13-week dosing period
End of recov: Day 57 of the recovery period; end of the 8-week recovery period, which only included the 0, 15, and 30 mg/kg groups

Urinalysis	A dose-related increase of urine occult blood in MD and HD males and females occurred during the dosing period; it was reversible.
Gross Pathology	Skin findings upon macroscopic examination were consistent with skin-related clinical signs.

Gross Pathology Findings (13-Week Study; Rats)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Scabs	0	6	7	2	4	5
Sores	0	1	1	0	2	3

Note: There were no findings in the male or female control group, nor any treatment-related findings in any of the recovery groups.

Organ Weights	In males and females, dose-dependent increases in spleen weight were accompanied by increased extramedullary hematopoiesis, which partially resolved during the recovery period.

Organ Weights (13-Week Study; Rats)

mg/kg/day	**0**	**7.5**	**15**	**30**
Spleen (Males)				
Absolute weight	0.990 g (1.102 g)	11% (NA)	36% (16%)	47% (37%)
Spleen (Females)				
Absolute weight	0.570 g (0.671 g)	6% (NA)	9% (2%)	39% (-2%)

Note: Values in parentheses are from the recovery period.
Note: Values for the dosed groups are expressed as percent change relative to controls
NA: Recovery groups included only 0, 15, and 30 mg/kg

Histopathology (Adequate Battery: Yes)	Refer to Table 10 for selected histopathology findings. The main histological target organs were the skin and spleen, correlating with skin lesions and clinical pathology findings of suppressed RBC indices, respectively. Minimal mononuclear cell infiltration was also present in several tissue types.
Toxicokinetics	• Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose in males and females on Days 1, 42, and 91. • Entrectinib exposures were slightly higher in females than males, while M5 exposures were generally lower in females than males. • Entrectinib accumulation ratios in all treatment groups on Day 42 and 91 ranged from 1.24 to 1.91. • M5 accumulation ratios in the MD and HD treatment groups on Day 42 and 91 ranged from 1.61 to 7.97 (M5 was below the limit of quantitation for the LD groups on Day 1.)

Toxicokinetic Parameters for Entrectinib (13-Week Study; Rats)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	4	4	4	4	4	8
Cmax (µM)	0.382	0.589	1.40	0.344	0.756	1.77
AUC(0-24) (µM*hr)	3.13	6.87	15.5	4.11	8.22	22.0
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	8	8	8	8	4
Cmax (µM)	0.458	0.879	1.41	0.474	1.05	1.67
AUC(0-24) (µM*hr)	4.70	11.4	20.0	6.74	14.0	27.3
AUC(0-24) AR	1.50	1.66	1.29	1.64	1.70	1.24
Day 91						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.631	0.851	1.45	0.629	1.13	2.57
AUC(0-24) (µM*hr)	5.98	10.5	19.4	6.71	15.4	29.6
AUC(0-24) AR	1.91	1.53	1.25	1.63	1.87	1.35

Dose exposure multiple*	0.13X	0.27X	0.51X			

AR: Accumulation ratio; NA: Not applicable
*** Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses [F2A formulation] in Study STARTRK-1); sexes averaged; Day 91**

Toxicokinetic Parameters for M5 Metabolite (13-Week Study; Rats)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	NA	8	4	NA	4	8
Cmax (µM)	0	0.0255	0.0802	0	0.0088	0.0567
AUC(0-24) (µM*hr)	0	0.177	0.892	0	0.576	0.627
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	4	4	NA	4	4
Cmax (µM)	0.0285	0.0689	0.155	0	0.0368	0.0914
AUC(0-24) (µM*hr)	0.215	0.905	2.43	0	0.321	1.01
AUC(0-24) AR	NA	5.11	2.72	NA	5.57	1.61
Day 91						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.0521	0.0965	0.193	0.0062	0.0465	0.112
AUC(0-24) (µM*hr)	0.349	0.950	2.54	0.0218	0.459	1.10
AUC(0-24) AR	NA	5.37	2.85	NA	7.97	1.75

AR: Accumulation ratio; NA: Not applicable

LD: low dose; MD: mid dose; HD: high dose.
- or + : indicates reduction or increase in parameters compared to control.

Table 10: Selected Histopathology Findings (13-Week Study; Rats)

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Animals examined (dosing/recovery)	10/5	10/0	10/4	9/4	10/5	10/0	9/4	10/4
MARROW, FEMUR								
Hypercellular; minimal			2	4			1	2
Inflammation, chronic; minimal			1					
MARROW, STERNUM								
Hypercellular; minimal			3	5			1	2
MUSCLE, BICEPS FEMORIS								
Infiltrate, mononuclear cell; minimal				2				1
SKIN/SUBCUTIS								
Acanthosis								
--minimal			4	3		1	4	3
--slight			2	3				2
Crust, serocellular; present			6	6		2	4	6
Erosion/ulcer								
--minimal			1				1	1
--slight							2	1
--moderate			1	4			1	4
Granuloma; minimal				2			1	1
Hemorrhage								
--minimal			2	2			1	2
--slight				1				1

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Animals examined (dosing/recovery)	10/5	10/0	10/4	9/4	10/5	10/0	9/4	10/4
Infiltrate, mononuclear cell; minimal	1		2		1, 1R	1		
Inflammation, mixed cell								
--minimal			2	4		1	2	1
--slight			2	1			2	3
--moderate				1				2
SPLEEN								
Hematopoiesis, extramedullary, increased; minimal	3	2	6	7, 1R			2	6

R: Recovery cohort; "9/9" for that tissue type, only 9 specimens were examined instead of 10; finding was present in 9 of 9 specimens.
Note: Histopathology was only performed on control and high-dose groups, with the exception of macroscopic skin lesions, spleen, sternum bone marrow, and femur bone marrow that were also examined for the low-dose and mid-dose groups.
Note: Table does not include data from a few unscheduled sacrifices/deaths.

Study title / Study number: RXDX-101: 13-Week Toxicity and Toxicokinetic Study in Dogs with an 8-Week Recovery Phase / 1087343

Key Study Findings

- Key target organs were the skin and gastrointestinal tract.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 7.5, 15, 30 mg/kg/day
Daily for 13 weeks
Route of administration: Oral gavage
Formulation/Vehicle: 0.5 % (w/v) methylcellulose in reverse osmosis-purified water
Species/Strain: Dog / Beagle
Number/Sex/Group: Main: 4/sex/group
Recovery: 2/sex/group, 0 and 30 mg/kg only
Age: 7- 9 months
Satellite groups/unique design: None
Deviation from study protocol affecting interpretation of results: None that affected interpretation

Observations and Results: changes from control

Parameters	Major findings
Mortality	There were no unscheduled test article-related deaths.
Toxicity Mitigation (Dosing Suspensions, Veterinary Treatments)	Dose suspensions (in 2 HD animals; for 3 and 6 days) mitigated gastrointestinal toxicity, canned food mitigated weight loss, and skin issues necessitated soft padding and lanolin, nonsteroidal anti-inflammatory drugs and/or antibiotics.
Clinical Signs	Footpad skin sores and other skin toxicity occurred most frequently in high-dose males and females. Animals may have lacked adequate pain feedback to avoid damaging their feet. Gastrointestinal toxicity occurred at all dose levels but only required dose suspension at the HD level. Skin issues are described in the table below. Clinical signs generally reversed during the recovery period.

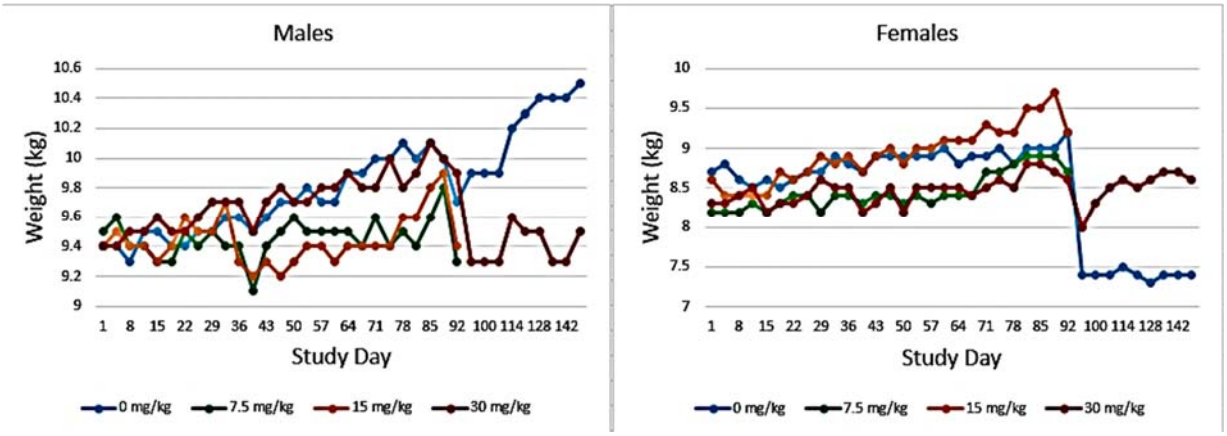
Skin-Related Clinical Signs (13-Week Study; Dogs)

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Dry skin; scaly skin; scabs	0	8	4	19, 2R	1	2	8	13, 1R
Sores; broken skin	0	3	0	14, 2R	0	0	2	8
Discolored skin	1	4	1	4	0	0	2	6
Swollen digits/limited use of leg/foot	0	1	0	4, 1R	0	0	2	4

R: Recovery groups (0 and 30 mg/kg only)

Body Weights and Feed Consumption	Overall, there was no clear dose-dependent effect on body weight or feed consumption during the dosing period, except for decreased feed consumption noted in several animals in (see Toxicity Mitigation section); an effect on weight loss was blunted by the humane use of canned food supplementation. During the recovery period, differences appeared to be based on recovery group (2/sex/group) mean weights at the start of that period, which did not closely reflect the respective means at the end of the dosing periods.

Mean Body Weights (13-Week Study; Dogs)



Note: Day 93 is the start of the recovery period (0 and 30 mg/kg; 2 animals/sex/group)

Ophthalmoscopy	Unremarkable

Electrocardiography	• In HD males during the dosing period, the QTc interval was higher than the control group on Days 40 and 90, predose and 2 hours post-dose; the change was statistically significant for Day 90 predose. • No notable changes in females.

QTc and QT Intervals in Males (13-Week Study; Dogs)

	Males			
mg/kg/day	**0**	**7.5**	**15**	**30**
QTc Interval (msec)				
Prior to start of dosing period	243	240	237	244
Day 40, predose	227	232	235	245
Day 40, 2 hours postdose	229	227	232	243
Day 90, predose	230	233	234	256*
Day 90, 2 hours postdose	236	232	243	252
Day 55 of the recovery period	239	NA	NA	239

*** p ≤ 0.05; NA: Only 0 and 30 mg/kg groups in the recovery period.**

Hematology and Coagulation	• Decreased RBC parameters occurred in males and females; these were partially reversible during the recovery period. • Increases in WBCs and neutrophils, likely associated with skin/footpad toxicities; these were partially reversible during the recovery period. A reversible increase in fibrinogen also occurred.

Hematology and Coagulation: % Change from Concurrent Control (13-Week Study; Dogs)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
RBC	End of dosing	-0.2%	-2.3%	-11.4%	-0.3%	-6.7%	-6.4%
	End of recov.			-1.0%			0%
RETIC	End of dosing	49.1%	20.3%	7.6%	-23.6%	-22.3%	-0.3%
	End of recov.			-0.7%			-33.7%
WBC	End of dosing	37.0%	31.8%	74.5%	4.3%	65.9%	27.4%
	End of recov.			-7.9%			-29.8%
NEUT	End of dosing	60.3%	63.4%	120.6%	19.7%	106.3%	43.3%
	End of recov.			-7.7%			-34.4%
MONO	End of dosing	40.0%	33.3%	96.7%	36.8%	142.1%	115.8%
	End of recov.			-35.6%			-23.2%
FIB	End of dosing	37.1%	29.0%	79.2%	3.9%	54.7%	79.7%
	End of recov.			7.4%			-23.0%

End of dosing: Day 90; end of 13-week dosing period
End of recov: Day 55 of the recovery period; end of the 8-week recovery period, which only included the 0 and 30 mg/kg groups

Clinical Chemistry	Partially reversible increases in globulin were likely associated with an inflammatory response to footpad/skin issues.

Clinical Chemistry: % Change from Concurrent Control (13-Week Study; Dogs)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
Albumin	End of dosing	-3.1%	-9.4%	-15.6%	-6.1%	-15.2%	-15.2%
	End of recov.			0%			0%
Calcium	End of dosing	-0.9%	-2.8%	-4.6%	-1.8%	-2.7%	-4.5%
	End of recov.			-4.5%			0%
Glucose	End of dosing	-7.5%	-6.5%	-6.5%	-1.0%	-10.4%	-7.3%
	End of recov.			3.2%			-2.9%
Phosphorus	End of dosing	2.0%	0.0%	-12.2%	-6.1%	0.0%	-18.4%
	End of recov.			-6.7%			-7.3%
Globulin	End of dosing	34.8%	21.7%	52.2%	19.0%	57.1%	47.6%
	End of recov.			9.5%			16.7%
Total Prot.	End of dosing	10.7%	1.8%	10.7%	3.7%	13.0%	9.3%
	End of recov.			5.6%			5.8%

End of dosing: Day 90; end of 13-week dosing period
End of recov: Day 55 of the recovery period; end of the 8-week recovery period, which only included the 0 and 30 mg/kg groups

Urinalysis	Unremarkable
Gross Pathology	After dosing period: Foot sores/scabs in 1 HD M and 2 HD F After recovery period: unremarkable
Organ Weights	Dose-dependent and non-reversible decreases in prostate weight occurred. Mild and reversible increases in liver weight at the MD and HD level in both sexes, and in spleen weight at the HD in both sexes, occurred.

Organ Weights (13-Week Study; Dogs)

mg/kg/day	**0**	**7.5**	**15**	**30**
Liver (Males)				
Absolute weight	284 g (296 g*)	11% (NA)	10% (NA)	17% (4%)
Liver (Females)				
Absolute weight	281 g (228 g)	-3% (NA)	10% (NA)	8% (13%)
Spleen (Males)				
Absolute weight	38.9 g (37.0 g)	-7% (NA)	-8% (NA)	44% (-10%)
Spleen (Females)				
Absolute weight	40.1 g (23.2 g)	-8% (NA)	20% (NA)	25% (-12%)
Prostate				
Absolute weight	7.3 g (9.5 g)	-8% (NA)	-19% (NA)	-35% (-33%)

*** Values in parentheses are from the recovery period.**
Note: Values for the dosed groups are expressed as percent change relative to controls
NA: Recovery groups included only 0 and 30 mg/kg

Histopathology **(Adequate Battery: Yes)**	Refer to Table 11 for selected histopathology findings. • The main histological target organ was the footpad. • Occasional findings in the kidney, liver, thymus, and rectum.
Toxicokinetics	Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose in males and females on Days 1, 42, and 91. No large differences in entrectinib or M5 exposure was noted in males versus females. Entrectinib accumulation ratios in all treatment groups on Day 42 and 91 ranged from 1.68 to 5.35. M5 accumulation ratios in all

	treatment groups on Day 42 and 91 ranged from 1.55 to 3.54.

Toxicokinetic Parameters for M5 Metabolite (13-Week Study; Dogs)

	Male			Female		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	4	3	4	4	4	4
Cmax (µM)	0.203	0.262	0.403	0.158	0.261	0.451
AUC(0-24) (µM*hr)	2.00	2.53	4.73	1.52	3.12	5.77
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.382	0.400	0.663	0.241	0.473	0.663
AUC(0-24) (µM*hr)	4.34	5.85	8.99	2.93	6.71	9.40
AUC(0-24) AR	2.85	2.49	1.92	1.80	3.11	2.00
Day 91						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.239	0.350	0.699	0.204	0.488	0.605
AUC(0-24) (µM*hr)	2.66	4.46	9.06	2.44	6.45	8.06
AUC(0-24) AR	1.92	2.13	1.95	1.55	3.54	1.59

AR: Accumulation ratio; NA: Not applicable

Toxicokinetic Parameters for Entrectinib (13-Week Study; Dogs)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	2	1.5	2	2	1.5	2
Cmax (µM)	0.195	0.274	0.528	0.136	0.229	0.564
AUC(0-24) (µM*hr)	1.06	1.52	3.31	0.773	1.92	4.17
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	2	2	3	2	2
Cmax (µM)	0.311	0.325	0.830	0.187	0.481	0.775
AUC(0-24) (µM*hr)	2.16	2.66	7.09	1.49	3.89	6.81
AUC(0-24) AR	3.73	1.79	2.01	1.97	3.15	1.93
Day 91						
Tmax (hr)	3	2	2	2	2	2
Cmax (µM)	0.276	0.496	0.912	0.226	0.978	0.839
AUC(0-24) (µM*hr)	1.93	3.39	8.04	1.81	5.04	7.09
AUC(0-24) AR	4.37	2.88	2.51	2.39	5.35	1.68
Dose exposure multiple*	0.04X	0.09X	0.16X			

AR: Accumulation ratio; NA: Not applicable
*** Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses [F2A formulation] in Study STARTRK-1); sexes averaged; Day 91**

LD: low dose; MD: mid dose; HD: high dose.
- or +: indicates reduction or increase in parameters compared to control.

Table 11: Selected Histopathology Findings (13-Week Study; Dogs)

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Animals examined (dosing/recovery)	4/2	4/0	3/0	4/2	4/2	4/0	4/0	4/2
ADRENAL, CORTEX								
Vacuolation; slight							1	1
FOOT/FOOTPAD								
Acanthosis; slight								2
Erosion/ulcer, skin								
--slight								1
--marked								1
Inflammation, acute; marked								1
Inflammation, mixed cell								
--slight								1
--moderate				1				
KIDNEY								
Dilatation, tubule(s); minimal		1						1
Infiltrate, mononuclear cell								
--minimal				1				1
--slight								
Regeneration, tubule cell								
--minimal			1	2	1			1
--slight								1
LIVER								
Infiltrate, mixed cell								
--minimal	1			2			1	1
--slight								1
PANCREAS								
Apoptosis, increased, acinar cell; min.	1		1				1	
RECTUM								
Erosion/ulcer, squamous epithelium, anus; minimal							2	1
Hemorrhage; minimal							1	
Infiltrate, neutrophils; minimal			1	1			2	2
URINARY BLADDER								
Mineralization; minimal			1			1		

R: recovery
Number per group: control and HD: 6/sex (4 to sacrifice at end of dosing; 2 to sacrifice at end of recovery)
LD and MD: 4/sex, 4 to sacrifice at end of dosing (none for recovery)
1 MD male was prematurely sacrificed due to behavior issues and is not included in the table.

General toxicology; additional studies

In a 4-week GLP-compliant toxicology study in Sprague Dawley rats (Study # 1087346), animals received entrectinib at doses of 50, 100, and 200 mg/kg/day via oral gavage. For the 200 mg/kg dose, the average exposure for males and females by AUC_{0-24} was 3.2 times the human exposure by AUC at the 600 mg dose. Findings were generally similar to those observed in the

13-week rat study; however, additional findings in the 4-week study included deaths of 3 high-dose females associated with CNS toxicity (lack of motor coordination), decreased female weights at the mid- and high-dose levels (no effect in males), corneal opacity at the high dose, and deficits in the modified Irwin's test (not performed in the 13-week study) predominantly at the high dose of 200 mg/kg, including abnormal gait and decreases in startle response, visual placing grip strength, and righting reflex.

In a 4-week GLP-compliant toxicology study in Beagle dogs (Study #1087335), animals received entrectinib at doses of 30, 60, and 120 mg/kg/day via oral gavage. For the 120 mg/kg dose, the average exposure for males and females by AUC_{0-24} was 3.2 times the human exposure by AUC at the 600 mg dose. Findings were generally similar to those observed in the 13-week dog study. Additional findings in the 4-week study included deaths of 4 females at the high dose associated with CNS toxicity (lack of coordination, abnormal gait, tremors, hypoactivity, and lateral recumbency) and gastrointestinal toxicity, additional CNS-associated clinical signs (stereotypy and depression), impaired weight gain (decreased weight gain compared to controls without weight loss), and QTc prolongation (observed in 2 of 4 males and in 4 of 4 females [mean increases of 29 and 80 msec, respectively] at 120 mg/kg; more pronounced than in the 13-week study).

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: NMS-1191372 (RO7102122; entrectinib): Bacterial Reverse Mutation Assay / 1087350

Key Study Findings:

- Entrectinib was not mutagenic in four *Salmonella typhimurium* strains or in one *Escherichia coli* strain, in the presence or absence of S9 activation
- Standard positive controls confirmed the sensitivity and validity of the assay.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA 1535, TA1537, and *Escherichia coli* strain WP2 uvrA; entrectinib tested up to 312.5 µg/plate; +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (Micronucleus and FISH) / 1087352

Key Study Findings:

- Entrectinib resulted in a statistically significant increase in micronuclei after a 24-hour incubation in the absence of S9 (Table 12); FISH analysis demonstrated that an aneugenic mechanism resulted in the micronuclei (data not shown).
- The performance of the positive controls confirmed the sensitivity and validity of the study.

Table 12: In Vitro Micronucleus Findings

	4 hours (no S9)		4 hours with S9		24 hours (no S9)	
Treatment	**% Cytotox.**	**Mean % MN**	**% Cytotox.**	**Mean % MN**	**% Cytotox.**	**Mean % MN**
Vehicle						
DMSO		0.4		0.3		0.5
Positive controls						
Mitomycin C	43-65	3.7**	NT	NT	NT	
Cyclophosphamide	NT	NT	43-72	1.3**	NT	
Vinblastine	NT	NT	NT	NT	32-64	1.3**
Entrectinib (µg/mL)						
3	4	NT	5	NT	6	**0.8**
7.5	12	**0.4**	13	**0.4**	22	**0.6**
15	30	**0.5**	32	**0.7**	53	**1.6****
20	49	NT	50	**0.6**	86	NT
25	52	**0.8**	51	NT	100	NT
30	81	NT	55	NT	100	NT
35	93	NT	57	NT		NT
40	98	NT	61	NT		NT
45	98	NT	74	NT		NT

4-hour doses:
24-hour doses:
Cytotox: Cytotoxicity, relative to DMSO vehicle control; MN: Micronuclei; NT: Not tested
** $p \leq 0.01$, relative to the DMSO control.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes; entrectinib up to 45 µg/mL; +/- S9
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: In Vivo Micronucleus and Comet Assay in Rats / 1087353
Key Study Findings:

- Entrectinib did not induce DNA damage in rat hepatocytes (as detected by a comet assay) or a significant increase in rat micronucleated bone marrow polychromatic erythrocytes.
- The performance of the positive controls confirmed the sensitivity and validity of the study.

GLP compliance: Yes
Test system: Rats, given entrectinib 0, 250, 1000, or 2000 mg/kg by oral gavage on Days 1, 2, and 3; (positive control: 200 mg/kg/day ethyl methanesulfonate [EMS] on Days 2 and 3; comet assay; bone marrow micronucleus assay
Study is valid: Yes

Other Genetic Toxicity Studies
None

5.5.3. Carcinogenicity

No studies were submitted or needed for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

While embryo-fetal development studies can detect anatomic malformations in brain structure, they are not designed to assess functional changes that might presage functional alterations in movement, nociception, behavior, or neuropsychiatric function. Numerous published reports describe the relationship between human congenital somatic mutations in the Trk signaling pathway and development of neuropsychiatric conditions such as schizophrenia and mood disorders (Krantz 2015; Otnaess et al., 2009; Knable 1999; Lewis et al., 2005). Others have demonstrated the role of Trk mutations in development of hyperphagic obesity, and peripheral sensory and motor disorders in humans (Indo et al., 1996; Yeo et al., 2004). Studies involving mice deficient in individual Trk receptors further support the crucial role of Trk signaling in development. Mice deficient in TrkA have sensory and sympathetic neuropathies but normal motor function; these animals typically die within 1 month of birth (Smeyne, 1994). Mice deficient in TrkB lack populations of motor neurons, dorsal root neurons, and trigeminal ganglia neurons and die shortly after birth (Klein, 1993). TrkC deficient mice appear normal at birth but develop abnormal posture and growth defects and generally die within a few weeks of birth (Klein, 1994). These studies demonstrate the critical role of Trk proteins in neural development.

Consistent with FDA guidance on the development of drugs to treat patients with advanced cancer, Genentech did not conduct a pre- and postnatal development study, though such a

study may have had greater capacity to detect relevant changes in functional endpoints, such as motor and nociceptive deficits.

Fertility and Early Embryonic Development; Prenatal and Postnatal Development
No studies were submitted or needed for the proposed indication.

Embryo-Fetal Development

Study title / number: RXDX-101: An Oral (Gavage) Study of the Effects on Embryo/Fetal Development in Rats / 1087361

Key Study Findings

- Entrectinib caused maternal toxicity at the HD (discharge from orifices) but did not cause maternal mortality or embryolethality.
- The incidence of the following malformations in the HD group (200 mg/kg; 2.7 times the human exposure by AUC at the 600 mg dose) exceeded the maximum historical control incidence: micromelia, omphalocele, gastroschisis, and adactyly, limb hyperextension, and filamentous tail.
- Skeletal malformations and variations occurred frequently in the HD group, and lower fetal weights and reduced skeletal ossification occurred at doses ≥12.5 and 50 mg/kg (approximately 0.2 and 0.9 times the human exposure by AUC at the 600 mg dose), respectively).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

<u>Methods</u>

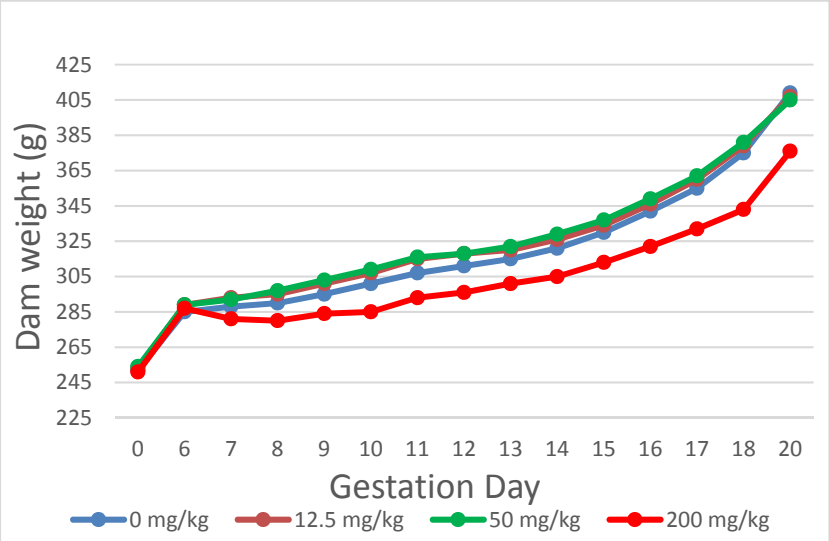
Dose and frequency of dosing:	0, 12.5, 50, or 200 mg/kg; daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in deionized water
Species/Strain:	Sprague Dawley [Crl:CD(SD)] rats
Number/Sex/Group:	25 females per group
Satellite groups:	Toxicokinetic groups (control: 4 rats; LD, MD, HD: 8 rats each)
Study design:	Time-mated rats were treated once daily via oral gavage from Gestation Days (GD) 6 to 17 Laparohysterectomies were performed on GD 20 TK was collected from 4 animals per group on GD 6 and 17 (1, 2, 4, 8, 12, and 24

	hours post dose)
Deviation from study protocol affecting interpretation of results:	None that affected study interpretation

Observations and Results

Parameters	Major findings
Mortality	No test article-related mortality
Clinical Signs	HD: Red material around nose (~4 hours post-dose, GD 13-20) HD: Red material around urogenital area; yellow material around urogenital area/rump; red vaginal discharge (~4 hours post-dose, GD 15-18)
Body Weights and Feed Consumption	Body weight gain and feed consumption were significantly decreased in HD dams.

Dam Weight (EFD Study; Rats)



Gravid Uterine Weights	Significant decreased mean gravid uterine weight in the HD group, attributed to lower fetal weights, was observed.
Necropsy Findings: Maternal, Gross	LD: Skin scabbing (1); Skin mass (1) MD: Nongravid (1); Skin scabbing (4) HD: Enlarged placenta (2); Red fluid in amniotic sac (1)
Necropsy Findings: Cesarean Section Data	No embryolethality was observed, but entrectinib caused intrauterine growth retardation in both sexes, statistically significant starting at the low dose.

Cesarean Section Data (EFD Study; Rats)

mg/kg/day	0	12.5	50	200
Pregnancy index (%)	100%	100%	96%	100%
# Females w/ viable fetuses for GD20 exam	25	25	24	25
Number pregnant	25	25	24	25
Number not pregnant	0	0	1	0
Gravid uterine weight (g)	87.5	↓0.1%	↓0.1%	↓23.8%**
Mean corpora lutea	17.4	17.2	17.5	16.8
Mean implantation sites	15.9	16.0	16.0	15.0
Mean % pre-implantation loss	7.7	6.3	7.6	8.5
Mean % post-implantation loss	6.5	3.8	4.3	4.2
Mean litter size***	14.8	15.4	15.4	14.4
Mean early resorptions	1.0	0.6	0.7	0.6
Mean late resorptions	1.0	0	1.0	0
Fetal weight change relative to controls				
Male (g)	3.9	↓5.1%*	↓10.3%**	↓35.9%**
Female (g)	3.7	↓5.4%*	↓10.8%**	↓35.1%**

*** Significantly different from control group (p<0.05)**
**** Significantly different from control group (p<0.01)**
***** Note: All fetuses were viable**

Necropsy Findings: Offspring	As shown in Table 13, the incidence of the following malformations in the HD group (200 mg/kg; 2.7 times the human exposure by AUC at the 600 mg dose) exceeded the maximum historical control incidence: micromelia, omphalocele, gastroschisis, and adactyly, limb hyperextension, and filamentous tail. Skeletal malformations and variations occurred frequently in the HD group and reduced skeletal ossification occurred at doses ≥ 50 mg/kg (approximately 0.9 times the human exposure by AUC at the 600 mg dose).
Toxicokinetics	Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose on GD 6 and 17. Entrectinib accumulation ratios in the 3 treatment groups on GD 17 ranged from 1.23 to 1.63. M5 accumulation ratios in the 3 treatment groups on GD 17 ranged from 1.72 to 7.05.

Toxicokinetic Parameters in Dams for Entrectinib and M5 (EFD Study; Rats)

	Entrectinib			M5 Metabolite		
mg/kg/day	12.5	50	200	12.5	50	200
Gestational Day 6						
Tmax (hr)	8	8	12	4	8	12
Cmax (µM)	0.518	2.43	5.12	0.005	0.079	0.184
AUC(0-24) (µM*hr)	6.24	33.8	89.5	0.016	0.851	2.96
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Gestational Day 17						
Tmax (hr)	8	2	12	4	4	4
Cmax (µM)	0.820	2.65	6.09	0.017	0.096	0.440
AUC(0-24) (µM*hr)	10.2	41.5	127	0.110	1.46	8.52
AUC(0-24) AR	1.63	1.23	1.42	7.05	1.72	2.88
Dose exposure multiple*	0.2X	0.9X	2.7X			

AR: Accumulation ratio; EFD: Embryo-fetal development; NA: Not applicable
*** Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses [F2A formulation] in Study STARTRK-1)**

LD: low dose; MD: mid dose; HD: high dose; GD: Gestation Day

Table 13: Fetal Malformations and Variations (EFD Study; Rats)

mg/kg/day	0	12.5	50	200
Number of Fetuses/Litters Evaluated	371/25	385/25	370/24	360/25
Gross malformations: # of fetuses affected, (% of fetuses); number of litters affected				
Micromelia				6 (1.7); 3
Omphalocele				2 (0.6); 2
Gastroschisis				2 (0.6); 2
Filamentous tail				1 (0.3); 1
Limb hyperextension				1 (0.3); 1
Adactyly				1 (0.3); 1
Localized fetal edema				1 (0.3); 1
Vertebral agenesis			1 (0.3); 1	
Hydrocephaly with or without dome head		1 (0.3); 1		
Gross variations: # of fetuses affected, (% of fetuses), # of litters affected				
Skin area(s) white				2 (0.6); 2
Visceral malformations: # of fetuses affected, (% of fetuses); # of litters affected				
Transposition of the great vessels				2 (0.6); 2
Situs inversus	2 (0.5); 2			
Trachea – cartilaginous rings absent				1 (0.3); 1
Retroesophageal aortic arch				1 (0.3); 1
Right-sided aortic arch				1 (0.3); 1
Lungs – lobular dysgenesis	1 (0.3); 1			
Visceral variations: # of fetuses affected (% of fetuses); # of litters affected				
Major blood vessel variation (HD:)		1 (0.3), 1	1 (0.3); 1	5 (1.4); 5
Renal papilla(e) not developed and/or distended ureter	6 (1.6); 5	2 (0.5); 2	2 (0.5); 2	3 (0.8); 3
Hemorrhagic ring around the iris		1 (0.3); 1	1 (0.3); 1	
Liver – accessory lobule(s)	2 (0.5); 1	2 (0.5); 1	1 (0.3); 1	
Thyroid gland(s) - small	1, 0.3, 1			
Skeletal malformations: # of fetuses affected (% of fetuses); # of litters affected				
Bent limb bone(s) (				50 (13.9**); 15
Only 12 pairs of ribs present				5 (1.4); 5
Vertebral anomaly and/or rib anomaly				4 (1.1); 4
Vertebral centra anomaly				3 (0.8); 3
Rib anomaly				3 (0.8); 3
Sternoschisis			1 (0.3); 1	1 (0.3); 1
Skeletal variations: # of fetuses affected (% of fetuses)				
Reduced ossification of the vertebral arches	4 (1.1)	2 (0.5)	31 (8.4)	320 (88.9)**
Bent rib(s)	1 (0.3)	3 (0.8)	32 (8.6)	280 (77.8)**
Unossified sternebra(e) #5 and/or 6	15 (4.0)	13 (3.4)	31 (8.4)	154 (42.8)**
Bent scapula(e)				147 (40.8)**
Reduced ossification of the skull	1 (0.3)	4 (1.0)	25 (6.8)	127 (35.3)**
Reduced ossification of the 13th rib(s)	2 (0.5)		5 (1.4)	119 (33.1)**
Reduced ossification of the rib(s)			9 (2.4)	77 (21.4)**
Sternebra(e) malaligned (slight or moderate)	1 (0.3)	5 (1.3)	6 (1.6)	19 (5.3)*
Unossified sternebra(e) #1, 2, 3, and/or 4			2 (0.5)	12 (3.3)
Unossified hyoid	3 (0.8)	7 (1.8)	3 (0.8)	12 (3.3)
Unossified pubis				5 (1.4)
Unossified ischium				1 (0.3)

mg/kg/day	0	12.5	50	200
Number of Fetuses/Litters Evaluated	371/25	385/25	370/24	360/25
Unco-ossified vertebral centra			1 (0.3)	1 (0.3)
25 presacral vertebrae			1 (0.3)	4 (1.1)
7th cervical rib(s)	6 (1.6)	4 (1.0)	4 (1.1)	8 (2.2)
Ossified cervical centrum #1	66 (17.8)	78 (20.3)	38 (10.3)	5 (1.4)
14th rudimentary rib(s)	25 (6.7)	34 (8.8)	10 (2.7)	1 (0.3)
27 presacral vertebrae		2 (0.5)	1 (0.3)	
14th full rib(s)		2 (1.5)		

* Significantly different from the control group at 0.05
** Significantly different from the control group at 0.01

+++In the summary tables, Genentech included a % by litter summary for malformations and variations, however, upon closer examination the calculations in these tables appears to represent the percentage of malformations in the total number of fetuses rather than a % litter calculation. Reproductive toxicology experts within the FDA confirm that the litter is the more appropriate read out for malformations and total numbers of litters with findings are therefore included in Table 13.

Juvenile Animal Data

Study title / number: RXDX-101: Oral (Gavage) 13-Week Toxicity Study in Juvenile Sprague-Dawley Rats with a 4-Week Recovery Period / 1087245

Key Study Findings

- Preterm deaths were associated with CNS toxicity (3 deaths), kidney toxicity (2), or skin toxicity (1).
- Key target organs were CNS, bone marrow, kidney, and skin
- Entrectinib caused decreased weight gain, femur length, delayed sexual maturation.
- CNS-related clinical signs included abnormal gait, tremors, decreased activity, convulsions, hunched posture, repetitive behavior, eyes partly closed, and piloerection; HD animals displayed deficits in spatial learning and memory (Morris water maze).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 4, 8, or 16 mg/kg, daily, Days 7 through 97
Route of administration: Oral gavage
Formulation/Vehicle: 0.5% (w/v) methylcellulose in reverse osmosis-purified deionized water
Species/Strain: Rats / Sprague-Dawley

Number/Sex/Group:	Subset 1: Main Study: 10M/10F/group Subset 2: Neurohistopathology:5M/5F/group Subset 3: Recovery: 20M/20F/group (of which 5M/5F for recovery neurohistopathology)
Satellite groups/unique design:	Subset 4: Toxicokinetics: 24M/24F/group, except 6M/6F in control group
Deviation from study protocol affecting interpretation of results:	None that affected study interpretation

Observations and Results

Parameters	Major findings
Mortality	Three preterm deaths associated with central nervous system (CNS) toxicity occurred at the HD. Two deaths (1 HD, 1 LD) were associated with kidney toxicity) and one death (HD) was accompanied by skin toxicity; deaths occurred after at least 2 weeks of dosing.
Clinical Signs	CNS-related clinical signs included abnormal gait, tremors, decreased activity, convulsions, hunched posture, repetitive behavior, eyes partly closed, and piloerection. Other clinical signs included dehydration (also seen in humans), skin scabs, and thin/lost fur.

Clinical Signs, Main Study Cohort, Dosing Period (Juvenile Study: Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Eyes, partly closed	10	10	10	10	10	10
Piloerection	10	10	10	10	10	8
Dehydration, suspected	4	2	5	2	3	6
Abnormal gait			5			5
Activity decreased					2	7
Tremors			3			
Hunched posture	1		2	1		
Convulsions, non-sustained			1			
Skin, scab						2
Breathing, labored						1
Prostration			1			
Low carriage						1
Skin, pale						1
Fur loss			1			
Fur staining, yellow						1
Fur staining, orange				1		

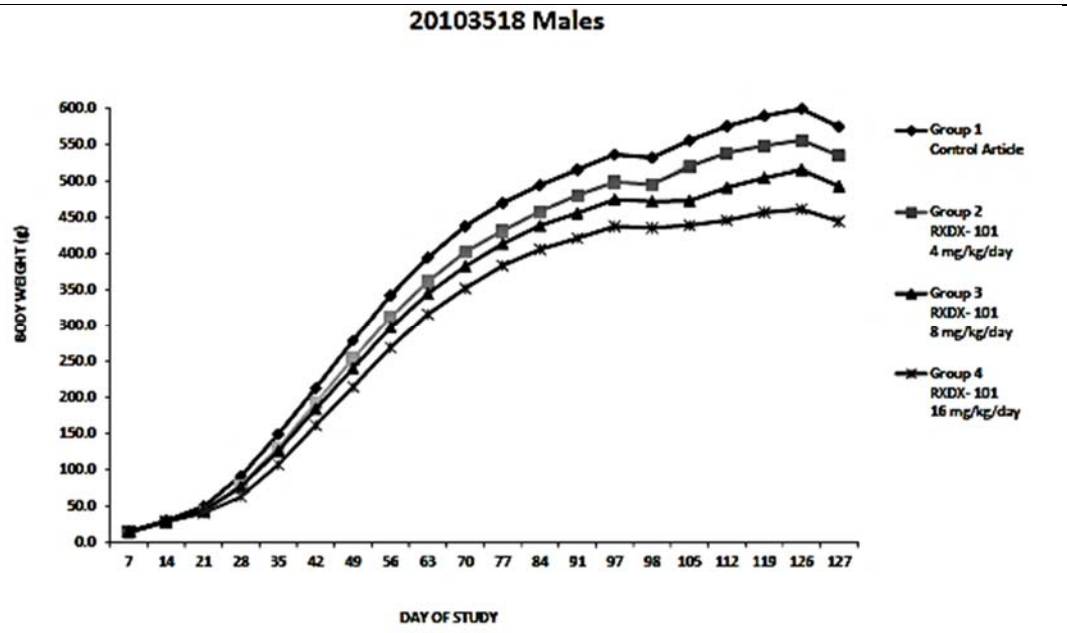
10/sex/group
There were no findings in any of the control animals.

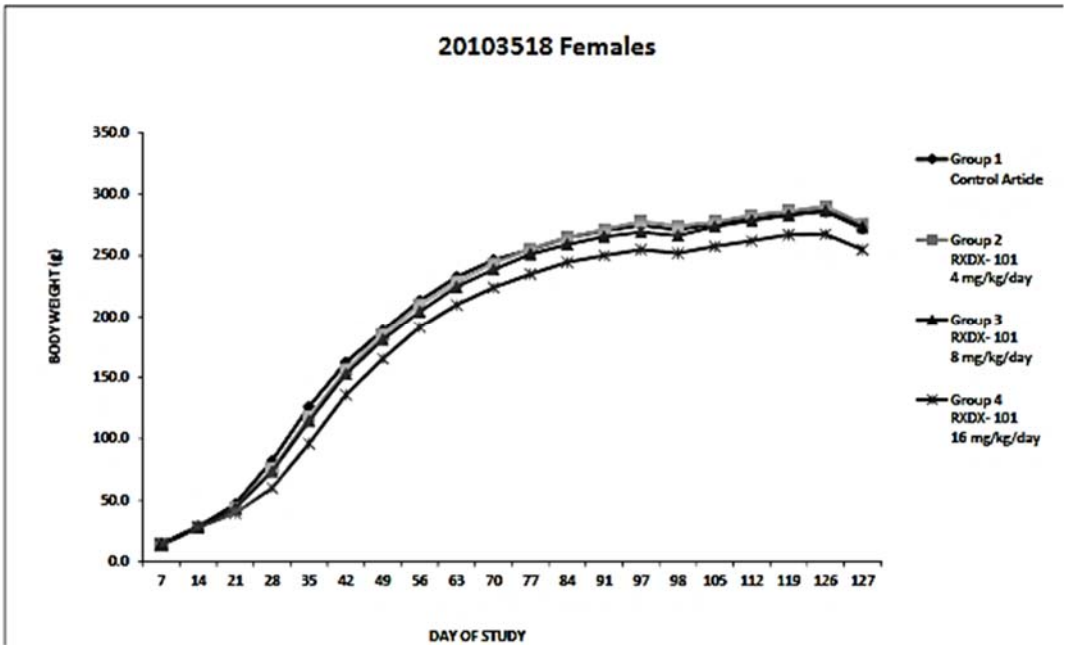
Clinical Signs, Recovery Cohort, Dosing and Recovery Periods (Juvenile Study: Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Activity decreased			7		4	12
Tremors			2			
Convulsions, non-sustained		1	1			
Respiratory rate increased			1			2
Skin, lesion	1					
Fur staining, orange					2	
Breathing, abnormal sounds	1					
Swelling						1
Malocclusion						1
Teeth, broken						1
Eyes, partly closed	19*	20*	20*			
Piloerection	19*	20	20*	20	20	16
Dehydration, suspected	6	6	11*	3	4	10
Abnormal gait			16*			14
Skin, scab	1	2*	4*		1	3*
Fur loss	1**	2*	3*			
Hunched posture	1		1*			2
Fur, thin cover		1**	1**			1**
Salivation			1**			
Repetitive behavior			1**			
Fur staining, red				1**		
Fur, ungroomed					1**	
Activity increased			1**			
Thin			1**			

20/sex/group; distinct subset of animals from the main study cohort.
There were no findings in any of the control animals, except for skin scabs (2 in M, 2 in F), and thin fur cover (2 in F).
No star: event that occurred only before Day 98;
* Event present during recovery period (≥Day 98) (at all; not necessarily in each animal)
** Event only occurred during recovery period

Body Weights and Feed Consumption	Impaired body weight gain and corresponding decreased food consumption, occurred at the HD for both sexes, and also in LD and MD males (with smaller decreases also occurring in the LD and MD females).





Femur Length	Slightly shorter femurs were observed in HD males and females (statistically significantly in females) at the end of the dosing period, with partial recovery by the end of the study.

Femur Length (Juvenile Study: Rats)

		Day 98				Day 128			
		Males		**Females**		**Males**		**Females**	
mg/kg/day	Length	RFL	LFL	RFL	LFL	RFL	LFL	RFL	LFL
0	mm	40.43	40.38	35.70	35.62	41.61	41.76	36.28	36.32
4	mm	39.82	39.18	35.51	35.29	41.50	41.61	35.61	35.58
	%Diff	-1.51	-2.97	-0.53	-0.93	-2.27	-0.37	-1.86	-2.04
8	mm	40.40	40.89	35.25	35.23	41.07	41.16	36.25	36.21
	%Diff	-0.07	1.26	-1.26	-1.10	-1.30	-1.44	-0.07	-0.29
16	mm	39.18	39.14	34.09**	34.20**	40.52	40.58*	35.31	35.25
	%Diff	-3.10	-3.08	-4.51	-3.99	-2.62	-2.83	-2.66	-2.95

RFL: Right femur length; LFL: Left femur length; mm: Mean femur length in millimeters; %Diff: percent change in length from concurrent control
Day 98: The day after the Day 7-97 dosing period; Day 128: The end of the recovery period.
*** p ≤ 0.05; ** p ≤ 0.01**

Sexual Maturation: (Balano-Preputial Separation and Vaginal Patency)	A dose-dependent delay in sexual maturation occurred in males and females (statistically significant for all dose groups), which was likely related to delayed growth.

Age at Sexual Maturation (Juvenile Study: Rats)

mg/kg/day	**0**	**4**	**8**	**16**	**Historical Control**
Balano-Preputial Separation (Mean Day) (Mean body weight [g])*	Day 43.9 (232.5 g)	46.7* (235.0)	48.5* (235.2)	50.1* (221.6)	41.3-49.7 (207.5-227.8)
Vaginal Patency (Mean Day) (Mean body weight [g])*	Day 31.9 (106.2 g)	33.3* (106.6)	34.7* (115.0)	36.8* (107.8)	30.1-35.3 (92.4-120.8)

Mean body weight: on the respective day
*** p ≤ 0.01**

Ophthalmology:	Mostly unremarkable; some sporadic blepharospasm occurred, possibly related to light sensitivity.
Functional Observation Battery	At the HD, decreased forelimb grip strength, hindlimb grip strength, and landing foot splay occurred (statistically significant in males, females, and males, respectively). Partially closed eyes occurred frequently. Although abnormal gait was not observed on the two instances where the functional observation battery was conducted, HD males and females displayed abnormal gait during daily observations for clinical signs.

Functional Observation Battery Results (Juvenile Study: Rats)

Dose Level (mg/kg/day)	0 (Control)		4		8		16	
Sex	Male	Female	Male	Female	Male	Female	Male	Female
PND 70 ± 3								
Palpebral Closure								
Wide open	20	20	9	20	0	6	1	3
Slightly drooping	0	0	10	0	15	14	5	11
Half-closed	0	0	0	0	5	0	13	5
Completely shut	0	0	0	0	0	0	0	0
Mean score	1.0	1.0	1.5**	1.0	2.3**	1.7**	2.6**	2.1**
Piloerection	0	0	0	0	0	0	0	0
Body Temperature (°C)	36.91	37.95	36.90	37.82	37.06	37.44*	36.95	37.39**
Body Weight (grams)	447.3	256.9	413.3**	247.6	386.6**	242.2*	358.1**	224.3**
PND 111 ± 3								
Palpebral Closure								
Wide open	10	10	5	10	3	9	3	4
Slightly drooping	0	0	5	0	6	1	4	6
Half-closed	0	0	0	0	1	0	3	0
Completely shut	0	0	0	0	0	0	0	0
Mean score	1.0	1.0	1.5*	1.0	1.8**	1.1	2.0**	1.6*
Piloerection	0	0	3	0	2	1	3	2
Forelimb Grip Test (grams)								
Maximum	1103.0	686.5	970.0	800.5	1087.0	727.0	721.0**	662.5
Average	945.8	580.0	836.0	689.3	895.8	562.0	579.3**	610.5
Hindlimb Grip Test (grams)								
Maximum	907.5	757.5	849.5	617.5*	877.5	678.0	795.0	584.5**
Average	854.5	677.0	779.0	569.3	808.0	608.0	727.0	548.5
Landing Foot Splay								
Average (cm)	7.91	6.23	7.64	5.84	6.15*	5.27	6.11*	7.06
Body Temperature (°C)	37.05	37.74	36.87	37.84	36.75	37.47	36.52	37.95
Body Weight (grams)	564.9	288.9	530.8	269.1	490.6**	282.3	442.3**	266.0

* = Statistically significant ($p \leq 0.05$)
** = Statistically significant ($p \leq 0.01$)

(Excerpted from Applicant's submission)

Motor Activity and Auditory Startle Response	Unremarkable
Morris Water Maze	Entrectinib treatment impaired spatial learning and memory, most evident at the HD. When a platform was present, HD animals failed to find it in the allotted time more frequently than did control animals. When the platform was absent, HD animals spent less time searching the location where it had been than did control animals. The observed impairment in memory is consistent with known effects of TrkA signaling deficiencies in humans (Indo et al., 1996).

Morris Water Maze: Control vs. High Dose (Juvenile Study: Rats)

Session	Sex/dose (mg/kg)/# rats	# Rats that did NOT reach 60 sec	# Rats that DID reach 60 sec	Total # of times reached 60 sec	% of time reached 60 sec
Session 1: On-treatment; between Days 80-96; platform present	Male / 0 / 20	9	11	25	16%
	Male / 16 / 19	2	17	52	34%
	Female / 0 / 20	7	13	34	21%
	Female / 16 / 19	2	17	74	49%
Session 2: On-treatment; between Days 80-96; platform present	Male / 0 / 20	18	2	2	1%
	Male / 16 / 19	10	9	22	14%
	Female / 0 / 20	14	6	11	7%
	Female / 16 / 19	12	7	19	13%
Session 1: Recovery; between Days 118-125; platform present	Male / 0 / 10	5	5	10	13%
	Male / 16 / 10	2	8	22	28%
	Female / 0 / 10	4	6	14	18%
	Female / 16 / 10	0	10	47	59%
Session 2: Recovery; between Days 118-125; platform present	Male / 0 / 10	10	0	0	0%
	Male / 16 / 10	9	1	2	3%
	Female / 0 / 10	8	2	2	3%
	Female / 16 / 10	3	7	22	28%

Note: There were 9 attempts per session. Attempt 1 of 9 for each session is not counted in this table.
Note: Maximum attempt time is 60 seconds. Assuming that a time of 60 seconds means the rat did not complete the task by the time limit.

Morris Water Maze: Percent of Time Searching Correct Quadrant (Platform Absent) (Juvenile Study: Rats)

	Males				Females			
mg/kg/day	**0**	**4**	**8**	**16**	**0**	**4**	**8**	**16**
Days 80 - 96	38.0	35.0	32.7	22.89*	29.0	36.7	30.8	30.0
Days 118 - 125	36.6	29.6	30.4	29.4	40.1	32.7	25.8**	22.6**

*** $p \leq 0.05$**
**** $p \leq 0.01$**

Hematology and Coagulation	In males and females, entrectinib resulted in partially reversible decreases in red blood cells, hemoglobin, and hematocrit (consistent with findings in adult rats and dogs, and clinical data).

Hematology % Change from Concurrent Control (Juvenile Study: Rats)

		Males			Females		
	mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Parameter	Time point						
RBC	End of dosing	-7.4%	-4.4%	-5.8%	-2.1%	-7.8%	-8.6%
	End of recov.	-1.8%	-5.2%	-1.4%	-0.8%	-3.1%	-3.0%
HGB	End of dosing	-7.1%	-4.5%	-5.8%	-2.1%	-7.8%	-8.6%
	End of recov.	-2.0%	-6.5%	-5.2%	-5.4%	-4.1%	-4.8%
HCT	End of dosing	-6.4%	-5.1%	-5.9%	-3.4%	-7.0%	-7.9%
	End of recov.	-1.9%	-7.8%	-4.8%	-4.9%	-5.6%	-4.5%

End of dosing: Day 98
End of recovery: Day 128

Clinical Chemistry	Increases in creatinine (also observed in humans) were noted in males; this change persisted in the recovery period.

Clinical Chemistry % Change from Concurrent Control (Juvenile Study: Rats)

		Males			Females		
	mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Parameter	Time point						
UN	End of dosing	16.7%	23.3%	43.3%	5.1%	9.5%	21.9%
	End of recov.	6.7%	23.5%	22.1%	-2.2%	-0.5%	7.7%
CREAT	End of dosing	4.3%	26.1%	21.7%	6.7%	3.3%	-6.7%
	End of recov.	6.9%	41.4%	34.5%	0%	2.6%	7.9%
TRIG	End of dosing	-38.0%	-46.5%	-32.4%	-13.9%	-19.4%	-13.9%
	End of recov.	-30.7%	-42.0%	-48.9%	-10.9%	-34.5%	-43.6%
GLU	End of dosing	-11.9%	-11.2%	-19.4%	-5.0%	-0.8%	-9.2%
	End of recov.	3.4%	8.2%	16.4%	-11.0%	-15.1%	-16.3%
ALB	End of dosing	-11.4%	-5.7%	-8.6%	2.7%	-2.7%	-5.4%
	End of recov.	-2.6%	-5.3%	-2.6%	4.9%	-2.4%	-4.9%
Ca	End of dosing	-6.7%	-5.6%	-4.4%	2.3%	-1.1%	0%
	End of recov.	0%	-3.2%	-2.1%	3.1%	-2.1%	-1.0%
AST	End of dosing	1.4%	8.2%	24.7%	2.5%	-3.8%	22.8%
	End of recov.	4.8%	2.4%	-3.6%	19.7%	35.5%	3.9%

End of dosing: Day 98
End of recovery: Day 128

Urinalysis	Unremarkable
Gross Pathology	Mostly unremarkable, except for the following: • HD male #3502, which was found dead: Kidney dilatation, adhesion, enlargement, and masses; liver adhesion; discoloration; abnormal appearance; and urinary bladder calculi • MD male #2802: Kidney dilatation • MD male #2804: Kidney dilatation • LD male #2201: Kidney dilatation • HD male #1303 (TK subset), preterm sacrifice: Kidney and jejunum dilatation; abnormal material accumulation in kidney, colon, and urinary bladder; discoloration of liver, lung, small intestine, and stomach
Organ Weights	Increased spleen weights occurred (statistically significant in males ≥ LD and in females at HD). This finding was accompanied by extramedullary hematopoiesis (more in males than in females).

Spleen Weights (Juvenile Study; Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Absolute weight	8.88% (8.76%)	7.28% (9.45%)	7.40% (9.84%)	2.15% (20.13%)	10.18% (27.90%)	20.20% (17.00%)
Body weight ratio (%)	17.34% (16.59%)	17.07% (33.01%)	25.59% (40.10%)	4.42% (15.69%)	14.06% (28.48%)	32.50% (26.37%)

Note: Values in parentheses are from the recovery period.
Note: Values are expressed as percent change relative to controls

Histopathology (Adequate Battery: Yes)	As shown in Table 14, key histological target organs were the spleen and skin.
Neurohistopathology	In HD males and females, statistically significantly lighter brains occurred; however, these were proportional to lower body weights in those dose groups. At the end of the dosing and recovery periods, there were no entrectinib-related neurohistopathology findings in the sections of the brain, spinal cord, Gasserian ganglia, 5th cranial nerve, eyes, dorsal root ganglia and spinal nerves, peripheral nerves or skeletal muscles examined.

Brain Measurements (nm)

	Males				Females			
mg/kg/day	**0**	**4**	**8**	**16**	**0**	**4**	**8**	**16**
Body weight (g)	555.4 (530.8)	480.2 (486.8)	545.6 (508.2)	452.8* (419.8**)	281.4 (276.4)	278.0 (260.6)	277.2 (279.8)	262.2 (266.8)
Brain weight (g)	2.41 (2.40)	2.29 (2.29)	2.30 (2.29)	2.11** (2.14**)	2.19 (2.02)	2.14 (2.18)	2.11 (2.10)	2.02** (2.03)
% of body weight	0.44 (0.46)	0.48 (0.47)	0.42 (0.46)	0.47 (0.51)	0.79 (0.74)	0.77 (0.84)	0.77 (0.76)	0.78 (0.77)
Cerebrum Length	17.89 (16.91)	17.25 (16.93)	17.11 (16.17)	16.85 (16.38)	17.30 (16.50)	16.85 (16.79)	16.01 (16.37)	16.32 (16.34)
Cerebellum Length	11.96 (11.52)	11.77 (11.63)	11.48 (11.46)	11.71 (11.42)	11.64 (11.63)	11.51 (11.71)	11.60 (11.37)	11.21 (11.58)
Brain Morphometry (µm, Day 98)								
Frontal cortex thickness	1926	NA	NA	1868	1978	NA	NA	1892
Parietal cortex thickness	2210	NA	NA	1939	2134	NA	NA	1985
Caudate-putamen width	3829	NA	NA	3395	3811	NA	NA	3504
Corpus callosum thickness	371	NA	NA	275	328	NA	NA	282
Hippocampus thickness	1594	NA	NA	1602	1554	NA	NA	1550
Cerebellum height	5649	NA	NA	5254	5153	NA	NA	5493

Values at Day 98 (Values at Day 127; end of recovery period)
*** p < 0.05; ** p < 0.01; NA: Not assessed**

Toxicokinetics	Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose in males and females on PND 7 (Dosing Day 1), and for the 4 mg/kg to 8 mg/kg dose interval on Day 97. Exposure was less than dose proportional between the 8 and 16 mg/kg doses on Day 97. Exposure was generally similar in males and females, except for higher entrectinib exposure in females at the 8 mg/kg and 16 mg/kg doses on Day 97. Entrectinib exposure was higher on Day 7 than on Day 97. Entrectinib accumulation ratios in all treatment groups on Day 97 ranged from 0.285 to 0.745. M5 accumulation ratios in all treatment groups on Day 97 ranged from 0.018 to 0.069.

Toxicokinetic Parameters for Entrectinib (Juvenile Study; Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Postnatal Day 7						
Tmax (hr)	4	8	8	4	12	8
Cmax (µM)	0.456	0.614	1.22	0.341	0.615	1.24
AUC(0-24) (µM*hr)	7.48	11.0	21.6	6.05	10.8	19.8
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Dose exposure multiple*	0.16X	0.23X	0.45X	0.13X	0.23X	0.41X
Postnatal Day 97						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.288	0.683	0.822	0.398	0.843	1.00
AUC(0-24) (µM*hr)	2.20	5.78	6.29	3.12	8.08	11.1
AUC(0-24) AR	0.285	0.526	0.291	0.516	0.745	0.560
Dose exposure multiple*	0.05X	0.12X	0.13X	0.07X	0.17X	0.23X
Dose exposure multiple compared to human*						
Day 7: both sexes	0.14X	0.23X	0.43X			
Day 97: both sexes	0.06X	0.14X	0.18X			
Average of Days 7 & 97: both sexes	0.10X	0.19X	0.31X			

AR: Accumulation ratio; NA: Not applicable
*** Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses of the F2A formulation in Study STARTRK-1)**

Toxicokinetic Parameters for M5 Metabolite (Juvenile Study; Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Postnatal Day 7						
Tmax (hr)	12	8	8	8	12	8
Cmax (µM)	0.025	0.037	0.061	0.024	0.030	0.054
AUC(0-24) (µM*hr)	0.326	0.420	1.08	0.297	0.359	0.882
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Postnatal Day 97						
Tmax (hr)	NC	4	4	NC	4	4
Cmax (µM)	BLQ	0.046	0.069	BLQ	0.018	0.031
AUC(0-24) (µM*hr)	NC	0.304	0.418	NC	0.062	0.192
AUC(0-24) AR	NC	0.725	0.389	NC	0.173	0.217

AR: Accumulation ratio; NA: Not applicable; NC: Not calculated

Table 14: Selected Histopathology Findings (Juvenile Study; Rats)

	Males				Females			
mg/kg/day	**0**	**4**	**8**	**16**	**0**	**4**	**8**	**16**
Animals examined (dosing/recovery)	10/15	10*/13	10*/15	9/13	10/15	10*/15	10*/15	10/14
BONE MARROW								
Increased cellularity; mild								1
ESOPHAGUS								
Regeneration; myofiber; wall; minimal								1
Infiltration, mononuclear cell; wall; min.								1
HEART								
Cardiomyopathy; minimal	3			7	1			3
Necrosis; vascular, adipose tissue; min.				1				
KIDNEY								
Nephropathy								
--minimal	6			3	3			2
--mild				1				
Dilatation; tubular; minimal	1			3				3
Dilatation; pelvis								
--minimal				1				
--mild				1				
LIVER								
Tension lipidosis; minimal				1				1
Inflammation, granulomatous; minimal								1
SKIN								
Hyperkeratosis; minimal	2R		1, 1R		1R		1, 1R	1
Fibrosis; dermal; minimal	2R	2	4, 2R	2, 3R	1, 3R	3, 5R	6, 6R	1
Hyperplasia; epidermal								
--minimal	4R	2, 1R	4, 3R	3, 4R	1, 6R	3, 7R	7, 7R	2
--mild			1, 1R					
Infiltration, mononuclear cell; dermal; minimal	2R	1R	1	2	1, 3R	1	2, 1R	2R
Infiltration, mononuclear cell; follicle; minimal								1
Crust; mild								
--minimal		1R			1R			1R
--mild			1, 1R					
Single cell necrosis; epidermal; min.			1R					
SPLEEN								
Increased hematopoiesis								
--minimal	2, 1R	4, 5R	4, 1R	4, 3R	1, 1R	2, 1R	1	2
--mild		3					1R	1
Congestion								
--minimal	4, 5R	4, 5R	7, 11R	2, 4R	3, 2R	4, 6R	2, 5R	6, 5R
--mild	2	5, 8R	1, 4R	7, 9R		8R	5, 6R	3, 6R

* Only spleen, skin (inguinal), and bone marrow were examined for the LD and MD groups.

5.5.5. Other Toxicology Studies

The results of a GLP-compliant neutral red uptake (NRU) assay in BALB/c 3T3 mouse fibroblast cells (Study #1087359), an in vitro screen for phototoxicity, indicated that entrectinib has some phototoxic potential, with a Photo Irritation Factor (PIF) of approximately 6 (PIF=60 for the promethazine positive control). A follow-up GLP-compliant in vivo phototoxicity study (Study #1087360) assessed the potential phototoxic effects of entrectinib (0, 50, 100, or 200 mg/kg/day for 3 days) in Long-Evans female pigmented rats (5/group). Grade 1 erythema and edema occurred in one animal at the 200 mg/kg dose. Microscopic examination of the eyes revealed neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium at 200 mg/kg, with and without ultraviolet radiation exposure (UVR), and at 100 mg/kg with UVR. Given the observations in the absence of UVR, changes were considered entrectinib-related but not indicative of significant phototoxicity.

A GLP-compliant skin irritation study (Study #1087357) indicated that entrectinib did not irritate the intact skin of New Zealand White rabbits. A GLP-compliant eye irritation study (Study #1087358) indicated that entrectinib (a single 100-mg application) caused a transient ocular irritation reaction in New Zealand White rabbits, which resolved within one week.

Brain penetration of entrectinib was confirmed in a non-GLP compliant 2-week oral repeat dose toxicology study in rats (Study #1087347) at 24-hour post dose. Entrectinib brain to plasma ratios reached 2.5 and 2.3 for males and females, respectively, when treated with 400 mg/kg of entrectinib daily for 2 weeks.

X _____ X _____

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6 Clinical Pharmacology

6.1. Executive Summary

The primary data supporting the clinical pharmacology component of the NDA are from patients enrolled in STARTRK-2 (Study RXDX-101-02) and STARTRK-1 (Study RXDX-101-01). In addition, clinical pharmacology studies were conducted to investigate following key clinical pharmacology characteristics: mass balance and metabolism, population PK (popPK) analyses of the effect of covariates on entrectinib systemic exposure, potential prolongation of QT/QTc interval, effect of food or proton-pump inhibitor (PPI) on entrectinib systemic exposure, potential PK drug-drug interactions (DDI) between entrectinib and a strong inhibitor or a strong inducer of Cytochrome P450 3A4 (CYP3A4), effect of entrectinib on the PK of a sensitive CYP3A4 substrate, exposure-response (E-R) relationship analyses for efficacy and safety.

Entrectinib is primarily metabolized by CYP3A4 to form a major active metabolite M5, with minimal excretion of both entrectinib and M5 into urine. The popPK analyses did not identify clinically significant covariates influencing entrectinib exposure. Entrectinib dose adjustment is not necessary in patients with mild hepatic impairment or in patients with mild or moderate renal impairment. Dose adjustment is recommended when entrectinib is coadministered with strong or moderate CYP3A4 inhibitors. Coadministration of strong or moderate inducers of CYP3A4 with entrectinib should be avoided. Results from a QTc sub-study did not suggest a clinically meaningful increase (i.e., 20 ms) from baseline in QTcF with entrectinib treatment.

The efficacy and safety profiles support the proposed entrectinib dosing regimen of 600 mg orally once daily (QD) without regard to food. ORR as assessed by BICR was 78% (95% CI: 65%, 89%) in 51 patients with *ROS1*-positive metastatic NSCLC who received entrectinib at various doses and schedules (90% received entrectinib 600 mg daily). The E-R analyses suggest a flat relationship for efficacy but a correlation of entrectinib and M5 exposures with the incidence of severe (Grade ≥3) AE, especially in patients achieving higher exposure when administered with 800 mg QD entrectinib dose.

Recommendations

The Office of Clinical Pharmacology has reviewed the data and information contained in NDA 212725. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Table 15: Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from the ALKA-372-001, STARTRK-1 and STARTRK-2 studies. ORR as assessed by BICR was 78% (95% CI: 65%, 89%) in 51 who received entrectinib at various doses and schedules (90% received entrectinib 600 mg daily) in the *ROS1*-positive primary efficacy set.
General dosing instructions	The recommended dosage is 600 mg once daily (QD) with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is needed for patients with mild hepatic impairment. The PK of entrectinib in patients with moderate and severe hepatic impairment is unknown. A PMR will be issued for a hepatic impairment study. • No dose adjustment is needed for patients with mild and moderate renal impairment. Although the PK of entrectinib in patients with severe renal impairment is unknown, significant effect of severe renal impairment on entrectinib exposure is not expected based on minimum involvement of renal elimination pathway. • Reduce dose to 100 mg QD or to 200 mg QD for patients concomitantly taking strong CYP3A4 inhibitors or moderate CYP3A4 inhibitors, respectively. • Avoid concomitant use with strong and moderate CYP3A4 inducers.
Bridging between the to-be-marketed formulation and clinical trial formulations	A bioequivalence is demonstrated between the main clinical trial formulation F2A and the to-be-marketed formulation F06 in the pivotal BE study RXDX-101-15.
Labeling	The review team has specific content and formatting change recommendations. Significant modifications to the label made by the FDA include languages regarding dose modifications for drug-drug interactions (DDI) in Section 2.4 and Section 7, the statement about E-R relationship and cardiac electrophysiology in Section 12.2, and the format and content in Section 12.3.

Table 16: Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Entrectinib dose in patients with moderate and severe hepatic impairment.	Entrectinib is extensively metabolized in liver and forms a major active metabolite M5. There is no pharmacokinetic data to recommend entrectinib dose for patients with moderate and severe hepatic impairment. The clinical trial can provide understanding for entrectinib dose adjustment for this patient subpopulation.	Complete planned clinical pharmacokinetic trial to determine an appropriate dose of entrectinib in patients with moderate and severe hepatic impairment.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Refer to the Clinical Pharmacology section in the multidisciplinary review for NDA 212726.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Genentech proposed a dosing regimen of 600 mg orally once daily (QD) with or without food, which is acceptable.

Therapeutic Individualization

Refer to the Clinical Pharmacology section in the multidisciplinary review for NDA 212726.

Outstanding Issues

No outstanding issues, other than the requested PMR study, identified from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Refer to the Clinical Pharmacology section in the multidisciplinary review for NDA 212726.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

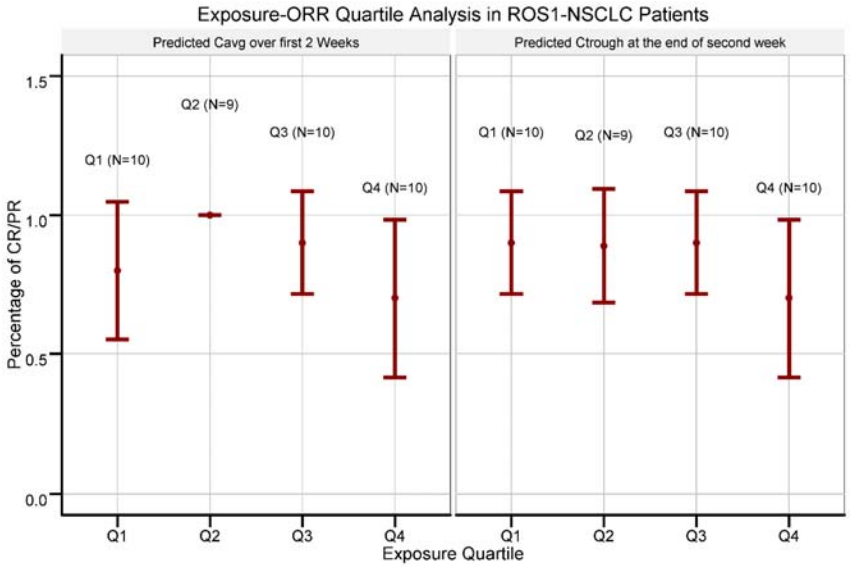
Yes, the clinical pharmacology information along with the efficacy results provided evidence of effectiveness.

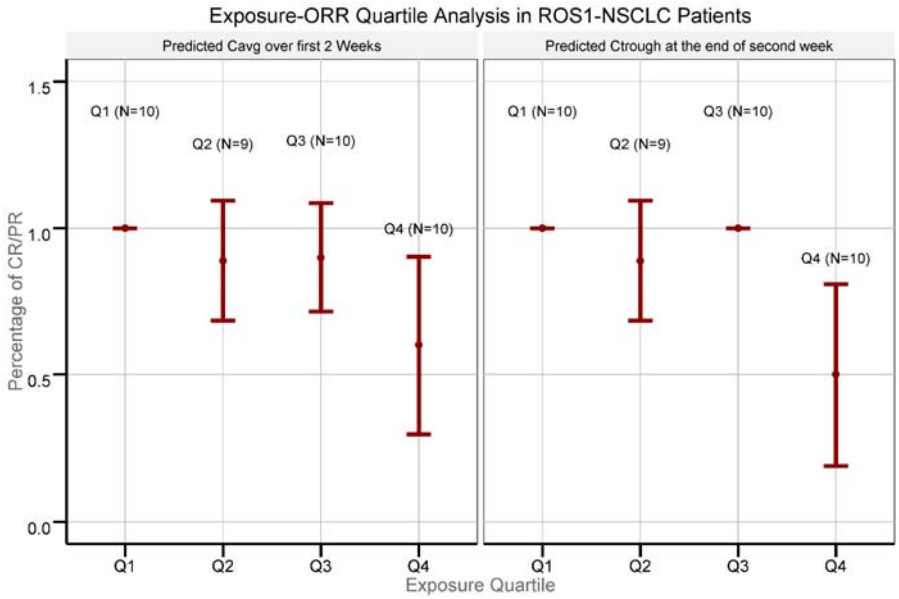
The primary evidence of effectiveness came from 51 patients with *ROS1*-positive metastatic NSCLC enrolled in the ALKA-372-001, RXDX-101-01, and RXDX-101-02 studies who received entrectinib at various doses and schedules (90% received entrectinib 600 mg daily) with the F2A formulation under fed condition. The estimated ORR as assessed by the BICR was 78% (95% CI: 65%, 89%).

Exploratory exposure-response (E-R) analyses were conducted to compare the response in 39 patients with *ROS1*-positive metastatic NSCLC. Caution should be used when interpreting these relationships as they were based on small sample size with one dosing regimen.

In the E-R analysis, there is no clear relationship between entrectinib and M5 exposure and ORR. The response rates were comparable across the different exposure quartiles (Figure 18).

Figure 18: Relationship Between Entrectinib (Top Panel) and M5 (Bottom Panel) Exposure and ORR in Patients With *ROS1*-Positive NSCLC

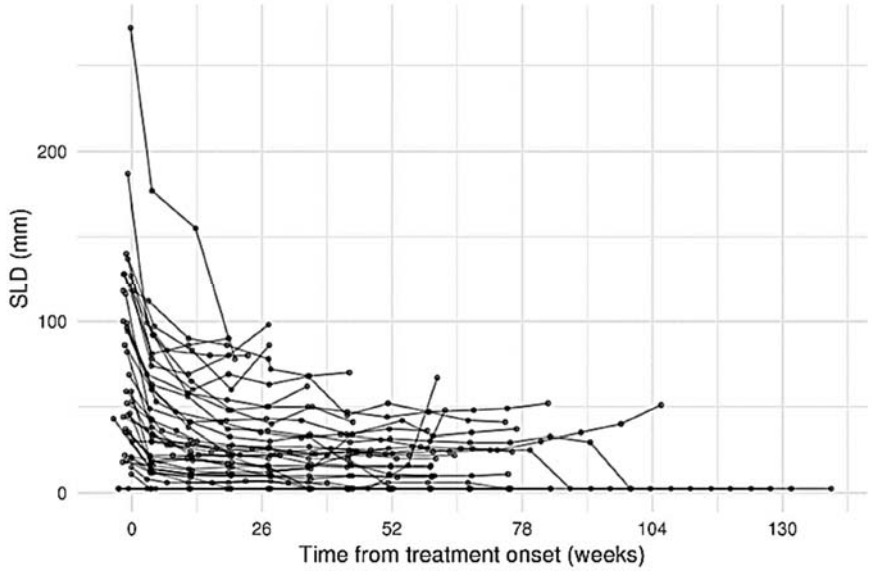




Source: Reviewer's Analysis based on "poppk.xpt" and "ars.xpt"

The effectiveness of entrectinib is also supported by the observed decrease in the sum of longest diameter (SLD) values in patients with *ROS1*-positive NSCLC treated with entrectinib as shown in Figure 19 below.

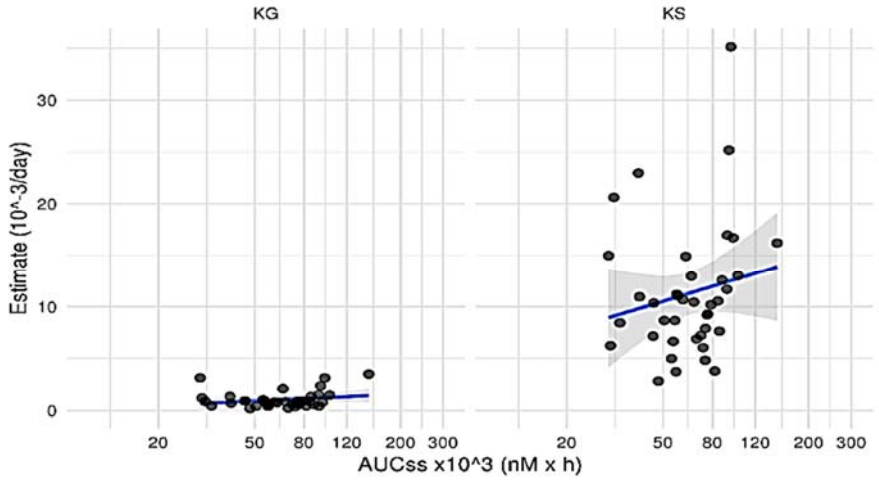
Figure 19: SLD Values Over Time in *ROS1*-Positive NSCLC Patients (N=39)



Source: Summary of Clinical Pharmacology, Figure 28

However, as shown in Figure 20, there is no significant trend between combined entrectinib and M5 exposure and tumor growth rate (KS) and tumor shrinkage rate (KS). The lack of correlation between PK exposure and the tumor growth and shrinkage parameters may be related to the limited exposure range assessed or the plateau of the pharmacological activity at the recommended therapeutic dose of 600 mg.

Figure 20: Tumor Growth (KG) and Tumor Shrinkage (KS) Rates as a Function of Exposure (AUC_{SS}) in *ROS1*-Positive NSCLC Patients



Note: The blue line and associated grey area represent linear regression models used for illustrative purpose only.

Source: Summary of Clinical Pharmacology, Figure 26

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

Yes. The proposed dosing regimen is generally supported by the E-R relationships in efficacy and safety. See the previous question for E-R in efficacy.

For tolerability, at 600 mg QD, there were 34% of the patients with *ROS1*-positive NSCLC who had entrectinib dose reduction due to an adverse event. The proposed dose reduction strategy (from 600 mg to 400 mg and then 200 mg QD) in the event of adverse events is acceptable. Dose re-escalation is not recommended due to the lack of supporting clinical data

For additional exploratory E-R analyses on safety, see Clinical Pharmacology section in the multidisciplinary review for NDA 212726.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

See Clinical Pharmacology section in the multidisciplinary review for NDA 212726.

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

See Clinical Pharmacology section in the multidisciplinary review for NDA 212726.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 17 lists the clinical trials included in the NDA submission. The evidence to support the clinical efficacy of entrectinib in patients with metastatic *ROS1*-positive NSCLC was obtained from the ALKA, STARTRK-1 and STARTRK-2 studies. The primary efficacy analysis population includes the first 51 consecutively enrolled patients with ROS1-positive NSCLC, who had not received prior treatment with a ROS1 TKI, had measurable disease at baseline and had ≥12 months follow up from date of first post-treatment tumor assessment.

The data used to characterize the safety profile of entrectinib are also from the ALKA, STARTRK-1 and STARTRK-2 studies, along with data from the STARTRK-NG study, a clinical trial in pediatric patients. The primary safety population includes all patients (n=355) enrolled on these studies who received at least one dose of entrectinib at any dose level and schedule.

Table 17: Summary of Studies Contributing to the Efficacy and Safety of Entrectinib in Patients With *ROS1* Fusion NSCLC

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients	Study Population
Studies Contributing to the Primary Efficacy Analysis Population for Assessment of Entrectinib in Patients with ROS1-positive NSCLC						
ALKA-372-001 (ALKA)	Phase I: First-in-human, single arm, multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Schedule A: 100, 200, 400, 800, 1200, or 1600 mg/m2 once daily (fasted) 4 -days on 3-days off schedule for 3 weeks followed by a 7-day rest in a 4-week cycle b Schedule B: 100, 200, 400 mg/m2/day, or 600 mg/day continuous once daily (fed) in a 4-week cycle c Schedule C: 400 or 800 mg/m2 once daily (fed) in a continuous 4-days on, 3-days off schedule in a 4-week cycle d	MTD	12-month f/u from first dose	9	Patients (≥18 years old) with advanced or metastatic solid tumors with TRKA/B/C, ROS1, or ALK molecular alterations
RXDX-101-01 (STARTRK-1)-	Phase I: Multicenter, single arm, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	100, 200, 400 mg/m2 once daily, 600, or 800 mg continuous once daily (fed) on 28-day (4-week) cycles	MTD, RP2D ORR	12-month f/u from first dose	7	Patients (≥18 years old) with solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations
RXDX-101-02 (STARTRK-2)	Phase II: Global, multicenter, single arm, open-label, basket study	600 mg, orally, once daily, in 28-day (4-week) cycles	ORR by BICR	12-month f/u from first dose	35	Patients (≥18 years old) with advanced or metastatic solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusion (excluding *ALK*-positive NSCLC)

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients	Study Population
Studies Contributing to Safety of Entrectinib						
ALKA-372-001 (ALKA)	Phase I: First-in-human, single arm, multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Schedule A: 100, 200, 400, 800, 1200, or 1600 mg/m2 once daily (fasted) 4 -days on 3-days off schedule for 3 weeks followed by a 7-day rest in a 4-week cycle b Schedule B: 100, 200, 400 mg/m2/day, or 600 mg/day continuous once daily (fed) in a 4-week cycle c Schedule C: 400 or 800 mg/m2 once daily (fed) in a continuous 4-days on, 3-days off schedule in a 4-week cycle d	MTD	12-month f/u from first dose	57	Patients (≥18 years old) with advanced or metastatic solid tumors with TRKA/B/C, ROS1, or ALK molecular alterations
RXDX-101-01 (STARTRK-1)-	Phase I: Multicenter, single arm, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	100, 200, 400 mg/m2 once daily, 600, or 800 mg continuous once daily (fed) on 28-day (4-week) cycles	MTD, RP2D ORR	12-month f/u from first dose	76	Patients (≥18 years old) with solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations
RXDX-101-02 (STARTRK-2)	Phase II: Global, multicenter, single arm, open-label, basket study	600 mg, orally, once daily, in 28-day (4-week) cycles	ORR by BICR	12-month f/u from first dose	206	Patients (≥18 years old) with advanced or metastatic solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusion (excluding *ALK*-positive NSCLC)
STARTRK-NG	Pediatric study: Phase I/Ib, single-arm, open-label, dose-escalation and expansion	Oral, QD F1 (3 patients received F2B), in a continuous daily dosing regimen 250 to 750 mg/m2/day	MTD or RP2D		16	Patients (≤22 years old) with advanced or metastatic solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions

7.2. Review Strategy

The FDA statistical and clinical review team for the review of efficacy in this application consisted of one primary clinical reviewer, Dr. Shanthi Marur and one primary statistical reviewer, Dr. Xiaoping Jiang. Since safety review involved data relevant to the indications under NDA 212725 and NDA 212726, a joint review of safety was conducted by Dr. Shanthi Marur and Dr. Leigh Marcus and reviewed by Dr. Erin Larkins and Dr. Martha Donoghue.

The clinical trials supporting the review of the safety and efficacy of entrectinib are listed in Table 17 above. The statistical and clinical review of efficacy focused on the pooled data from ALKA, STARTRK-1, and STARTRK-2, the clinical study reports (CSR), case report forms (CRF), and statistical analysis plan (SAP); independent analyses using submitted datasets were also conducted. The safety and efficacy update with a data cut-off of October 31, 2018 included an additional 5 months of safety follow-up for patients in the original NDA dataset and updated duration of response for the responders in the original NDA dataset. For a description of the efficacy analysis populations, see Section 8.1.

The clinical review of safety was based on the safety population in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG, defined as patients who received at least one dose of entrectinib. The review of safety included review of CSRs, SDTM and analysis datasets, line listings, CRFs, and case narratives from all four trials.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on ROS1 fusion protein
- Review of ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG, including CSR, protocol, protocol amendments, SAP, and SAP amendments.
- Review and assessment Genentech's analyses of entrectinib safety and efficacy in the clinical study reports
- Review of datasets submitted as SDTM, analysis, and SAS transport files
- Review of patient narratives of SAEs and deaths
- Review of minutes of key meetings conducted during entrectinib development
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy, and Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, and proposed labeling modifications for entrectinib
- Review of consultation reports from the Office of Scientific Investigations
- Requests for additional information from Genentech and review of their responses
- Review and evaluation of proposed labeling

Data Sources

The electronic submission including protocols, SAPs, CSRs, SAS transport datasets in legacy, SDTM, and ADAM format, and SAS codes for the NDA submission are located in the following network paths:

- Original submission: SDN 1 Application 212725 - Sequence 0001 - 0001 (1) 12/18/2018 ORIG-1 /Multiple Categories/Subcategories

Data and Analysis Quality

Upon further clarifications from Genentech in response to FDA's information requests (IRs), the reviewer was able to:

- Reproduce Genentech's analysis dataset and analysis results from legacy datasets
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy analyses

Datasets

There were three analysis sets from all four supportive studies: ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG. All safety analyses were performed using the integrated safety population, defined as all patients enrolled up to November 30, 2017 who received at least one dose of entrectinib, with data collected up to the clinical cut-off date (CCOD) of May 31, 2018 in studies ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG. Pooling of safety data was performed as all four studies had similar design, treatment regimens, collection of safety data, and patient populations, except for Study STARTRK-NG which enrolled only pediatric patients (n=16). The integrated safety population consists of 355 patients, including 339 adult patients with solid tumors and 16 pediatric patients. The analysis sets are described below and in Figure 21 and Figure 22.

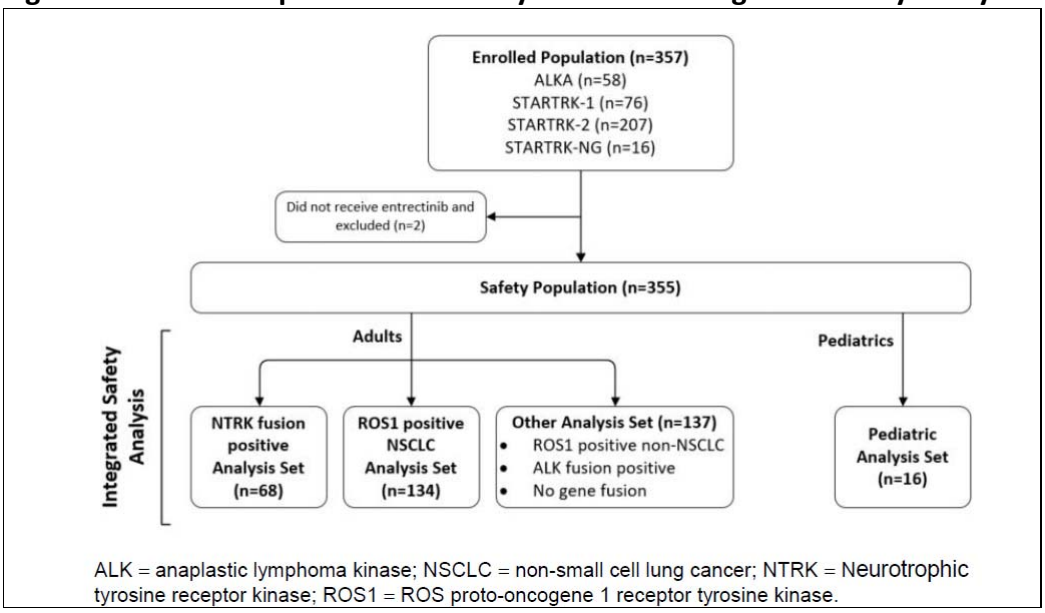
Adult safety analysis sets:

- ***NTRK* fusion-positive analysis set (n = 68):** Patients from the ALKA, STARTRK-1, and STARTRK-2 studies in the safety population who have *NTRK* fusion-positive solid tumors
- ***ROS1*-positive NSCLC analysis set (n = 134):** Patients from the ALKA, STARTRK-1, and STARTRK-2 studies in the safety population who have *ROS1*-positive NSCLC
- **Other analysis set (n = 137):** Patients from the ALKA, STARTRK-1, and STARTRK-2 studies in the safety population with either *ROS1*-positive non-NSCLC, *ALK* fusion-positive tumors, or no gene fusion identified

Pediatric safety analysis sets:

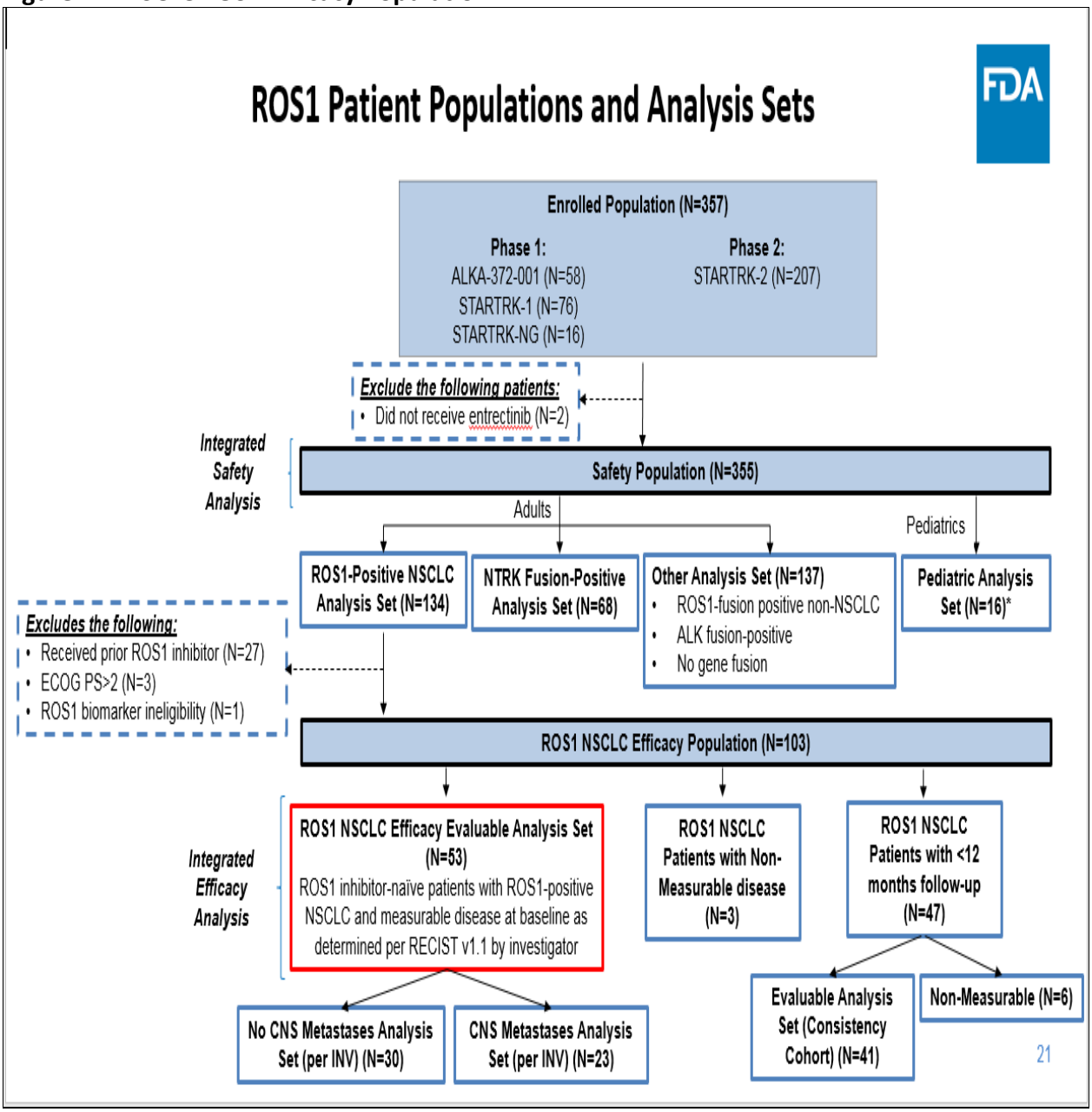
- **Pediatric analysis set (n = 16):** Patients from the dose escalation portion (Phase 1) of STARTRK-NG study in the safety population
- **75-day safety (n = 26):** safety population [Total, inclusive of Pediatric analysis set at original submission] who have either *NTRK* fusion-positive solid tumor or no gene fusion identified; and efficacy update n = 5 efficacy population who have *NTRK* fusion-positive solid tumors)

Figure 21: Patient Population and Analysis Sets for Integrated Safety Analysis



Source: Summary of Clinical Safety, Module 2.7.4

Figure 22: NSCLC *ROS1* Efficacy Population



Source: Summary of Clinical Safety, Module 2.7.4

Clinical/Statistical Reviewer comment:
By the definitions agreed upon at the pre-NDA meeting, the three analysis sets described were to be limited to patients who had not previously received treatment with a ROS1 inhibitor. Late in the review process, it was discovered by the review team that two patients included in the analysis sets had received prior treatment with crizotinib. After this discovery, all primary analyses were re-done based on a primary efficacy set of 51 ROS1 inhibitor-naïve patients. Given time limitations, it was not possible for analyses to be re-done for the efficacy analysis set and measurable disease set excluding the two patients who had received prior treatment with

crizotinib; therefore, the results in this review for those two analysis sets include the two patients previously treated with crizotinib.

At the pre-NDA meeting it was agreed that the primary analysis set for efficacy would include the first 53 consecutively enrolled patients with ROS1-positive NSCLC and measurable disease who were followed for a minimum of 12 months from onset of response or had discontinued study treatment before the data cut-off date. While this is the definition used by Genentech in the SCE for the "ROS1 NSCLC efficacy-evaluable analysis set", intended to serve as the primary efficacy analysis set, it was discovered by the review team during the review that two of the patients included in this set had ongoing response with <12 months of follow-up from onset of response at the time of the data cut-off date (May 31, 2018) for the initial NDA submission. In response to an information request, Genentech confirmed that two patients were included who had <12 months follow up since onset of ongoing responses (11.9 months and 8.6 months). Based on this, and in order to accurately describe the patients included in the primary efficacy set, the definition of the primary analysis set was modified from "followed for a minimum of 12 months from onset of response or had discontinued study treatment before the data cut-off date" to "had ≥12 months follow up from date of first post-treatment tumor assessment".

7.3. Review of Relevant Individual Trials Used to Support Efficacy

The integrated data to support efficacy are derived from a pooled subgroup of patients with *ROS1*-positive metastatic NSCLC who received entrectinib at various doses and schedules (90% received entrectinib 600 mg daily) in one of three multicenter, single-arm, open-label clinical trials: ALKA-372-001, RXDX-101-01, and RXDX-101-02. Table 17 and Table 18 contain brief descriptions of each of these studies. For detailed descriptions of each study, including trial design, protocol amendments, data quality and integrity, compliance with Good Clinical Practice (GCP), and financial disclosure specific to the study, see Appendix, Section 19.6 Description of Relevant Individual Trials Supporting the NDA.

8 Statistical Analysis Plan for Integrated Summary of Efficacy (ISE)

8.1. *ROS1*-Positive NSCLC Study Population

Genentech submitted data from 134 patients with *ROS1*-positive NSCLC enrolled and treated with entrectinib across three studies (ALKA, STARTRK-1, STARTRK-2: Table 18) in the original NDA submission. This included both patients who were ROS1 TKI-naïve and patients who had received prior ROS1 TKI; patients with measurable or non-measurable disease; and patients with ≥12 months and <12-months follow-up from first dose of entrectinib.

Table 18: Summary of Studies and Patients Contributing to the Primary Efficacy Analysis Set

Study	Study Design	Patient Population	Entrectinib Dose, Route, Regimen	Primary Analysis Set (n=51)
ALKA-372-001 (ALKA) (Phase I) Ongoing	First-in-human, multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Patients (≥18 years old) with advanced or metastatic solid tumors with TRKA/B/C, ROS1, or ALK molecular alterations	Schedule A: 100, 200, 400, 800,1200, or 1600 mg/m2 once daily (fasted) 4 -days on 3-days off schedule for 3 weeks followed by a 7-day rest in a 4-week cycle b Schedule B: 100, 200, 400 mg/m2/day, or 600 mg/day continuous once daily (fed) in a 4-week cycle c Schedule C: 400 or 800 mg/m2 once daily (fed) in a continuous 4-days on, 3-days off schedule in a 4-week cycle d	**9**
RXDX-101-01 (STARTRK-1) (Phase I) Ongoing	Multicenter, open-label, ascending-dose study with dose escalation according to a standard 3+3 scheme	Patients (≥18 years old) with solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations	100, 200, 400 mg/m2 once daily, 600, or 800 mg continuous once daily (fed) on 28-day (4-week) cycles	**7**
RXDX-101-02 (STARTRK-2) (Phase II) **Ongoing**	Phase II, global, multicenter, **open-label, basket study**	Patients (≥18 years old) with advanced or metastatic solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* gene fusion **(excluding ALK-positive NSCLC)**	600 mg, orally, once daily, in 28-day (4-week) cycles	**35**

[Source: Table 1 in Summary-clin-efficacy-ros1.pdf]

For Genentech's definitions of the "*ROS1* patient populations and analysis sets", see Figure 22 in Section 0. For purposes of this review, there are three defined analysis sets based on subgroups of the 134 patients with *ROS1*-positive NSCLC (see Figure 22). The three defined analysis sets are described as the following:

- **Efficacy Analysis Set (n=103)**: Consists of 101 patients who were ROS1 inhibitor-naïve and two patients who received prior treatment with crizotinib (see Reviewer comment below), ECOG PS <2, measurable and non-measurable disease assessed by investigator.

- **Measurable Disease Set (n=94)**: Consists of 94 patients who are in the Efficacy Analysis Set, including the two patients who received prior treatment with crizotinib (see Reviewer comment below), and had measurable disease regardless of duration of follow-up.
- **Primary Analysis Set (called the "*ROS1* NSCLC Efficacy Evaluable Analysis Set" by Genentech, n=51):** Consists of 51 patients from the Efficacy Analysis Set who were ROS1 inhibitor-naive and had measurable disease and ≥12 months follow-up from the time of first post-treatment tumor assessment.

Clinical/Statistical Reviewer comment:
By the definitions agreed upon at the pre-NDA meeting, the three analysis sets described were supposed to be limited to patients who had not previously received treatment with a ROS1 inhibitor. Late in the review process, it was discovered by the review team that two patients included in the analysis sets had received prior treatment with crizotinib. After this discovery, all primary analyses were then re-done based on a primary efficacy set of 51 ROS1 inhibitor-naïve patients. Given time limitations, it was not possible for analyses to be re-done for the efficacy analysis set and measurable disease set excluding the two patients who had received prior treatment with crizotinib; therefore, the results in this review for those two analysis sets include the two patients previously treated with crizotinib.

At the pre-NDA meeting it was agreed that the primary analysis set for efficacy would include the first 53 consecutively enrolled patients with ROS1-positive NSCLC and measurable disease who were followed for a minimum of 12 months from onset of response or had discontinued study treatment before the data cut-off date. While this is the definition used by Genentech in the SCE for the "ROS1 NSCLC efficacy-evaluable analysis set", intended to serve as the primary efficacy analysis set, it was discovered by the review team during the review that two of the patients included in this set had ongoing response with <12 months of follow-up from onset of response at the time of the data cut-off date (May 31, 2018) for the initial NDA submission. In response to an information request, Genentech confirmed that two patients were included who had <12 months follow up since onset of an ongoing response (11.9 months and 8.6 months). Based on this and in order to accurately describe the patients included in the primary efficacy set, the definition of the primary analysis set was modified from "followed for a minimum of 12 months from onset of response or had discontinued study treatment before the data cut-off date" to "had ≥12 months follow up from date of first post-treatment tumor assessment".

Integrated Analysis Study Endpoints

The efficacy endpoints for the primary integrated analysis are based on BICR assessment and are described below.

Primary Efficacy Endpoints

Objective Response Rate (ORR): the proportion of patients with confirmed CR or PR; a confirmed response was a response that persisted 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. Non-responders included the following:

- Patients without a confirmed objective response
- Patients without a baseline or post-baseline tumor assessment
- Patients who received at least 1 dose of entrectinib and who discontinued for any reason prior to undergoing one post-baseline response evaluation.

Duration of Response (DOR): DOR (months) was calculated only for responders (as defined above). It was measured from the date of first objective response (either CR or PR) to first documentation of radiographic disease progression or the date of death due to any cause, whichever was earlier. For patients without disease progression or death, DOR was censored at the last tumor assessment date prior to the clinical cut-off date (CCOD).

Best Overall Response (BOR): BOR was the best radiologic overall response recorded at any single time point from the start of treatment until disease progression and was based on RECIST v1.1. A BOR status of CR or PR required confirmation no earlier than 4 weeks from the first response. Stable disease (SD) could have been assigned only after a patient met SD criteria for at least 5 weeks (≥35 days) following the first dose of treatment. Otherwise, the best response was not evaluable. Other cases of a BOR that were not evaluable included: no post-baseline scans available and missing subsets of scans at all timepoints. In addition, patients with only non-target lesions could only have been assessed as CR, non-CR/non-progressive disease (PD), PD or not evaluable, as per RECIST v1.1.

Secondary Efficacy Endpoints

Other efficacy endpoints for the integrated analysis included clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), intracranial objective response rate (IC-ORR), and intracranial duration of response (IC-DOR). All secondary efficacy endpoints are described below.

Clinical Benefit Rate (CBR): CBR was the proportion of patients who met one of the following criteria:

- Confirmed CR or confirmed PR
- SD for at least 6 months following start of entrectinib
- Patients without a post-baseline tumor assessment or patients who received at least 1 dose of entrectinib and discontinued for any reason prior to undergoing one post-baseline response evaluation were counted as not achieving clinical benefit.

Time to CNS Progression: Time to CNS progression was defined as time (months) from first dose of entrectinib to first documentation of radiographic CNS disease progression or death

due to any cause. Radiographic CNS disease progression was defined as an occurrence of a new CNS lesion or progression in any CNS lesion per RECIST v1.1.

Progression-Free Survival (PFS): PFS was defined as time (months) from first dose of entrectinib to first documentation of radiographic disease progression or death due to any cause. PFS data for patients without progression or death were censored on the date of the last tumor assessment (or, if no tumor assessment was performed after the baseline visit, at the date of first dose of entrectinib) prior to the CCOD.

Overall Survival (OS): OS was defined as the time (months) from the first dose of entrectinib to the date of death due to any cause. Patients who were alive at the time of the analysis were censored on the last known date that they were alive on or prior to CCOD. In addition, the following censoring rules applied:

- Patients with no post-baseline information were censored on the date of first dose of entrectinib
- Patients who were lost to follow-up or withdrew consent for further follow-up were censored on the last known date that they were alive on or prior to CCOD

In the subgroup of patients with CNS disease at baseline among the *ROS1* NSCLC efficacy evaluable analysis set (the Primary Efficacy Set), ORR, DOR, and BOR were summarized. The following intracranial-specific objective response endpoints were also evaluated:

Intracranial Objective Response Rate (IC-ORR): Selecting only CNS lesion(s) (target, non-target, or both, as determined by BICR) for each patient, the RECIST v1.1 for time-point response and BOR assessment were used to determine intracranial response. Patients with confirmed CR or confirmed PR in the CNS lesion(s) were referred to as intracranial responders. A confirmed intracranial response was a CNS response that persisted on repeat-imaging ≥4 weeks after initial documentation of CNS response. The analysis of IC-ORR was performed for patients presenting with measurable CNS lesions at baseline, as well as for patients with only non-measurable CNS lesions at baseline.

Intracranial-Duration of Response (IC-DOR): In this same CNS subpopulation, IC-DOR was summarized. IC-DOR was calculated only for intracranial responders and was measured from the date of first intracranial response to first documentation of radiographic CNS disease progression or date of death due to any cause, whichever was earlier. For patients without CNS disease progression and who did not die within 30 days of the last dose of study treatment, IC-DOR was censored at the last tumor assessment date prior to any date of subsequent anticancer therapy, including surgery or radiotherapy to the brain.

Intracranial Progression-Free Survival (IC-PFS): In this same CNS subpopulation, IC-PFS was defined as time (months) from first dose of entrectinib to first documentation of radiographic CNS disease progression or death due to any cause. Radiographic CNS disease progression was defined as an occurrence of a new CNS lesion or progression in any CNS lesion per RECIST v1.1.

Similar censoring rules as defined above were applied: patients without radiographic CNS progression or death were censored on the date of the last tumor assessment prior to the CCOD.]

Statistical Reviewer's Comments:

- *Clinical Benefit Rate (CBR), which includes stable disease, is not an acceptable endpoint* (b) (4) *in a single arm study; this endpoint was not evaluated in this review.*
- *Time-to-event endpoints such as OS or PFS are not interpretable in a single-arm study; the results of PFS, OS and other time-to-event endpoints, with the exception of DOR and IC-DOR, were not evaluated in this review.*

Statistical Analysis Plan for Integrated Summary of Efficacy (ISE)

The statistical analysis plan (SAP) describes an integrated efficacy analysis pooled across the three clinical trials in adult patients (STARTRK-2, ALKA, STARTRK-1) to support the approval of entrectinib for the treatment of patients with *ROS1*-positive NSCLC. Per the SAP, the definitions of efficacy endpoints for this integrated analysis have been standardized across studies. No formal statistical test was planned in the SAP.

Target lesions for assessment of systemic response were identified as measurable lesions present at baseline. If more than one measurable lesion was present, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs were selected as target lesions. This meant that one of the target lesions selected for assessment of systemic response could include a brain lesion.

The primary integrated analysis of efficacy would be based on BICR determinations of ORR using RECIST v1.1. Tumor scans for patients in the STARTRK-2 study were evaluated in a prospective manner. Tumor scans for patients from the ALKA and STARTRK-1 studies included in the primary analysis set were evaluated by the same BICR team using equivalent Imaging Review Charters, in a retrospective manner.

The primary analysis of the primary endpoint ORR was to provide the point estimator of ORR (the proportion of patients with confirmed CR or PR with its two-sided 95% CI) using the Clopper-Pearson exact method. Kaplan-Meier method would be used to summarize DOR including estimating the median DOR and its 95% CI using the method of Brookmeyer and Crowly (1982) and Klein and Moeschberger (1997). Per the SAP, final analysis would be performed for marketing application submission after approximately 50 patients with *ROS1*-positive NSCLC had been enrolled across the three studies. All responding patients would have at least 12 months of efficacy follow-up from the time of response or would have discontinued study treatment at the time of final database snapshot for analysis.

Assuming the true ORR assessed by BICR was 70%, a sample size of at least 50 patients could provide 82% power to exclude 50% from the lower bound of a two-sided 95% confidence interval.

Per the SAP, efficacy analyses would be presented only for the *ROS1* NSCLC efficacy-evaluable population, which is called the "primary analysis set" throughout this review. The primary analysis set was defined as ROS1 inhibitor-naïve patients with *ROS1*-positive NSCLC with measurable disease at baseline as determined per RECIST v1.1 by investigator. Patients would have at least 12 months of efficacy follow-up from the time of response or would have discontinued study treatment at the time of final database snapshot for analysis.

Per the SAP, assessment of IC-ORR and IC-DOR was to be based on only the CNS lesion(s) (target, nontarget, or both, as determined by BICR) selected for each patient, with the RECIST 1.1 algorithms for timepoint response and best overall response assessment used to determine intracranial response. Patients with confirmed CR or PR in the CNS lesions were referred to as intracranial responders. A confirmed intracranial response was documented with a repeat imaging at ≥ 4 weeks after initial documentation of CNS response. Intracranial objective response rate (IC-ORR) was the ORR for intracranial responders. The IC-ORR would be assessed for patients presenting with measurable CNS lesions at baseline, as well as for patients with only non-measurable CNS lesions at baseline. In this same CNS subpopulation, intracranial DOR (IC-DOR) was summarized.

Per the SAP, quality of life and health status information would be collected from self-administered instruments for patients enrolled in STARTRK-2 only. The instruments used to assess the patient reported outcome (PRO) include Core Quality of Life Questionnaire (QLQ-C30) and Lung Cancer Module (QLQ-LC13). The QLQ-C30 comprises 30 questions assessing global QOL, functioning, and symptoms of both multi-item and single-item measures. QLQ-LC13 comprises 13 questions assessing lung cancer-specific symptoms. For multi-item subscales, if ≥50% of items within the multi-item subscale are non-missing at a given timepoint, the multi-item score would be calculated on the basis of the non-missing items. If ≥50% of items are missing or if a single-item measure is missing, the subscale is missing.

Per the SAP for STARTRK-2, all of the scales and single-item measures would be linearly transformed so that each score would range from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/HRQoL represents a high HRQoL; however, a high score for a symptom scale/item represents a high level of symptomatology/problems. PRO population included All enrolled population who had received at least one dose of entrectinib who completed the QLQ-C30 and QLQ-LC13 questionnaires on Cycle 1 Day 1 and answered at least one question on an on-study time point thereafter. The PRO analyses included summarizing the completion rates via the number and proportion of patients among those expected to complete each questionnaire at each time point and descriptive statistics (including 95% confidence intervals) of scores and mean change from baseline scores by cycle and across cycle for specified QLQ-C30 and QLQ-LC13 scales. Per

the SAP for Study STARTRK-2, a change of >=10-point in the symptom subscale score is perceived by patients as clinically significant (Osoba et al. 1998). Hence, for functioning scales and global HRQOL, a patient would be deemed:

- Improved, if the change from baseline is a 10-points or greater increase
- Worsened, if the change from baseline is 10-point or greater decrement
- Stable otherwise
- For analysis of symptom scales and single items, the opposite is true:
- Improved, if the change from baseline is a 10-points or greater decrement
- Worsened, if the change from baseline is 10-point or greater increase
- Stable otherwise

Statistical Reviewer's Comment:

- *There were very few patients who completed QLQ-CR29; therefore, no results for QLQ-CR29 are presented in this review.*

- *Although the study protocol further defined the improvement or worsening of global QOL functioning domains and symptom domains based on 10-point change, there was no agreement on the clinically meaningful threshold (e.g. change of >=10-point) for the symptom subscale score between FDA and Genentech.*

Clinical Reviewer Comment: The rarity of NSCLC harboring ROS1 rearrangements precludes the conduct of randomized controlled trials; the size of the primary efficacy set population (n=51) was sufficient to provide substantial evidence of effectiveness (effects on ORR and DOR) in patients with metastatic ROS1-positive NSCLC.

8.2. Pooled Study Results

Data Quality and Integrity

With clarifications from Genentech provided in response to multiple FDA information requests (IRs), the reviewers were able to:

- Reproduce Genentech's analysis results from the submitted datasets
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy and safety analyses

Compliance with Good Clinical Practices

The "Clinical Overview" (Module 2.5), section 1.9 states: "All studies were conducted in accordance with the principles of Good Clinical Practice (GCP) (the ICH guidelines on good clinical practice [ICH E6], the US FDA regulations, the Declaration of Helsinki [October 1996],

and applicable local, state, and federal laws, as well as other applicable national legal requirements). The study designs also considered statistical principles (ICH E9) and FDA and EMA guidelines on clinical trial endpoints for the approval of cancer drugs (FDA Guidance to Industry, 2007 and EMA/CHMP/205/95 Rev. 5, 2018). The studies were approved by the appropriate Ethics Committees and Institutional Review Boards, were audited for GCP and were source document verified."

Study Population

FDA's review of efficacy is primarily based on analyses of ORR and DOR for the first 51 ROS1 TKI-naïve patients consecutively enrolled across the three studies (ALKA, STARTRK-1, and STARTRK-2) with *ROS1*-positive NSCLC with measurable disease and at least 12 months follow-up from the first post-treatment tumor assessment, as described in Section 8.1. The clinical data cutoff dates for the final ORR and DOR analyses are May 31, 2018 and October 31, 2018 ("75-day update"), respectively.

Among the 51 patients in the primary efficacy set, 46 patients received entrectinib 600 mg daily (90%). According to details provided by Genentech in response to an information request, one patient received entrectinib at a dose intensity lower than 600 mg daily (800 mg 4 days on, 3 days off), while the remaining four patients received entrectinib at a dose intensity higher than 600 mg daily: one received 650 mg daily; one received 2600 mg 4 days on 3 days off for 3 weeks, followed by a 7-day rest period in a 4-week cycle (recorded as receiving treatment at this dose for 17 days); one received 2000 mg 4 days on 3 days off for 3 weeks, followed by a 7-day rest period in a 4-week cycle; and one received 800 mg daily.

Primary Endpoints

The primary endpoint for the integrated analysis of effectiveness is ORR according to BICR assessment.

Secondary and Other Endpoints

Secondary endpoints relevant to this review are DOR, IC-ORR, and IC-DOR. For Study RXDX-101-02 only, EORTC QLQ-C30 and CLC-C13 data were collected and used to evaluate PRO. See Section 8.1.

Patient Disposition

As of the data cutoff date of May 31, 2018 for the original NDA submission, the last patient was enrolled on April 30, 2017. Median follow-up was 16.6 months. There are 134 patients with *ROS1*-positive NSCLC from the three studies in the submitted data. As described in Section 8.1, there are three defined analysis sets: efficacy analysis set (n=103), primary analysis set (n=51), and measurable disease set (n=94). Among the 103 patients in the efficacy analysis set, there

are 51 patients (primary analysis set) who were ROS1 inhibitor-naïve, had measurable disease and had at least 12 months follow-up from first post-treatment tumor assessment at the time of final analysis.

Table 19 summarizes the FDA statistical reviewer's results of the patient disposition for the three analysis sets based on the data cut-off date of May 31, 2018. Among the 51 patients in the primary analysis set, about 51% of the patients were still on study, while 41% were discontinued. Among the 21 (41%) patients who discontinued study, 8 (36%) patients died. There were 30 (59%) patients who discontinued treatment. The most common reason for treatment discontinuation was disease progression (77%).

Table 19: Patient Disposition (Date of Data Cut-off: May 31, 2018)

Populations	**Primary Analysis Set (n=51)**	**Measurable Disease Set* (n=94)**	**Efficacy Analysis Set* (n=103)**
Study Status			
Completed	4 (7.8%)	4 (4.3%)	5 (4.9%)
Ongoing	26 (51.0%)	58 (61.7%)	65 (58.3%)
Discontinued	21 (41.2%)	32 (34.0%)	33 (36.9%)
Reasons for Discontinued Study	n=22	n=32	n=33
Death	8 (36.4%)	17 (53.1%)	17 (51.5%)
Informed Consent Withdrawn	6 (27.3%)	7 (21.9%)	7 (21.2%)
Withdrawal by Subject	2 (9.0%)	2 (6.3%)	2 (6.1%)
Others	6 (27.3%)	6 (18.8%)	7 (21.2%)
Reasons for Discontinued Treatment	n=30	n=48	n=51
Progressive Disease	23 (76.7%)	35 (72.9%)	37 (72.6%)
Adverse Event	5 (16.7%)	9 (18.8%)	10 (19.6%)
Informed Consent Withdrawn	2 (6.7%)	3 (6.3%)	3 (5.9%)

** Includes two patients who received previous treatment with crizotinib and are excluded from the primary analysis set*

<u>Clinical Reviewer Comment</u>: The disposition of the patients in the efficacy population, with death the most common reason for study discontinuation and progressive disease the most common reason for treatment discontinuation, is consistent with expectations for a population of patients with metastatic NSCLC.

Protocol Violations/Deviations

The definition of protocol violations and summary of all protocol violations among the total enrolled patients in each individual trial are provided below.

Major protocol deviations were defined as any change, divergence, or departure from the study design or procedures described in the protocol, as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. These included but were not limited to the following:

- Patients enrolled but not meeting exclusion and inclusion criteria
- Patient developed treatment withdrawal criteria but did not discontinue study
- treatment (unless there was evidence of clinical benefit as defined by primary
- physician despite radiological progression)
- Failure to perform procedures related to safety, primary outcome, and key secondary
- outcomes that could undermine the scientific value of the study
- Administering/taking incorrect treatment or dose as per protocol
- Taking excluded concomitant medications
- GCP protocol deviations such as:
    - o Informed consent not appropriately obtained
    - o Mishandling of study drugs
    - o Noncompliance with principal investigator (PI) responsibilities
    - o Noncompliance with safety/serious adverse event (SAE) reporting.

<u>ALKA:</u>
Eligibility criteria was not met in 39% of the major violations; other major protocol violations included errors in treatment administration (16%), radiologic assessment (11%) (including the timing of assessment [2%]), concomitant treatments that were not allowed (2%), informed consent document (ICD) not signed (2%), and issues with documentation (2%).

<u>STARTRK-1:</u>
“Important protocol deviations” were defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Overall, 15 (19.7%) patients had important protocol deviations. The most common (occurring in ≥5% of patients) important protocol deviations were in the category of Study Conduct/Procedures and were primarily in the subcategories of Study Restrictions/Withdrawal Criteria (5 [6.6%] patients) or Inclusion/Exclusion Criteria (4 [5.3%] patients). These important protocol deviations included receiving prohibited concomitant medication (Phenergan, Levaquin, ciprofloxacin), pregnancy test not collected, the washout period from prior crizotinib or radiation therapy was shorter than protocol specification, or patient given or took incorrect dose (a smaller dose [400 mg instead of 800 mg]

was given to one patient and a higher dose [600 mg instead of 400 mg] was taken by one patient).

Clinical Reviewer Comment: A tabular listing of deviations noted as "non-important" versus "important" was submitted within the CSR, and an analysis was done with pooled data. IR-33 dated May 10, 2018 clarified the major protocol violations and was incorporated into Table 20 below.

STARTRK-2:
A protocol violation occurs when the patient or Investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, patient safety or primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

1. Failure to meet inclusion/exclusion criteria
2. Dose modifications (e.g., wrong treatment or incorrect dose) that are not within the protocol specifications
3. Use of a prohibited concomitant medication
4. Any other deviation that presents significant risk or safety concerns to the patient, e.g., pregnancy on study

Overall, 48 (23.3%) patients had a major protocol deviation; these were related to informed consent (15 patients [7.3%]), eligibility and entry deviation (10 patients [4.9%]) and IP compliance (10 patients [4.9%]).

Clinical Reviewer Comment: Although a total of 117 major/important protocol deviations occurred in 88 patients, the applicant stated that none of the protocol violations were considered to have an effect on the assessment of safety or efficacy outcomes. The most frequently reported major protocol violations were those relating to "Inclusion/Exclusion criteria" in 22 of 355 patients and "Issues with informed consent" in 16 of 355 patients. Although it is challenging to ascertain the impact of protocol violations in single arm trials with small sample sizes, this clinical reviewer agrees with Genentech's conclusion that the protocol deviations described below in Table 20 did not materially alter the assessment of safety or effects on ORR and DOR for entrectinib in patients with ROS1-positive NSCLC.

Table 20: Summary of Major/Important Protocol Violation Across All Studies With Entrectinib

Protocol Violation	Overall Safety Analysis Population N=355 n (%)
Patients with major protocol violation (%)	88 (24.8)
Total number of major protocol violations	117
Issues with informed consent	16 (4.5)
Protocol procedures/visits not performed/missing	4 (1.1)
Inclusion/Exclusion criteria violated	22 (6.2)
Incorrect response assessment	6 (1.7)
Out of window visits/procedure	0
Medication errors	13 (3.7)
Other[1]	2 (0.6)

Copied from submission of IR-33 dated May 10, 2018; reviewed with data from CSRs submitted to NDA Module 5.3.5.2

8.2.1. Demographic Characteristics

As described in Section 8.1, there are three defined analysis sets in the 134 *ROS1* NSCLC patients from the three studies in submitted data. The demographic and baseline characteristics of patients included in the three analysis sets are provided in Table 21.

As shown in Table 21, among the 51 patients in the primary analysis set, the median age was 53 years (range: 27 to 72), 67% female, 59% White, 36% Asian, 6% Black, Hispanic or Latino (4%), and 59% never smoked; 89% had ECOG performance status 0-1, 100% had had metastatic disease, 94% had adenocarcinoma, 33% had no prior therapy for metastatic disease and 69% received prior platinum-based chemotherapy for metastatic or recurrent disease or had progressed within 6 months of completing platinum-based adjuvant or neoadjuvant therapy. *ROS1* positivity was determined by NGS in 72% and by FISH in 28%. Of those patients enrolled based on local laboratory testing, 77% had prospective or retrospective central laboratory confirmation of *ROS1* positivity using an analytically validated NGS test.

Table 21: Demographic Characteristics

	Primary Analysis Set (n=51)	Measurable Disease Set* (n=94)	Efficacy Analysis Set* (n=103)
Age, year			
Median (min, max)	53 (27, 72)	53 (27, 86)	53 (27, 86)
Age group, n			
>=65	10 (19.6%)	19(20.2%)	22 (21.4%)
<65	41 (80.4%)	75 (79.8%)	81 (78.6%)
Gender, n			
Female	34 (66.7%)	60 (63.8%)	64 (62.1%)
Male	17 (33.3%)	34 (36.2%)	39 (37.9%)
Race, n			
Asian	19 (37.3%)	41 (43.6%)	43 (41.8%)
Black or African American	3 (5.9%)	5 (5.3%)	5 (4.9%)
White	29 (56.9%)	46 (48.9%)	53 (51.5%)
Ethnicity			
Hispanic or Latino	2 (3.9%)	2 (2.1%)	2 (1.9%)
Not Hispanic or Latino	38 (74.5%)	79 (84.0%)	86 (83.5%)
Missing	9 (17.7%)	9 (9.6%)	11 (10.7%)
Unknown or Not Reported	2 (3.9%)	4 (4.3%)	4 (3.9%)
Region, n			
North America	14 (28.3%)	25 (26.6%)	26 (25.2%)
Europe	19 (35.9%)	26 (27.7%)	32 (31.1%)
APAC**	18 (35.9%)	43 (45.7%)	45 (43.7%)

** Includes two patients who received previous treatment with crizotinib and are excluded from the primary analysis set*
***APAC is the region that includes patients from Hong Kong, Japan, Korean, Singapore, and Taiwan.*

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

The major baseline disease characteristics for patients included in of the three analysis sets are summarized in Table 22.

Table 22: Baseline Patient and Disease Characteristics

	Primary Analysis Set (n=51)	Measurable Disease Set* (n=94)	Efficacy Analysis Set* (n=103)
ECOG Performance Status			
0	19 (37.2%)	35 (37.2%)	38 (36.9%)
1	26 (51.0%)	48 (51.1%)	53 (51.5%)
2	6 (11.8%)	11 (11.7%)	12 (11.7%)
Smoking Status			
Never Smoker	29 (56.9%)	38 (40.4%)	60 (58.3%)
Former/Current Smoker	22 (43.1%)	56 (59.6%)	43 (41.8%)
Number of Prior Systemic Therapies**			
0	7 (13.7%)	23 (24.5%)	38 (36.9%)
1 or 2	20 (39.2%)	29 (30.9%)	53 (51.5%)
≥3	24 (47.1%)	42 (44.7%)	12 (11.7%)
Extent of Disease at Start of Treatment			
Localized	1 (2.0%)	1 (1.1%)	1 (1.0%)
Local Advanced	2 (03.9%)	2 (2.1%)	6 (5.8%)
Metastatic Disease	48 (94.1%)	91 (96.8%)	96 (93.2%)
Histology			
Adenocarcinoma	48 (94.1%)	91 (96.7%)	100 (97.1%)
Others	3 (5.9%)	3 (3.3%)	3 (2.9%.)
CNS Measurable Disease at Baseline (BICR)			
No	7 (13.7%)	19 (20.2%)	19 (18.5%)
Yes	12 (23.5%)	16 (17.0%)	17 (16.5%)
CNS Metastases Baseline (BICR)			
No	32 (62.8%)	59 (62.8%)	67 (65.1%)
Yes	19 (37.2%)	35 (37.2%)	36 (35.0%)
CNS Metastases Baseline (INV)			
No	29 (56.9%)	54 (57.5%)	60 (58.3%)
Yes	22 (43.1%)	40 (42.5%)	43 (41.7%)
Any Prior Radiotherapy of the Brain***			
No	37 (72.6%)	73 (77.7%)	78 (75.7%)
Yes	14 (27.4%)	21 (22.3%)	25 (24.3%)

**includes two patients who received previous treatment with crizotinib and are excluded from the primary analysis set*
***33% of the 51 patients in Primary Analysis Set had no prior line of systemic therapy for metastatic disease; 67% of the 51 patients in Primary Analysis Set received prior platinum-based chemotherapy for metastatic or recurrent disease; one patient started treatment with entrectinib within 6 months of completion of platinum-based neoadjuvant/adjuvant chemotherapy*
****one patient who had prior radiotherapy of the brain with missing data for time from end of prior radiotherapy to first dose of entrectinib*

Statistical Reviewer's Comment:
Among the 51 patients, approximately 62.7% of patients had a status of "missing" for CNS measurable disease at baseline assessed by BICR.

Clinical Reviewer Comment:
The median age and the higher proportion of females and non-smokers are consistent with the expected characteristics of patients with ROS1 NSCLC.

Table 23 provides a summary of the incidence of specific *ROS1* rearrangements identified in the 51 patients in the primary efficacy set. The most common *ROS1* fusion was *CD74-ROS1* (39%) and the second most common was *SLC34A2-ROS1* (14%). The number of patients with tumors with unknown *ROS1* fusion partners was 24%. Out of the 51 patients in the primary analysis set, 27 patients were enrolled based on genomic alterations in tumor samples determined by RNA-based NGS, 15 by FISH, 7 by DNA-based NGS, and 2 by DNA and RNA-based NGS. The fusion partner was initially unknown in 15 patients enrolled by FISH. Among the 15 patients enrolled by FISH, fusion partners were identified in 3 patients by re-testing tumor tissue with RNA-based NGS and are presented as footnotes the table. The presence of concomitant oncogenic driver mutations was assessed for 9 of the 51 patients.

Table 23: *ROS1* Molecular Testing in the Primary Efficacy Set

Study	Patient N	Test type	Fusion Partner	Concomitant Oncodriver assessed (Y/N)	Tissue available for re-testing
ALKA	9	FISH[1,2,3]	UNK	N	N
RXDX-101-01					
	6	FISH	UNK	N	N
	1	NGS	*CD74-ROS1*	N	N
RXDX-101-02					
	18	NGS	*CD74-ROS1*	N in 11 Y in 7	N
	5	NGS	*SDC4-ROS1*	N	N
	2	NGS	*TPM3-ROS1*	N in 1 Y in 1	N
	7	NGS	*SLC34A2-ROS1*	N	N
	3	NGS	*EZR-ROS1*	N	N

[1] *SDC4-ROS1* fusion was identified by re-testing with RNA-based NGS
[2] CD74-ROS1 fusion was identified by re-testing with RNA-based NGS
[3] *EZR-ROS1* fusion was identified by re-testing with RNA-based NGS

Clinical Reviewer Comment: Due to the small sample size and single-arm data, assessment for differences in efficacy based on ROS1 gene fusion partner is not feasible.

8.2.2. Efficacy Results – Primary Endpoint

The efficacy data provided in the NDA submission was based on a data cutoff date of May 31, 2018.

During the review process, Genentech submitted updated DOR data for the 40 responders as part of the "75-day update". The data cut-off for the updated data was October 31, 2018, which provided an additional 5 months of follow-up past the original data cut-off date.

Table 24 summarizes the results of FDA's analyses of ORR and DOR according to BIRC based on data in the original NDA submission and the "75-day update".

Table 24: Results of ORR and DOR Per BIRC for the Primary Analysis Set

Objective Response Rate (ORR)	**n=51**	
Responders, n	40	
CR	3 (5.9%)	
PR	37 (72.5%)	
ORR (95%CI)	78.4% (64.7%, 88.7%)	
Duration of Response (DOR)*	**n=40**	
Date of Data cutoff	May 31, 2018	Oct 31, 2018
Median DOR in Months (95% CI)	15.7 (9.5, 34.8)	15.7 (11.4, 34.8)
DOR>=6 months**, n (%)	30 (75.0)	30 (75.0)
DOR>=9 months**, n (%)	27 (67.5)	28 (70.0)
DOR>=12 months**, n (%)	17 (42.5)	22 (55.0)
DOR>=18 months**, n (%)	7 (17.5)	12 (30.0)

**Among the 40 responders, 21 events (17 disease progression and 4 deaths) had occurred at the time of data cutoff on October 31, 2018*
***Observed DOR*

Statistical Reviewer's Comment:
In the updated dataset ("75-day update"), there was one additional responder (upgraded from non-CR/non-PD at initial data cut-off date) in the primary analysis set; this patient had DOR of at least 3.7 months. FDA's intent for submission of the updated data was to update DOR only, not to update ORR based on a later cut-off date. Therefore, the product labeling includes ORR results based on the initial data cut-off (May 31,2018) with the DOR results for the 40 responders based on the later cut-off date of October 31,2018 in order to provide a better assessment of the durability of responses.

Table 25 summarizes the results of Genentech's ORR and FDA's DOR analyses based on investigator assessment as of the data cutoff date of May 31, 2018.

Table 25: Sensitivity Analyses of ORR and DOR Per Investigator for the Primary Analysis Set

Objective Response Rate (ORR)	**n=51**
Responders, n	39
CR	6 (11.8%)
PR	33 (64.7%)
ORR (95%CI)	76.5% (62.5%, 87.2%)
Duration of Response (DOR)	**n=39**
Median DOR in Months (95% CI)	16.8 (12.7, 21.4)

[Source: t-ef_borinv_REENEW.pdf submitted to respond an IR]

Table 26 summarizes the results of FDA's sensitivity analyses of ORR and DOR according to the BIRC assessment for the other two analysis sets, measurable disease set and efficacy analysis set, based on initial data in the NDA submission with a DCO of May 31, 2018 and the updated data with a DCO of October 31, 2018.

Table 26: Sensitivity Analyses of ORR and DOR Per BIRC

	Measurable Disease Set*		**Efficacy Analysis Set***	
Date of Data Cut-off	5/31/2018	10/31/2018	5/31/2018	10/31/2018
Objective Response Rate	**n=94**		**n=103**	
Responders, n	68	69	70	71
CR	7	11	9	13
PR	61	58	61	58
ORR (95%CI)	72.3% (62.2%, 81.1%)	73.4% (63.3%, 82.0%)	70.0% (58.0%, 76.8%)	68.9% (59.1%, 77.7%)
Duration of Response (DOR)	**n=68**	**n=69**	**n=70**	**n=71**
Median DOR in Mons** (95% CI)	15.7 (12.6, 34.8)	15.3 (12.6, 34.8)	19.0 (12.6, 34.8)	15.7 (12.6, 28.6)
DOR>=6 mons***, n (%)	41 (60.3%)	52 (75.4%)	43 (61.4%)	54 (76.1%)
DOR>=12 mons***, n (%)	18 (26.5%)	30 (43.5%)	19 (27.1%)	32 (45.1%)
DOR>=18 mons***, n (%)	7 (10.3%)	12 (17.4%)	8 (11.4%)	13 (18.3%)

** Includes two patients who received previous treatment with crizotinib and are excluded from the primary analysis set*
***Mons = months*
****Observed DOR*

Statistical Reviewer's Comment:
The ORR and DOR results for the other two analysis sets are consistent with the results in the primary analysis set.

8.2.3. Efficacy Results – Secondary and other relevant endpoints

Efficacy by CNS Metastases at Baseline

All patients on the three studies were required to have a baseline CNS imaging study.

Besides DOR for overall systemic disease, IC-ORR and IC-DOR were analyzed as secondary endpoints. There were 22 patients identified with CNS metastases at baseline per investigator assessment in the primary efficacy set and 19 patients identified with CNS metastases at

baseline per BICR assessment in the primary efficacy set. Among the 19 patients with CNS metastases at baseline identified by BICR, 12 patients were classified as having measurable CNS disease.

The FDA statistical reviewer confirmed Genentech's results for IC-ORR and IC-DOR included in the Summary of Clinical Efficacy. Table 27 summarizes Genentech's and the FDA statistical reviewer's results for IC-ORR and IC-DOR for patients with CNS disease per BICR assessment in the primary efficacy set (n=51). The reviewers noted 4 of the 9 responders with measurable CNS disease at baseline had received prior radiation to brain (SRS or WBRT) within 2 months of first dose of entrectinib. There were 7 patients with measurable CNS metastases at baseline per BICR who had not received radiation to the brain within 2 months of first dose of entrectinib, and 5 of these 7 patients had a confirmed IC response.

Table 27: Results of IC-ORR and IC-DOR for Patients With CNS Metastases at Baseline Per BICR in Primary Efficacy Population (N=51)

	Measurable CNS (n=12*)	CNS (n=19**)
IC-Responders	9	11
CR	2	4
PR	7	7
IC-ORR (95%CI)	75% (42.8%, 94.5%)	57.9% (33.5%, 79.7%)
IC-DOR	n=9	n=11
Median IC-DOR in Months	12.9 (4.6, NE)	12.9 (5.6, NE)
IC-DOR>=6 months***	6 (66.7%)	7 (63.6%)
IC-DOR>=12 months***	3 (33.3%)	3 (27.3%)

** 7 patients who had not received RT to the brain within 2 months prior to receiving entrectinib, 5 who had received SRS or WBRT within 2 months of first dose of entrectinib*
*** 11 patients who had not received RT to the brain within 2 months prior to receiving entrectinib, 8 who had received SRS or WBRT within 2 months of first dose of entrectinib*
**** Observed IC-DOR*
Source: Table 22 in Summary of Clinical Efficacy

<u>Statistical and Clinical Reviewer's Comment</u>:
All patients in the primary efficacy set had baseline brain imaging. While IC-ORR and IC-DOR CNS efficacy were prespecified as secondary endpoints, the results should be interpreted with caution due to the small sample size. Four out of the 9 patients with confirmed IC response had received radiation to the CNS ≤ 2 months prior to receiving first dose of entrectinib. It is not clear if the target lesions were in the previously irradiated field or if there was evidence of progression of such lesions at baseline. In these four responders, the contribution of recent radiation to the CNS response cannot be excluded, making it difficult to determine if entrectinib contributed to the response in these patients. Among the 7 patients with measurable CNS metastases at

baseline per BICR who had not received radiation to the brain within 2 months prior to the first dose of entrectinib, there were 5 patients with confirmed IC response, indicating that entrectinib does have anti-tumor activity in the CNS in patients with ROS1-positive NSCLC with brain metastases.

Intracranial Durability of Response

See IC-DOR results in Table 27. Among 9 patients with an intracranial response, 67% had an IC-DOR of ≥6 months and 33% had an IC-DOR ≥12 months.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Per the SAP, PRO data were collected for the patients in STARTRK-2 only. The instruments that were used to assess PRO include Core Quality of Life Questionnaire (QLQ-C30) and Quality of Life Questionnaire lung cancer module (QLQ-LC13). Compliance rate at an assessment time point was defined as the number of patients who provided data divided by the number of patients on study at that time point. A patient was considered to provide date (complied) if the patient answered at least one item of the questionnaire at a time point.

For the 37 patients in STARTRK-2, including two patients who previously received crizotinib and are excluded from the primary analysis set, patient-rated overall health and quality-of life was assessed using the global health status / QoL scale in QLQ-C30. The scale ranges from 0 to 100. A high score for the global health status / QoL represents a high QoL.

Table 28 summarizes the statistical reviewer's results for compliance rate for QLQ-C30 and QLQ-LC13. The compliance rate ranges from 87.5% to 100% and from 83.9% to 100% from cycle 1 to cycle 17 for QLQ-C30 and QLQ-LC13, respectively. The compliance rate at the end of treatment is 41.7% for both QLQ-C30 and QLQ-LC13.

Table 28: Compliance Rates of QLQ-C30 and QLQ-LC13 by Cycle in STARTRK-2

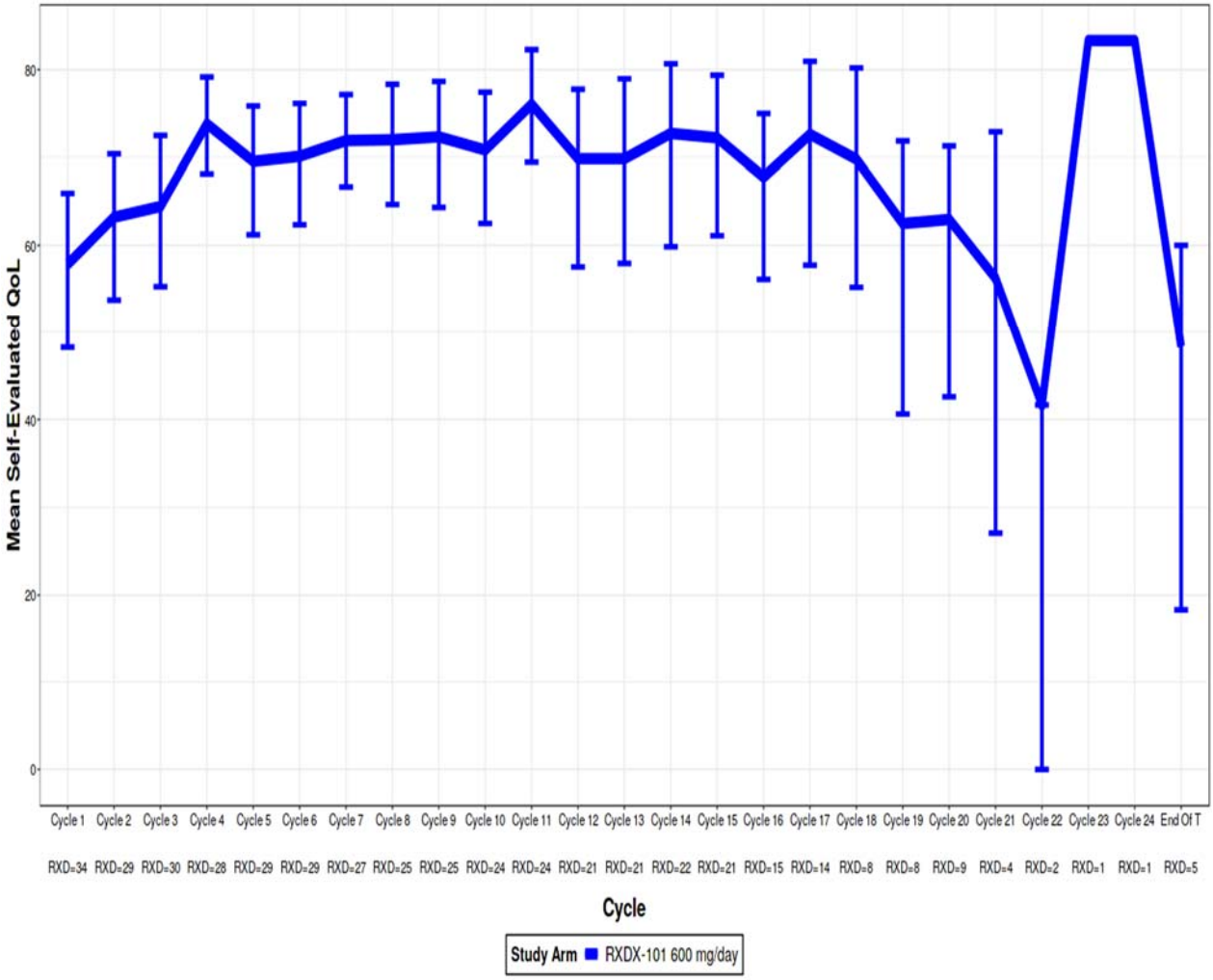
	QLQ-C30			QLQ-LC13		
Assessment Time	**Complied**	**On Study**	**Compliance Rate**	**Complied**	**On Study**	**Compliance Rate**
Cycle 1	34	37*	91.9	33	37*	89.2
Cycle 2	29	33	87.9	30	33	90.9
Cycle 3	30	32	93.8	29	32	90.6
Cycle 4	28	32	87.5	27	32	84.4
Cycle 5	29	31	93.5	29	31	93.5
Cycle 6	29	31	93.5	26	31	83.9
Cycle 7	27	30	90.0	26	30	86.7
Cycle 8	25	28	89.3	25	28	89.3
Cycle 9	25	25	100.0	25	25	100.0
Cycle 10	24	25	96.0	24	25	96.0
Cycle 11	24	24	100.0	24	24	100.0
Cycle 12	21	24	87.5	21	24	87.5
Cycle 13	21	22	95.5	21	22	95.5
Cycle 14	22	22	100.0	22	22	100.0
Cycle 15	21	21	100.0	21	21	100.0
Cycle 16	15	17	88.2	15	17	88.2
Cycle 17	14	15	93.3	14	15	93.3
End of Treatment	5	12	41.7	5	12	41.7

**Includes two patients who received previous treatment with crizotinib and are excluded from the primary analysis set*

<u>Statistical Reviewer's Comments:</u>
The compliance rates should be interpreted with caution due to the definition of compliance in the study. For example, the compliance rate for QLQ-C30 ranges from 87.5% to 100% from cycle 1 to cycle 17, while the number of the patients who were on the study decreases from 37 patients at cycle 1 to 15 patients at cycle 17. Notice that the compliance rate is 41.7 with only 12 patients still on the study at the time of the end of treatment.

Figure 23 displays the statistical reviewer's plot of mean score of global health status / QoL scale in QLQ-C30 over assessment visit with accelerated bias−corrected 95% bootstrap confidence intervals.

Figure 23: Mean Score of Patient-Rated Global Health Status/QoL by Cycle



<u>Statistical Reviewer's Comments:</u>
The mean score of patient-rated overall health status/QoL increases from baseline (Cycle 1) to Cycle 4, then decreases to cycle 5 and stays stable from cycle 6 to cycle 10. However, there is no consistent trend in mean score of patient-rated overall health status/QoL by cycle. Please note that the number of patients on the study is less than 15 after cycle 16 and less than 5 after cycle 20. Caution should be exercised in interpreting the results based on the small sample size of patients. No inference can be drawn based on the data.

Figure 24 displays the statistical reviewer's plot of mean change from baseline of global health status/QoL scale in QLQ-C30 over assessment visit with accelerated bias−corrected 95% bootstrap confidence intervals. Cycle 1 assessment is the baseline assessment.

Figure 24: Mean Change From Baseline of Patient-Rated Global Health Status/QoL by Cycle

**Mean change in Score from baseline to cycle m = mean ([Cycle m Score] − [Baseline Score])*

<u>Statistical Reviewer's Comments:</u>
The mean change from baseline is negative after cycle 12. Please note that the number of patients on the study is less than 15 after cycle 16. Caution should be exercised in interpreting the results based on the small sample size of patients. No inference can be drawn based on the data.

QLQ-LC13 includes questions assessing symptoms attributed to the underlying lung cancer including dyspnea and cough, which Genentech identified as the lung cancer-associated symptoms of clinical interest. The statistical reviewer conducted descriptive analyses for the items that the patients reported: extent of cough, cough up blood, short breath when rested, and short breath when walked. The percentage of patients who reported 'Not at All' to the question 'How much did you cough?' ranges from 6% to 66% to cycle 10. Please see the statistical reviewer's plots of patients who reported cough and dyspnea by cycle in Section 19.5. These descriptive analyses are considered exploratory.

8.2.4. Assessment of Efficacy in Subpopulations Across Trials

Subpopulations

The statistical reviewer conducted subgroup analyses of BICR-assessed ORR by age, gender, race, and region in the primary efficacy set. Table 29 summarizes the statistical reviewer's ORR demographic subgroup analyses.

Table 29: Reviewer's ORR Results of Demographic Subgroups in the Primary Efficacy Set

Subgroup	Patients, n	Responders, n (ORR, %*)	95% CI
Age			
>=65	10	8 (80.0%)	(44.4%, 97.5%)
<65	41	32 (78.0%)	(62.4%, 89.4%)
Gender			
Female	34	26 (76%)	(58.8%, 89.3%)
Male	17	14 (82.4%)	(56.6%, 96.2%)
Race			
Asian	19	16 (84%)	(60.4%, 96.6%)
White	29	22 (75.9%)	(56.5%, 89.7%)
Region			
USA	14	11 (78.6%)	(49.2%, 95.3%)
Non-USA	37	29 (78.4%)	(61.8%, 90.2%)

Statistical Reviewer's Comment:
The subgroup analyses results are considered exploratory. The results should be interpreted with caution given the small sample size overall and the limited number of patients in each subgroup. No outlier subgroup was observed.

In addition, the statistical reviewer conducted ORR subgroup analyses by some baseline disease characteristics. Table 30 summarizes the statistical reviewer's ORR subgroup analyses by ECOG performance status, smoking status, prior number of systemic therapies, and receipt of prior platinum-based chemotherapy.

Table 30: Reviewer's ORR Results of Baseline Disease Characteristics Subgroups in the Primary Efficacy Set

Subgroup	Patients, n	Responders, n (ORR, %*)	95% CI*
ECOG performance status			
0	19	18 (94.7%)	(73.9%, 99.9%)
1	26	19 (73.1%)	(52.2%, 88.4%)
2	6	3	--
Smoking Status			
Never Smoker	29	23 (79.3%)	(60.2%, 92.0%)
Former/Current Smoker	22	17 (77%)	(54.6%, 92.2%)
Prior platinum-based chemotherapy**			
N	16	14 (87.5%)	(61.7%, 98.4%)
Y	35	26 (74.3%)	(56.7%, 87.5%)

*% ORR and 95% CI not reported for subgroups with <10 patients
**Platinum-based chemotherapy for recurrent/metastatic disease or progression within 6 months of completion of platinum-based neoadjuvant/adjuvant chemotherapy

Statistical Reviewer's Comment:
The subgroup analyses results are considered exploratory. The results should be interpreted with caution given the small sample size overall and the limited number of patients in each subgroup. No outlier subgroup was observed.

Clinical Reviewer's Comment
In the subgroup of 7 patients who received entrectinib as first-line treatment for metastatic NSCLC, all seven had a confirmed response. This, supported by results in patients who had received prior treatment, suggest that entrectinib is an appropriate treatment option for the first-line treatment of metastatic ROS1-positive NSCLC.

Among the 51 patients in the primary analysis set, the most frequent gene fusion partner was *CD74-ROS1* (39%) and the estimated ORR among these patients was 85.0% (95% CI: 62.1%, 97.0%). Table 31 summarizes the statistical reviewer's ORR results by gene fusion partner. Among patients with unknown fusion partners identified by FISH at initial enrollment, two patients were non-responders.

Table 31: Reviewer's ORR Results by Gene Fusion Partner

Fusion Partner	Patients, n	Responders
CD74-ROS1	20	17
EZR-ROS1	4	4
SDC4-ROS1	6	4
SLC34A2-ROS1	7	4
TPM3-ROS1	2	1
Unknown	12	10

Statistical Reviewer's Comment: These results should be interpreted with caution due to the small sample size. The subgroup analyses results are exploratory.

Additional Efficacy Considerations

Not applicable.

8.2.5. Integrated Assessment of Effectiveness

The clinical and statistical review teams conclude that Genentech has provided substantial evidence of the effectiveness of entrectinib in adult patients with metastatic *ROS1*-positive NSCLC. This application is supported by demonstration of a large and clinically meaningful ORR with long durability (≥ 12 months) in 51 patients with metastatic ROS-1-positive NSCLC who had not received prior treatment with a ROS1 TKI enrolled and received entrectinib at various doses and schedules (90% received entrectinib 600 mg daily) in one of three multicenter, open-label, single-arm clinical trials (ALKA, STARTRK-1, STARTRK-2). FDA accepted data from single arm trials due to the rarity of *ROS1*-positive NSCLC, which renders conduct of a randomized trial not feasible. Demonstration of an ORR of this magnitude and durability establishes the clinical benefit of entrectinib in this rare, genetically defined subgroup of patients with NSCLC.

Among the 51 patients in the primary efficacy set, the ORR was 78% (95: CI% 65%, 89%), including 5.9% of patients with a CR and 72.5% of patients with a PR. Responses were durable. Among the 40 responding patients, 55% had a DOR of ≥12 months and 30% had duration of response of ≥18 months. This ORR and the proportion of responders with DOR ≥12 months is similar to that observed with crizotinib, which was FDA-approved for the treatment of patients with metastatic *ROS1*-positive NSCLC based on ORR and demonstration of durable responses in 50 patients with metastatic *ROS1*-positive NSCLC. The lower limit of the 95% CI for ORR with entrectinib (65%) in the primary efficacy set, the majority of whom had received prior systemic therapy for the treatment of metastatic disease, excludes the ORR observed in clinical trials of other therapies approved for the first-line treatment of an unselected population of patients with NSCLC or non-squamous NSCLC (i.e., chemotherapy plus anti-PD-(L)1 antibody, ORR 48% to 58%).

Assessment of the anti-tumor activity of entrectinib in the CNS was pre-specified in the plan for analysis of the pooled data with pre-specification of IC-ORR and IC-DOR as secondary endpoints. Among the 7 patients with measurable CNS metastases at baseline per BICR who had not received radiation to the brain within 2 months of first dose of entrectinib, there were 5 patients with confirmed IC response. Given the limited number of patients, the results need to be interpreted with caution; however, the results support a conclusion that entrectinib does have anti-tumor activity in the CNS in patients with *ROS1*-positive NSCLC but are insufficient to characterize the magnitude and durability of the anti-tumor activity in the CNS. Anti-tumor activity in the CNS was not assessed in the study supporting the approval of crizotinib.

The review team considers that the ORR, which is large in magnitude, along with the observed duration of responses, in patients treated with entrectinib is sufficient to establish clinical benefit in the genetically defined, rare subgroup of patients with *ROS1*-positive metastatic NSCLC.

8.3. Review of Safety

8.3.1. Safety Review Approach

The clinical assessment of the safety of entrectinib is based on data from four single-arm trials: ALKA-372-001, RXDX-101-01, RXDX-101-02, and RXDX-101-03 (also referred to as “ALKA”, “STARTRK-1”, “STARTRK-2”, and “STARTRK-NG”, respectively). The pooled safety population, which comprises 355 patients who received at least one dose of study drug (58 patients in ALKA, 76 patients in STARTRK-1, 207 patients in STARTRK-2, and 16 patients in STARTRK-NG; although a total of 357 patients were enrolled, 2 patients did not receive entrectinib and were excluded). The safety monitoring period spanned the time of first administration of entrectinib until 28 days following discontinuation of entrectinib, and for all AEs or related SAEs reported beyond the discontinuation (approximately 28 days [+ 7 days] after the final dose of the last cycle of treatment). All safety analyses were performed for the safety evaluable population and presented by the adult and pediatric safety population analysis sets.

Studies were ongoing during the original NDA submission except for ALKA; therefore, interim clinical study reports were reviewed for STARTRK-1, STARTRK-2, and STARTRK-NG, all of which used a data cut-off date 31 May 2018. Data from the 75-day update included safety data using a data cut-off date of 31 Oct 2018. Narratives of deaths and SAEs from all 4 studies were reviewed for events that occurred through the time of the data cut-off date. The review of safety included consideration of the submitted CSR, SDTM and analysis datasets, line-listings, CRFs, and patient narratives from all 4 trials. The clinical reviewers confirmed Genentech’s safety analyses, conducting analyses of primary data using the MedDRA-based Adverse Event Diagnostics (MAED) tool and JMP programs.

Safety data from 10 clinical pharmacology studies (N=323), and 8 single patient protocols (N=8), were also reviewed; however, these data were not included in the integrated summary of safety (ISS) analyses as the former studies enrolled healthy volunteers and the latter did not systematically collect safety data in the same fashion as a clinical trial, making data pooling not appropriate.

Clinical Reviewer Comment: Analyses of safety data from the 75-day safety update performed by Genentech were reviewed and verified by the FDA clinical reviewer. The majority of safety analyses presented below reflect data included in the original NDA submission that used a data cut-off date of May 31, 2018 (N=355). When warranted, clinically important new safety information that was provided in the safety update are also described below.

8.3.2. Review of the Safety Database

Overall Exposure

At the time of the data cutoff for the original NDA and for the 75-Day Update, three trials (STARTRK-1, STARTRK-2, and STARTRK-NG) were ongoing with patients still being treated and new patients being enrolled, and ALKA was completed. Three hundred fifty-five patients across the four trials had been enrolled as of the original NDA data cutoff and were eligible for inclusion in the integrated analysis. The safety data derived from the adult population reflects the safety of entrectinib across multiple dose levels; the majority of adult patients (76%) received the entrectinib 600 mg daily as a starting dose. In the original dataset (data cut off: May 31, 2018) 259 out of 355 patients (73%) had discontinued entrectinib.

The median duration of entrectinib treatment was 5.5 months (range: 1 day - 42 months) across the overall safety population of 355 patients treated, with a median of 7 cycles (range 1 - 92) as summarized in Table **32** and a mean cumulative dose of 123405.93 mg received as summarized in Table **33**. The overall median dose intensity was 96.89%. With regards to duration of exposure, 61.4% of patients had received entrectinib for >3 months, 48.5% for >6 months, 33.2% for > 9 months, and 23.7% for > 12 months.

Clinical Reviewer Comment: The median duration of exposure to entrectinib is longer in efficacy-evaluable NTRK fusion population (N=54) compared to the "all-comers" safety population (N=355), and by clinical study, the largest proportion of patients exposed were enrolled in the STARTRK-2 study. These findings were expected as the eligibility criteria in STARTRK-2 selected patients based upon the presence of NTRK fusions (or ROS fusions, in the case of patients with NSCLC) and the hypothesis was the patients with tumors harboring an NTRK-fusion would respond to entrectinib and thus have a longer duration of exposure to entrectinib than patients without the molecular fusion. Patients generally discontinued entrectinib due to disease progression. STARTRK-NG enrolled pediatric patients who tended to have a shorter duration of

exposure compared adults, although 2 patients (12.5%) were exposed to larotrectinib for over one year. The median dose intensity in STARTRK-NG was similar to the other studies.

Similarly, the median duration of exposure to entrectinib is longer in the efficacy-evaluable ROS1 fusion population (N=133) compared to the "all-comers" safety population (N=355), and by clinical study, the largest proportion of patients exposed were enrolled in the STARTRK-2 study. These findings were expected as the eligibility criteria required ROS1 fusion and the hypothesis was the patients with the ROS1-fusion NSCLC would respond to entrectinib, and thus have a longer duration of exposure to entrectinib compared to patients with cancers that did not have ROS-1 fusions. Patients generally discontinued entrectinib due to disease progression.

Notwithstanding the limited size of the safety population, the clinical review team considered the exposure to entrectinib adequate to conduct a risk:benefit assessment, particularly given the observed ORR and DOR. The majority of adult patients (76%) received entrectinib 600 mg daily as a starting dose. There were 4 pediatric dose cohorts in STARTRK-NG; this trial used BSA-based dosing and duration of drug exposure and dose intensity in pediatric patients did not materially differ across the cohorts.

Table 32**:** Summary Exposure of Entrectinib

Parameter	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Median treatment duration (Months)	7.9 (0.1, 24.7)	8.3 (0.1, 42.1)	2.0 (0.0, 37.0)	1.9 (0.2,12.7)	5.5 (0.0, 42.1)
Median no. of cycles	9.5 (1.0, 49.0)	10.0 (1.0, 92.0)	3.0 (1.0, 70.0)	4.0 (1.0, 16.0)	7.0 (1.0, 92.0)
Median no. of missed doses	1.0 (0.0, 34.0)	1.0 (0.0, 24.0)	0.0 (0.0, 17.0)	2.0 (0.0, 37.0)	1.0 (0.0, 37.0)
Median dose intensity, %*	94.1 (40.5, 105.3)	96.5 (29.8, 133.3)	98.6 (12.6, 388.3)	96.3 (32.6, 115.1)	96.9 (12.6, 388.3)

*Defined as total cumulative dose actually received/total planned dose x 100%. Factors contributing to dose intensity >100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.
Source: Reviewer generated table based on: Module 5.3.5.3 Analysis dataset_AEX. Derivations: BASKGRP3; TRTSDTM: Date/time of first exposure to treatment; TRTEDTM: Date/time of last exposure to treatment; TRTDURM: Duration of exposure (months)

Table **33** summarizes entrectinib exposure for ALKA, STARTRK-1, STARTRX-2, and STARTRX-NG.

Table 33**:** Entrectinib Exposure by Study and Overall

	ALKA	STARTRK-01	STARTRK-02	STARTRK-NG	Overall
N	57	76	206	16	355
Duration of Exposure					
≥3 month exposure	29 (50.9)	28 (36.8)	156 (76.1)	5 (31.3)	218 (61.4)
≥6 month exposure	18 (31.6)	20 (26.3)	130 (63.4)	4 (25.0)	172 (48.5)
≥9 month exposure	16 (28.1)	18 (23.7)	82 (40.0)	2 (12.5)	118 (33.2)
≥12 month exposure	14 (24.6)	13 (17.1)	55 (26.8)	2 (12.5)	84 (23.7)
Duration of treatment (weeks)					
n	57	76	205*	16	354*
Median	13.65	6.36	31.43	8.21	23.94
Mean	36.06	26.00	36.15	17.38	33.11
Range	2.5, 183.1	0.1, 148.9	0.3, 116.6	0.9, 55.3	0.1, 183.1
Number of cycles received					
Median	6.00	2.00	10.00	4.00	7.00
Mean	15.77	6.86	10.86	5.88	10.57
Range	1.0, 92.0	1.0, 38.0	1.0, 49.0	1.0, 16.0	1.0, 92.0
Cumulative dose (mg)					
n	57	76	205*	16	354*
Median	72800.00	27450.00	115800.00	22550.00	82500.00
Mean	166407.89	98516.45	124938.54	68800.00	123405.93
Range	2200.0, 1411600.0	200.0, 791600.0	1200.0, 367200.0	2400.0, 399200.0	200.0, 1411600
Dose intensity (%)					
n	57	76	205*	16	354*
Median	96.43	100.00	95.45	96.29	96.89
Mean	95.68	94.59	84.57	88.10	88.67
Range	25.0, 3883	33.3, 150.0	12.6, 112.4	32.6, 115.1	12.6, 388.3

Copied from submission to NDA as IR-33 on May 10, 2019, and verified from Module 5.3.5.3 Analysis dataset_AEX.

Relevant characteristics of the safety population:

Given the rarity of *NTRK* fusion solid tumors and *ROS1*-fusion NSCLC, FDA considered the safety database to be adequate to characterize risks in the population who would be treated with entrectinib in the postmarket setting, aside from the pediatric population**.**

The safety population from Studies ALKA, STARTRK-1, and STARTRK-2 primarily consisted of adult patients with solid tumors, and the safety population from STARTRK-NG consisted primarily of pediatric patients (there were 2 patients over 18 years of age). There were no Black patients enrolled on the trials with a solid tumor with an *NTRK*-gene fusion, and the number of patients enrolled in any specific demographic subpopulation is low, given the rarity of *NTRK* fusions in most primary tumors and the small study sample size. ECOG status was predominately 0-1.

Additional exploratory analyses were conducted based on gender, race, performance score, *NTRK*-gene fusion protein, and tumor type. Limitations of these subgroup analyses are the small sample sizes and lack of internal control in all studies. For a summary of demographics across all trials, see Table **34**.

Table 34**: Demographics**

	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult (non *NTRK*, *ROS1*) (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Sex					
Male (%)	46	40	49	62	45
Female (%)	54	60	51	38	55
Median Age (yrs)	58	53	55	10	55
Range	21-83	15-86	15-80	4-20	4-86
Age (yrs)					
<65 (%)	63	76	76	100	75
≥65 (%)	37	24	24	0	25
Ethnicity					
Hispanic or Latino (%)	6	2	3	6	3
Not Hispanic or Latino	86	92	88	81	89
Not stated (%)	6	2.5	1	6	3
Unknown (%)	1.5	4	8	6	5
Race					
White (%)	77	53	72	81	66
Asian (%)	13	38	16	0	23
Black or AA (%)	1.5	5	4	19	4.5
Not reported (%)	9	3	4	0	4.5
ECOG PS (%)					
0	38	39	45	0	41
1	49	50	51	0	50
2	10	8	4	0	7
3	3	0.7	0	0	0.9
4	0	0.7	0	0	0.3

Source: Reviewer generated table based on ADL dataset submitted to NDA 212726 Module 5.3.5.3

Adequacy of the safety database:

The safety database of 355 entrectinib-treated patients is sufficient to observe any serious risk occurring at an incidence of ≥1%, which is generally adequate to permit a risk:benefit assessment in patients with metastatic solid tumors, which are serious and life-threatening diseases, and in NSCLC in particular, where the 5-year survival is less than 5%.

The safety population from ALKA, STARTRK-1, and STARTRK-2 primarily consisted of adult patients with solid tumors, and the safety population from STARTRK-NG consisted primarily of pediatric patients (total pediatric patients across all trials N=30; 7% were < 2 years [n = 2], 77% were 2 to < 12 years [n = 23], 17% were 12 to < 18 years [n = 5]). There was insufficient information to establish a safe and effective dose in pediatric patients less than 12 years of age (see Sections 1.3, 6.2, 6.3, 8.4, and 10 for further details).

Overall, the safety database submitted by Genentech was adequate to conduct a risk:benefit assessment, given the observed ORR and DOR, in adult and pediatric patients ≥ 12 years of age. Given the rarity of solid tumors with an activating *NTRK* rearrangement and the observed adverse reaction profile in the context of the entrectinib exposure achieved in the safety population, FDA considered the safety database sufficient to characterize the safety profile of entrectinib in patients ≥ 12 years of age and identify AEs that occur at an incidence of approximately 2%.

Safety monitoring in the entrectinib studies consisted of collection of adverse events (AEs), serious adverse events (SAEs), laboratory tests (standard hematology and blood chemistries), physical observations/measurements (vital signs, electrocardiograms [ECGs], Eastern Cooperative Oncology Group [ECOG] status in adult studies and Lansky or Karnofsky performance status in the pediatric study, eye exams, chest X-rays), and pregnancy test in female patients of childbearing potential.

For all four oncology patient studies, vital signs (blood pressure [systolic and diastolic], heart/pulse rate, and body temperature [except for Study ALKA]) were measured. In addition, respiration rate was measured in Study STARTRK-2 and STARTRK-NG. Vital signs were measured at screening, during each treatment cycle, and at end of treatment visit. Weight and BMI have been integrated and analyzed collectively across all four oncology patient studies. Weight (kg), change from baseline, and percent change from baseline were summarized by cycle.

To monitor for potential corneal-related visual disturbances during treatment with entrectinib, eye examinations were required at screening, during treatment, at the end of treatment, and as clinically indicated. Additionally, neurological functions were assessed as part of physical examinations to monitor potential neurological toxicities during treatment with entrectinib. ECGs were performed in triplicate and assessed by a central reader for STARTRK-1 sites and all U.S. and Japan sites for STARTRK-2. ECGs was performed at screening, throughout treatment cycles, end of treatment visits, and if clinically indicated.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted was organized and of adequate quality to perform a comprehensive review of the safety of entrectinib. Several information requests were sent to Genentech during the review of safety to confirm data, request additional data, request alternative presentations of safety data, or clarify minor discrepancies. On the whole, Genentech provided timely and adequate responses, including additional analyses and clarifications as required. Data was verified and characterized (see final prescribing information for entrectinib).

Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) v15.1, 17.0, 18.0, and 19.0 were used for coding adverse events for the CSRs for Study ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG, respectively.

Genentech coded verbatim AE terms for all 4 studies and the integrated database using MedDRA version 21.0 for the primary analyses (ISS) and the data submitted at the 75-day data safety update. According to the Summary of Clinical Safety (SCS): NDA location Module 2.7.4, treatment-emergent adverse events (TEAEs) were defined as all AEs occurring from initiation of study drug through 30 days after the last dose of entrectinib, but according to the protocol for ALKA, AEs were defined as all AEs occurring from initiation of study drug through 28 days after the last dose of entrectinib. In response to an IR (IR-29 dated 14 May 2019), Genentech clarified that both ALKA and STARTRK-NG collected AEs from the time of initiation of study drug through 28 days (and not 30 days) after the last dose. Information regarding deaths occurring within 30 days of receiving entrectinib was also collected. Regardless of the differences in AE reporting periods between ALKA and the other 3 clinical protocols, there was one death event which occurred outside of the period of 30 days after the last dose of entrectinib but is included in the analysis of death events. National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE Version 4.03) was used for toxicity grading.

The clinical reviewer assessed the adequacy of Genentech's mapping of AE verbatim terms to MedDRA preferred terms (PTs) for 100% of the four studies' primary AE.xpt datasets. The majority of nonidentical terms were due to spelling differences (e.g., anemia versus anaemia), use of abbreviations instead of full text (e.g., ALT increase versus alanine aminotransaminase increased), and verbatim terms that included descriptors (e.g., abdominal cramping versus abdominal pain). Some verbatim terms were miscoded or FDA did not agree with Genentech's coding such as "giddiness" to "dizziness"; such terms were recoded for accuracy. During the audit of the case report forms, several discrepancies were noted between AE information included in the case report forms and the AE datasets, including missing records. Overall, the MedDRA PTs listed in the dataset adequately represented the verbatim terms from the CRFs.

Safety and tolerability assessment was based on the frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments (hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. Multiple occurrences of the same event for a patient were counted once at the maximum severity reported. All events were followed to their resolution, until the Investigator assessed them as stable or otherwise explained, or until the patient was lost to follow-up, whichever occurred first.

Safety data was available for treatment-emergent AE (TEAE). A treatment-emergent AE (TEAE) was defined as any event arising or worsening after the start of study drug administration until 30 days after the last administration of entrectinib. For the purpose of the AE tables, an event

was considered related to entrectinib if the investigator reported that it was possibly, probably, or definitely related in the AE electronic CRF (eCRF) form for the individual study.

Safety data were available for treatment-related SAEs, AE of special interest (AESIs), and all listings of AEs include all events that occurred during or after the first study drug treatment up to the data cutoff date. AESIs included were neurologic toxicity, changes in weight, congestive heart failure, increased creatinine and other renal events, eye disorders, QTc interval prolongation, elevated liver laboratory tests and other liver abnormalities, pneumonitis events, and hematologic events. FDA reviewed each AESO (see Section 8.2.4 for the reviewers conclusions).

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation and causes of death were summarized. For the integrated safety analysis, deaths due to disease progression were not included in SAE analysis across all four studies.

For laboratory test results, standard normal ranges were used by Genentech to identify values outside the normal ranges. Abnormal laboratory results were graded according to the NCI CTCAE v4.03 except for creatinine, which was revised and graded according to NCI CTCAEv5.0. A shift summary of baseline grade by maximum post-baseline CTCAE grade was included in the analyses. For each laboratory parameter, the baseline laboratory value was defined as the last laboratory value collected on or prior to the date of first dose of entrectinib. Only laboratory parameters common to all 4 studies were included. Potential liver abnormalities were included.

ECG analyses was based on central ECG readings that included the following parameters: heart rate, PR duration, QRS duration, QT duration, QTcB [Bazett's Correction], QTcF [Fridericia's Correction], and RR duration. Local ECG readings for Studies STARTRK-2 and STARTRK-NG included ventricular rate, PR duration, QRS duration, QT duration, QTcB, QTcF, and QTc Unknown. ECGs for Study ALKA included ventricular rate, QT duration, QTc (unspecified) and overall interpretation (normal/abnormal).]

<u>Clinical Reviewer Comment</u>: Genentech considers it unlikely that the discrepancy in the reporting period of ALKA had an impact in the analysis of adverse events and the clinical reviewers agree. An analysis performed by FDA identified one patient ([redacted] (b) (6)) who died 33 days from the last dose of entrectinib ([redacted] (b) (6)). This patient's death, which was attributed to progressive disease, occurred outside of the 28-day window and was also outside of the 30-day window. Regardless, this patient most likely succumbed to underlying cancer (see ***Error! Reference source not found.****,* ***Error! Reference source not found.*** *"****Deaths****" below). The discrepancies noted between AE information included in the case report forms and the AE datasets, including missing records, were resolved or were not considered relevant to the overall safety assessment.*

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Routine Clinical Tests

Laboratory assessments were performed within 7 days of enrollment for ALKA, 30 days for STARTRK-1, STARTRK-2, and 14 days for STARTRK-NG and on Day 1 of all four studies, at regularly scheduled intervals, and when medically necessary during drug administration. Vital sign measurements were obtained at least once prior to each cycle. Monitoring for cardiac-related toxicities included ECGs prior to each cycle with the exception of ALKA, in which an ECG was performed on D18 of cycle 1 and 3, at the end of therapy, and at the discretion of the Investigator, with the exception of STARTRK-NG in which pediatric patients underwent ECG assessment prior to Cycle 1 Day 1 until Cycle 7 only. (Refer to the Monitoring Plan in Section 19.6 for details).

8.3.4. Safety Results

APPEARS THIS WAY ON ORIGINAL

In the overall integrated safety population, 99% of patients experienced at least one AE, and of those, Grade 3-4 events were experienced in 60%. The most frequently reported AEs (see **Error! Reference source not found.**) were fatigue (48%), constipation (46%), dysgeusia (44%), dizziness (38%), edema (40%), diarrhea (35%), nausea (34%), dysesthesia (34%), dyspnea (30%), cough (24%), cognitive impairment (27%), peripheral sensory neuropathy and headache (18% each), ataxia (17%) and mood disorders (10%). The most frequently reported Grade 3-4 AEs (see **Error! Reference source not found.**) were anemia (9%), increased weight (7%), dyspnea (6%), fatigue/asthenia (5%), pneumonia, pulmonary embolism, hypoxia, and AST increased (each 3.4%), cognitive impairment (4.5%), pleural effusion and AST increased (each 3.1%), hypotension/orthostatic hypotension and hypophosphatemia (each 2.8%), neutropenia and syncope (each 2.5%), UTI (2.3%), diarrhea, hypokalemia, hyponatremia, and lipase increased (2.0%).

An overview of the safety profile in patients treated with entrectinib in the overall integrated safety population (n=355) is provided below in Table **35**.

Table 35**:** Overview of Safety Profile in Integrated Safety Population

	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult non*NTRK*, non*ROS1* (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Patients with AE (%)	100	100	99	100	99
Patients with treatment related AE (%)	100	100	98	100	99
Patients with SAE (%)	47	37	40	13	39
Patients with related SAE (%)	10	13	5	6	9
Patients with ≥Grade 3 AE (%)	74	61	56	50	61
Patients with AE leading to discontinuation (%)	13	9	6	6	9
Patients with AE leading to dose reduction (%)	41	34	16	25	28
Patients with AE leading to drug interruption (%)	56	45	43	38	46
Patients with AE leading to death (%)	9	7	4	0	6

Source: Reviewer generated table based on AAE.xpt. Derivation: Variables: BASKGRP3, AEOUT, AEACN, AETOXGR, AESER, AETRTEM (treatment emergent flag) AEACN, AEREL, AESHOP

Deaths

There were 20 patients (6%) who died (Grade 5) due to an AE within 30 days of last dose of entrectinib. The causes of death in >2 patients were acute respiratory failure, cardiorespiratory arrest, dyspnea, meningeal metastases, pneumonia, sepsis/septic shock (Table 36).

Table 36: Overview of Deaths in Entrectinib Trials

Cause of Death	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non*NTRK*, non*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total no. of deaths (%)	22 (32)	29 (22)	37 (27)	5 (31)	93 (26)
Total no. of deaths due to AE	6 (9)	9 (7)	5(4)	0 (0)	20 (6)
Death < 30 days of last dose					
Total	8 (12)	21 (16)	17(12)	2 (13)	48 (14)
PD	4 (6)	15 (11)	11(8)	2(3)	32 (9)
Other	4 (6)	3 (2.2)	1 (0.7)	0	8(2.3)
Unknown	0	3 (2.2)	5 (3.6)	0	8(2.3)
Death > 30 days of last dose					
Total	14 (21)	8(6)	20 (15)	3 (19)	45 (13)
PD	12 (18)	7 (5)	12 (9)	3 (19)	34 (10)
Other	1 (1.5)	1 (0.7)	8(6)	0	10 (3)
Unknown	1(1.5)	0	0	0	1 (0.3)

Source: Reviewer generated table based on Dataset AAE.xpt. Derivation: Variables: BASKGRP3, AEOUT

Clinical Reviewer Comment: *There were no deaths evaluated by the investigator to be attributed to an AE. See comment below after* Table 37*and* Table 38 *for further comment of reviewers' attribution.*

Table 37: Adverse Event Resulting in Death

Preferred Term	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non*NTRK*, non*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total number (%)	6 (9)	9 (7)	5 (4)	0 (0)	20 (6)
Acute Respiratory Failure	2 (3)	0 (0)	1 (0.7)	0 (0)	2 (0.6)
Cardio-respiratory Arrest	2 (3)	0 (0)	0 (0)	0 (0)	2 (0.6)
Dyspnea	0 (0)	1 (0.7)	1 (0.7)	0 (0)	2 (0.6)
Meningeal Metastases	0 (0)	2 (1.4)	0 (0)	0 (0)	2 (0.6)
Pneumonia	1 (1.5)	1 (0.7)	0 (0)	0 (0)	2 (0.6)
Sepsis/Septic Shock	1 (1.5)	1 (0.7)	1 (0.7)	0 (0)	3 (0.9)
Cardiogenic Shock	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Cerebral Infarction	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Completed Suicide	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)
Large Intestine Perforation	0 (0)	1(0.7)	0 (0)	0 (0)	1 (0.3)
Pulmonary Embolism	0 (0)	1 (0.7)	0 (0)	0 (0)	1(0.3)
Tumor Lysis Syndrome	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)

Source: Reviewer generated table based on Dataset AAE.xpt. Derivation: Variables: BASKGRP3, AEOUT, AEDECOD

The reviewer conducted analyses of the narrative summaries and AEs to verify the cause of death described by Genentech for all deaths that occurred within 30 days of the last dose of entrectinib, presented in Table 38**Error! Reference source not found.**.

Table 38: Patient Narratives of Death due to Adverse Event

Patient ID/Study/Dose/ Treatment Dates	Death AE PT	Narrative
(b) (6) /ALKA/Schedule B, 400mg/m^2/day, (b) (6) (b) (6)	Pulmonary Embolism	67-year-old female patient with *ROS1* NSCLC experienced abdominal pain on treatment D569. CT abdomen revealed fluid collection and diverticulitis. On D579, abdominal pain continued and CT scan chest revealed pulmonary embolism. Patient expired same day.
(b) (6) /RXDX-101/600mg/day, (b) (6) (b) (6)	Tumor Lysis Syndrome	28-year-old male patient with widespread metastatic sarcoma was hospitalized on treatment D15 for fatigue, lethargy, with decreased urine output. Labs revealed increased ALT, AST, bilirubin, creatinine, uric acid, PT, PTT, INR and anemia. Uric acid was 11.5mg/dl. Entrectinib was discontinued. Patient was stabilized and improved. On D20, patient developed acute respiratory failure, shock and acidosis. Patient was started on dialysis, pressors, and BIPAP. On D23 patient condition deteriorated and expired the same day.
(b) (6) /RXDX-101-01/600mg/day, (b) (6) (b) (6)	Large Intestine Perforation	64-year-old male patient with metastatic *ROS1* NSCLC was hospitalized on treatment on D29 for dyspnea and fever. CXR revealed large pneumoperitoneum, CT abdomen revealed sigmoid diverticulitis and perforation. On D30 patient underwent exploratory laparotomy and weaned off the ventilator. Patient died on D36.
(b) (6) /RXDX-101-01/700mg/day, (b) (6) (b) (6)	Hypoxic Respiratory Failure	50-year-old female patient with metastatic breast cancer became restless, agitated on treatment D7 and pleural effusion was drained. Received her last dose of entrectinib on D8 and arrived at study site lethargic and hypotensive. On D9 was hospitalized for mental status changes, increasing SOB. CXR revealed pulmonary edema, right pleural effusion. Effusion was drained every other day. On D15 patient was transitioned to hospice and died due to hypoxic respiratory failure secondary to metastatic breast cancer.
(b) (6) /RXDX-101-01/ 400mg/m2/day, (b) (6) (b) (6)	Worsening dyspnea, Pulmonary embolism	59-year-old female patient with metastatic *ALK+* NSCLC discontinued entrectinib on D 88 due to disease progression. On D92 was hospitalized for hypoxia during a red blood cell transfusion. CT revealed bilateral pulmonary embolism and bilateral pleural effusion. On D104 patient was discharged. On D114 patient was admitted for serious dyspnea and noted to have increasing pleural effusion Patient condition deteriorated and transitioned to hospice. On D120 patient died due to disease progression.

Patient ID/Study/Dose/ Treatment Dates	Death AE PT	Narrative
(b) (6) /RXDX-101-02/600mg/ day, (b) (6) (b) (6)	Pneumonia	58-year-old male patient with metastatic NSCLC with extensive lung metastases was hospitalized for bilateral peripheral edema and hypotension on treatment D14. Noted to have grade 3 pericardial effusion and grade 2 CHF with normal EF. Drug discontinued on D16. On D21, patient underwent pericardiocentesis and the fluid was not malignant. On D37 patient was diagnosed with Grade 4 pneumonia and continued hospitalization. On D43 patient died due to grade 5 pneumonia.
(b) (6) /RXDX-101-02/600mg/ day, (b) (6) (b) (6)	Dyspnea	43-year-old female patient with metastatic NSCLC with extensive mets was hospitalized on D28 for worsening dyspnea (Grade 3). Last dose was D28. Patient died on D55 due to dyspnea and respiratory failure related to underlying metastatic disease.
(b) (6) / RXDX-101-02/ 600mg/ day, (b) (6)	Cerebral Infarction	34-year-old female patient with metastatic NSCLC was hospitalized on D16 for worsening pyrexia and grade 3 neutropenia. On D16 entrectinib was interrupted. On D24 a CT head revealed grade 4 subarachnoid hemorrhage that was drained on D25. On D28 patient experienced grade 4 bilateral cerebral infarction. On D37 patient died due to grade 5 cerebral infarction. The death was attributed to underlying metastatic disease.

Source: Reviewer generated table based on narratives from each CSR submitted to NDA Module 5.3.5.2

One fatal event of large intestine perforation was reported in a patient (b) (6) /RXDX-101-01 with concurrent diverticulitis; the fatal perforation was attributed to the co-morbid condition of diverticulitis.

Patient (b) (6) /RXDX-101 died from tumor lysis syndrome, which is attributed to entrectinib as the patient was not receiving any other concomitant anti-neoplastic treatment. The patient had advanced disease and multiple prior lines of systemic cancer therapy before being treated with entrectinib, and heavy tumor burden at baseline with numerous metastases with increasing size at the time of the event. The investigator assessed the event as not related to entrectinib but related to tumor burden and disease treatment.

One patient committed suicide in the hospital subsequent to confirmation of disease progression. Given the documented CNS effects of entrectinib, this event is possibly/probably attributable to entrectinib.

Two patients reported fatal events of metastases to meninges, both of which were considered by the investigators as related to progression of the underlying disease.

Fatal events of sepsis or septic shock occurred in three patients; these patients had a past medical history of sepsis, previous hospitalization or intensive care unit admission, or cancer as risk factors.

One fatal event of cerebral infraction was reported in a patient with a medical history of deep vein thrombosis and a concurrent event of subarachnoid hemorrhage. The event was considered to be secondary to the patient's underlying hypercoagulable state due to lung cancer.

One fatal case of cardiogenic shock was reported in a patient with NSCLC due to pericardial effusion and pericardial tamponade. The patient developed cardiogenic shock two days after starting entrectinib and died, and it was noted that the patient had suspected pericardial, bilateral pleural, omental and peritoneal carcinomatosis at baseline, as well as diffused lung, liver, and bone metastases. Although entrectinib cause a decrease in ejection fraction, the presence of pericardial metastases make attribution to disease more likely.

Clinical Reviewer comment: The reviewers conducted analyses of the narrative summaries and AE listings to verify the cause of death provided by Genentech for all deaths attributed to a TEAE or that occurred within 30 days of the last dose of study therapy regardless of attribution. The majority of Grade 5 AEs were reported in the context of worsening of underlying diseases or complications of the underlying malignancy. None of the 20 deaths due to AE were assessed by the investigator as being related to entrectinib. While the reviewers agree that the majority of deaths are unlikely to be related to entrectinib, due to the single arm nature of these studies and temporal relationship between the onset of death and initiation of entrectinib in some cases, it is possible that there is a causal relationship for entrectinib in some of these deaths. Additionally, FDA does not agree with the attribution of certain fatal events as noted above. Therefore, the package insert will include information regarding all Grade 5 AEs (deaths).

Serious Adverse Events

The protocols defined a serious adverse event (SAE) as an adverse event that meeting one of the following criteria, in accordance with 21 CFR 312.32(a):

- Resulted in fatality (i.e., the adverse event actually causes or leads to death)
- Was life threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death)
- Required or resulted in prolongation of inpatient hospitalization
- Resulted in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Caused a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Was a significant medical event in the Investigator's judgment (e.g., that jeopardized health of the patient or required medical/surgical intervention to prevent one of the outcomes listed above)

The SAE definition did not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.

The analyses of SAEs presented by Genentech are based on the adverse event dataset and include the overall analysis safety population using the data included in the NDA submission for patients who reported an AE that met any of the serious criteria, whether or not the event was judged to be related to study drug.

SAEs occurred in 39% patients; the most frequently reported SAEs (in >1 % of patients) by MedDRA System Order Class (SOC) were: respiratory and mediastinal disorders (13%), infections (10%), nervous system and psychiatric disorders (10%), cardiac disorders (4%), general disorders (4%), gastrointestinal (4%) and vascular disorders (2%) (**Error! Reference source not found.**). The most frequently reported AEs by preferred term (PT) were dyspnea (4%), pneumonia (3.9%), pleural effusion (3%), pulmonary embolism (2%), acute respiratory failure (2%), and pyrexia (2%). SAEs were less common among pediatric patients compared to the adult population.

The majority of the SAEs in the “respiratory thoracic and mediastinal disorders” SOC were reported in patients with primary lung cancer or with secondary lung metastasis. The most frequently reported (≥ 2% of patients) PTs in this SOC included dyspnea (3.7%), pleural effusion (3.4%), and pulmonary embolism (2.3%), as pneumonia was listed under the “infections and infestations” SOC, described below.

The most frequently reported PTs (≥ 2% of patients) in the “infections and infestations” SOC was pneumonia (3.9%). Other respiratory infections included upper respiratory tract infection (0.6%), lung infection (0.6%), lower respiratory tract infection (0.3%). The majority of respiratory infections were reported in patients with primary lung cancer or with secondary lung metastasis.

SAEs in the nervous system disorders SOC occurred in 10% of patients, and the most frequently reported PT was cognitive disorder (1.4%). Other SAEs in this SOC (occurring in ≥ 2 patients) included syncope (0.8%), ataxia (0.6%), and dizziness (0.6%), which were consistent with the CNS activity of entrectinib and the known association of TRK receptor involvement in the nervous system. Other nervous system SAEs (occurring in ≥ 2 patients) included hydrocephalus (0.8%) and seizure (0.8%); the patients with these events were noted to have brain metastases at baseline.

No particular pattern by timing or duration of AE were observed in the type and frequency of SAEs reported with the exception of fractures (discussed further below). A smaller proportion (12.5%) of pediatric patients experienced SAEs compared to adults; however given the limited number of patients, a conclusion cannot be made regarding whether there are differences in the safety profile based on age. There was no specific SAE with an incidence that was ≥ 4%.

Table 39 provides a summary of the per-patient incidence of SAEs regardless of causality by SOC and PT in order of decreasing frequency.

Table 39: Serious Adverse Events by System Organ Class and Preferred Term (>1% total incidence)

SOC/Preferred Term	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non-*NTRK*, non-*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total n (%)	32 (47)	50 (37)	53 (39)	2 (13)	137 (39)
Respiratory and Mediastinal disorders	11 (16)	16 (12)	17 (12)	2 (13)	46 (13)
Dyspnea	2 (2.9)	6 (4.5)	5 (3.6)	0	13 (3.7)
Acute respiratory failure/respiratory distress	3 (4.4)	0	4 (2.9)	0	7 (2)
Pleural Effusion	3 (4.4)	5 (3.7)	3 (2.1)	2 (13)	12 (3.4)
Pulmonary embolism	2 (2.9)	3 (2.2)	3 (2.1)	0	8 (2.2)
Infections and Infestations	11 (16)	13 (10)	11 (8)	1 (6)	36 (10)
Pneumonia	2 (2.9)	2 (1.5)	10 (7)	0	14 (3.9)
Sepsis	2(2.9)	1 (0.7)	6 (4.4)	0	9 (2.5)
Nervous System Disorders and Psychiatric Disorder	8 (12)	16 (12)	11 (8)		35 (10)
Cognitive disorder	1 (1.5)	2(1.5)	2 (1.4)		5 (1.4)
Syncope	0 (0)	2 (1.5)	1 (0.7)		3 (0.8)
Ataxia	1 (1.5)	1 (0.7)	1 (0.7)		3 (0.8)
Dizziness	1 (1.5)	1 (0.7)	0		2 (0.6)
Mental status changes/confusion	1 (1.5)	2 (1.5)	3 (2.1)		5 (1.4)
Depression	1 (1.5)	0	0		1 (0.3)
Cardiac Disorders	5 (7)	6(4.5)	2 (1.4)		13 (3.7)
Vascular disorder	2 (2.9)	3(2.2)	2 (1.4)		7 (2)
Hypotension	2 (2.9)	3(2.2)	1		6 (1.7)
Gastrointestinal Disorder	0	4 (3)	10 (7)		14 (4)
General Disorders and administration site	2 (2.9)	6 (4.4)	7 (5)		15 (4.2)
Pyrexia	0	4 (3)	3 (2.1)		7 (2)

Source: Reviewer generated table based on dataset AAE.xpt. Derivation Variables: BASKGRP3, AESER, AETERM, AEBODYSYS, AEDECOD

Patient narratives for selected SAEs (not inclusive of patient deaths, Grade ≥ 3 AEs, in which the reader should refer to those sections in 8.3.4) are presented in Table 40.

Table 40: Selected Patient Narratives for Serious Adverse Events

Patient ID/Study/Dose/ Treatment Dates	SAE AE PT	Narrative
(b) (6) /ALKA/Schedule A, 200mg/m^2/day, 400mg/m^2/day (D114), 800 mg/m^2/day (D318) (b) (6)	Pneumonia Grade 3 Confusion Grade 3	60-year-old male patient with NSCLC was admitted on treatment D341 for pneumonia and Grade 1 confusion. On D348 was discharged and on D365 was noted to have Grade 3 confusion and admitted for low BP and confusion. Drug was interrupted between D365 to D389. On D370, confusion and pneumonia had resolved and patient was discharged and entrectinib was resumed on D390.
(b) (6) /ALKA/Schedule B, 600mg/day; (b) (6)	Hydrocephalus Grade 3	41-year-old female with metastatic GBM was hospitalized on D20 for decreased level of consciousness. CT revealed hydrocephalus and progression of GBM and had a valve placed. Last dose of Entrectinib was D20. Patient died on D30 due to progression of disease. Hydrocephalus did not resolve.
(b) (6) /ALKA/Schedule B, 400mg/m2/day; (b) (6)	Syncope Grade 3	67-year-old male with metastatic NSCLC was hospitalized on D385 for an episode of post-micturition syncope the day prior. Patient continued the drug until D456, and had no additional episodes of syncope.
(b) (6) / RXDX-101/, 600mg /day; (b) (6)	Hyponatremia Ventricular extrasystoles	55-year-old female with metastatic HNSCC was admitted on D19 for worsening dyspnea, generalized edema, fever and urinary incontinence. Labs revealed a sodium of 127 mmol/L (normal at baseline) and hypomagnesemia. EKG revealed ventricular extrasystoles. Patient was stabilized and discharged on D23. On D33 her sodium was 139mmol/L and entrectinib was restarted at reduced dose of 400 mg/day. On D43 patient experienced ventricular extrasystoles with no symptoms and entrectinib was discontinued.
(b) (6) / RXDX-101/, 800mg/day; (b) (6)	Hip Fracture	72-year-old female with metastatic ovarian cancer experienced fatigue starting D12, and on D14 entrectinib was skipped due to intolerable fatigue. On D31 patient fell and x-ray revealed a right hip stress fracture. On D32, underwent right hip arthroplasty and intramedullary rod placement. Biopsy of right femoral head revealed no tumor, marrow edema, mild fibrosis, fat necrosis, osteoclastic activity and reactive new bone formation.

Patient ID/Study/Dose/ Treatment Dates	SAE AE PT	Narrative
(b) (6) / RXDX-101/, 600mg/day; (b) (6)	Altered mental status Ataxia Febrile Neutropenia	67-year-old female with *ALK+* NSCLC experienced significant weight gain, dizziness on D7 and drug was interrupted. On D8 patient was admitted with mental status changes and ataxia. On admission was noted to be febrile. Head CT was normal. With symptomatic treatment with intravenous fluids and interruption of entrectinib, the mental status changes and ataxia resolved on D10. On D14 entrectinib was restarted at 200 mg/day without recurrence of similar symptoms. On D380 patient was hospitalized for neutropenic fever and treated with antibiotics and drug was interrupted. WBC recovered on D382. Patient was taken off study on D499 for disease progression.
(b) (6) / RXDX-101-02/, 600mg/day; (b) (6)	Dizziness	43-year-old male with metastatic MASC experienced Grade 1 dizziness on D115 that worsened to Grade 2 on D131 and Grade 3 on D154, with Grade 2 ataxia. Patient was noted to have Grade 3 syncope on the same day. CT head was negative, Holter was negative for arrhythmias. On D 169 drug was interrupted and on D171 dizziness resolved. Entrectinib was restarted on D176 at a reduced dose (400mg). Grade 1 dizziness remained ongoing.

Source: Reviewer generated table based on narratives submitted to each CSR NDA Module 5.3.5.2

Clinical Reviewer Comment: *In general, this reviewer considers the attributions of the SAEs by the investigator generally accurate. The majority of SAEs appear to be either wholly or in part attributed to the underlying cancer diagnosis and disease progression, or common complications of cancer therapy, with those SAEs possibly related to the drug described above. Because attribution may be unreliable in single arm trials, these data are described in the package insert for entrectinib.*

Treatment Interruptions, Dose Reductions and/or Discontinuations Due to Adverse Effects

Of the 259 patients (73%) off-treatment at the time of database cutoff (31 May 2018), the most common reason for discontinuation was disease progression (n=197, 76%) with 12% of patients (n=30) discontinuing due to an AE.

Table 41 summarizes the reasons for discontinuation of entrectinib for the 54 patients in the *NTRK* efficacy population using the data cutoff date for the original NDA submission, for all efficacy-evaluable patients with *NTRK* fusion tumors enrolled across the four trials and for the overall safety analysis population (both with and without documented *NTRK* fusion tumors).

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AEs requiring discontinuation of study drug treatment across all entrectinib trials occurred in 9% of patients (**Error! Reference source not found.**). The most common reasons for treatment discontinuation (in ≥ 1% of patients by SOC) were respiratory and mediastinal disorders (2%),

cardiac disorders (2%) and infections (1%). Table 41summarizes AEs leading to discontinuation of entrectinib in all patients.

Table 41: Adverse Events Leading to Drug Discontinuation in ≥ 1% Patients

SOC/Preferred Term	*NTRK* Adult (n=68)	*ROS1* NSCLC Adult (n=133)	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric (n=17)	All (n=355)
Total %	13	9	6	6	9
Respiratory and Mediastinal disorders					
Total	3	2	0.7	6	2.0
Dyspnea	0	0.7	0	6	0.6
Acute respiratory failure	3	0	0	0	0.6
Pneumonitis	0	0.7	0	0	0.3
Pulmonary edema	0	0	0.7	0	0.3
Pulmonary embolism	0	0.7	0	0	0.3
Cardiac Disorders					
Total	4.4	1.5	1.5	0	2.0
Cardio-respiratory arrest	2.9	0	0	0	0.6
CHF	1.5	0	0	0	0.3
A Fib/Extrasystoles	0	0	0.7	0	0.3
Myocarditis	0	0.7	0	0	0.3
Cardiogenic shock	0	0.7	0	0	0.3
Pericardial Effusion	0	0.7	0	0	0.3
Infections and Infestations					
Total	3	0.7	0.7	0	1.1
Pneumonia/Lower RTI/Lung infection	1.5	0.7	0.7	0	0.8
Sepsis	1.5	0	0	0	0.3
General disorders and administrative site conditions					
Total	1.5	0.7	1.5	0	1.1
Fatigue	1.5	0	0.7	0	0.6
Malaise	0	0	0.7	0	0.3
Peripheral edema	0	0.7	0	0	0.3

Source: Reviewer generated table based on Dataset AAE.xpt. Derivation Variables: BASKGRP3, AEOUT, AETERM, AEBODYSYS, AEDECOD; A Fib=atrial fibrillation, RTI=respiratory tract infection

AEs requiring treatment interruption occurred in 46% of patients. The most common reasons for dose interruption (in >2% of patients) were increased creatinine (4%), fatigue (4%), anemia (3%), diarrhea and pyrexia (each 3%), dizziness (3%), nausea (2%), dyspnea (2%), pneumonia (2%), cognitive disorder (2%), and neutropenia (2%). Table 42 describes AEs leading to dose interruption that occurred in at least 1% of patients that received entrectinib.

Table 42: Adverse Events Leading to Treatment Interruption in ≥ 1% of Patients

Preferred Term	*NTRK* Adult n=68	*ROS1* NSCLC Adult n=133	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric n=17	All n=355
Total %	56	45	43	38	46
Increased creatinine/AKI	6	4	1.5	12.5	3.9
Fatigue	7	1.5	4	6	3.7
Anemia	9	0	4	0	3.1
Diarrhea	3	2	3	6	2.8
Pyrexia	3	2	4	0	2.8
Dizziness	1.5	5	0.7	0	2.5
Nausea	4	1.5	2	0	2.3
Dyspnea	3	3	1.5	0	2.3
Pneumonia	3	2	3	6	2.3
Cognitive disorder	0	4.5	0.7	0	2.0
Neutropenia	0	0.7	1.5	6	2.0
AST increase	3	1.5	1.5	0	1.7
Pleural Effusion	1.5	3	0.7	0	1.7
Vomiting	0	1.5	3	6	1.4
ALT increase	3	1.5	0.7	0	1.4
Lipase increase	0	0.7	3	0	1.4
UTI	1.5	1.5	1.5	0	1.4
Peripheral edema	1.5	2	0	0	1.1
Ataxia/fall/gait disturbance	4	2	3	0	1.1
Confusional state/Mental Status change	1.5	0.7	3	0	1.1
Decreased appetite	1.5	0	1.5	0	1.1
Hypotension	0	0	0.7	0	1.1
Hypoxia	4	0	0	0	0.8

Source: Reviewer generated table based on dataset AAE.xpt. Derivation Variables: BASKGRP3, AEOUT, AETERM, AEBODYSYS, AEDECOD

AEs requiring dose reduction was seen in 28% of patients. The most common reasons for dose reduction were dizziness (3.9%), increased creatinine (3.1%), fatigue (2.3%), anemia (1.7%), increased weight (1.4%), neurological disorders (ataxia, cognitive changes, peripheral sensory neuropathy, gait disturbance, mental status changes) in 1% of patients.

Table **43** shows AEs that led to dose reductions in at least 1% of patients.

Table 43**:** Adverse Events that Led to Dose Reduction in ≥ 1% of Patients

Preferred Term	*NTRK* Adult (n=68)	ROS1 NSCLC Adult (n=133)	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric (n=17)	All (n=355)
Total %	41	34	16	25	28
Dizziness	4.4	6	2.2	0	3.9
Increased creatinine	6	4	0.7	6	3.1
Fatigue	6	2	0.7	0	2.3
Anemia	7	0	0.7	0	1.7
Increased weight	1.5	0.7	0.7	6	1.4
Ataxia/ Gait disturbance/balance disorder	3	3	1.5	0	1.0
Cognitive disorder	1.5	2	0	0	1.0
Peripheral sensory neuropathy/paresthesia/peripheral neuropathy	3	4	1.5	0	1.0
Gait disturbance	3	0.7	0.7	0	1.0
Arthralgia	0	1.5	1.5	0	1.0
Confusional state/mental status change/somnolence/depressed level of consciousness /depression/agitation/disturbance in attention	1.5	4	1.5	0	1.0

Source: Reviewer generated table based on dataset AAE.xpt. Derivation Variables: AEACN, BASKGRP3, AEDECOD, USSUBJID

Dose interruptions and dose reductions due to AE occurred in 55% of patients. The most frequent adverse reactions (≥ 2%) that resulted in interruption were increased creatinine (6%), neutropenia (5%), fatigue (5%), dizziness (5%), anemia (4%), diarrhea (3%), pyrexia (3%), nausea (3%), dyspnea (3%), cognitive disorder (3%), pneumonia (2%), ataxia (2%), AST increase (2%), confusional state (2%), hypotension (2%) and pleural effusion (2%) and increased weight (2%).

Clinical Reviewer Comment: The reasons for discontinuation of entrectinib are primarily attributable to progressive disease, which is often seen in clinical trials in oncology. The reasons for discontinuation due to AE are summarized in ***Error! Reference source not found.*** *and the total incidence (9%) is relatively low and similar to other drugs approved for a refractory cancer population. It is difficult to reliably assess attribution of any specific event to entrectinib given the single arm nature of the trials providing safety data. Dose modifications are outlined in the package insert for the most common and serious AEs.*

Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of SAEs also be considered significant AEs. These laboratory abnormalities are described in the Laboratory Findings section of this review.

In addition, the ICH E3 guidance considers other potentially important abnormalities, such as severe AEs (i.e., adverse events of ≥ Grade 3 severity as graded by the NCI CTCAE criteria that do not meet the definition of a serious AE) as potentially significant.

Grade 3-4 AEs

Grade 3 or 4 adverse reactions occurred in 60% of patients; the most common (≥2%) were lung infection (6%), increased weight (7%), dyspnea (6%), fatigue (5%), cognitive impairment (4.5%), syncope (2.5%), pulmonary embolism (3.4%), hypoxia (3.4%), pleural effusion (3.1%), hypotension (2.8%), diarrhea (2%), and urinary tract infection (UTI) (2.5%). One patient developed Grade 4 myocarditis after one dose of entrectinib, confirmed by myocardial biopsy and cardiac magnetic resonance imaging (MRI), which resolved after discontinuation of entrectinib and administration of high-dose corticosteroids. Grade 3-4 laboratory abnormalities will be discussed in "Laboratory Findings." See the clinical reviewer comment below regarding attribution of adverse events.

Interpretation of the causality of adverse events related to increased weight was challenging due to the single arm design of the entrectinib clinical trials and presence of confounding factors. Two percent had an adverse reaction of increased appetite (none were Grade 3-4). Additionally, 2.3% percent of patients had an adverse event of decreased weight with 0.6% having Grade 3 weight loss, and 13% of patients had an adverse reaction of decreased appetite, 0.3% of which was Grade 3. See "**Weight gain**" in Section 8.3.5 AESI below for further details.

Table 44: Grade 3-5 AEs in ≥ 2% of patients in Safety Population

Preferred Term	Grades 3-5
N =355	%
Anemia	9
Neutrophil Count Decreased	7
Hypophosphatemia	7
Weight increased	7
Lung Infection	6
Dyspnea	6
Fatigue/Asthenia	5
Cognitive Impairment	4.5
Alanine aminotransferase increased	2.9
Hypotension	2.8
Aspartate aminotransferase increased	2.7
UTI	2.3
Diarrhea	2

Source: Reviewer generated table from dataset AAE submitted to NDA Module 5.3.5.3 (ISS) variables AETOXGR, USUBJID, and AEDCOD.

Clinical Reviewer Comment: Grade 3-4 adverse events are discussed throughout the review. The related preferred terms fatigue and asthenia were combined to calculate the incidence of significant fatigue, which has a similar incidence compared to other drugs approved for the treatment of solid tumors. Lung infections were inclusive of multiple PTs: lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, and the incidence reflects the underlying population of patients with NSCLC, lung metastases, and cancer, which confers susceptibility to infection due to prior chemotherapy and decreased immunity. Dyspnea and hypoxia were also seen in the setting of lung infections and patients with NSCLC. Pulmonary embolism could also be attributed to patients' underlying cancer, which increases the risk of embolic events. Adverse events of increased and decreased weight occurred in patients treated with entrectinib and a causal relationship for entrectinib is biologically plausible based on its mechanism of action of TRK inhibition. However, due to the single arm nature of the entrectinib

trials, cofounding factors such as comorbidities, and small sample size, it was difficult to ascertain the extent to which the changes in weight observed were related to entrectinib or other factors. In some cases, it is also difficult to decipher if the increased weight was due to decreased food consumption/caloric intake vs. fluid retention and respiratory issues (about half of the patient narratives describe fluid retention due to respiratory issues like pneumonia in the setting of NSCLC while the other appear to be pure increased weight). Increased food consumption and increased weight was observed in toxicology studies of entrectinib in rats, which is consistent with the observed effects of Trk inhibition in animals and humans with deficiencies in TrkB signaling. Thus, it is likely that the observed increased weight in some patients was related to entrectinib. Changes in weight are also discussed in the section of this review discussing AESI. Cognitive effects, further discussed in the AESI section of this review, appear to be due to the mechanism of action of the drug, given that entrectinib crosses the blood:brain barrier. Hypotension, which is also discussed in in the AESI section of this review, was often observed concomitantly with other AEs such as dehydration, diarrhea, vomiting, acute infections, and cardiac events. Some cases of hypotension occurred with syncopal episodes.

Treatment Emergent Adverse Events

The overall safety database (N=355) was analyzed at each level of the MedDRA hierarchy for common AEs. The tables in this section summarize the incidence of treatment-emergent adverse events (TEAEs), defined as AEs that occurred from the time of the first dose until 30 days (28 days for ALKA: see prior comment in Section 19.6.1) following the last dose of entrectinib. Almost all patients in the safety analysis population (99%) had at least one AE during treatment with entrectinib. Sixty-one percent of patients had 1 or more AEs that were severe (CTCAE Grade 3 or greater); 60% had Grade 3-4 AEs. See Table 44 and Table 45 for further details.

Table 45: Summary of Adverse Events

	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult non*NTRK*, non*ROS1* (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Patients with AE (%)	100	100	99	100	99%
Patients with SAE (%)	47	37	40	13	39
Patients with ≥Grade 3 AE (%)	74	61	56	50	61

Source: Reviewer generated table modified from Table 35

The reviewers analyzed common TEAEs in the overall safety analysis dataset submitted in the original NDA based upon system organ class (SOC), high-level term (HLT), high-level group term (HLGT), and referred term (PT) levels of the MedDRA hierarchy.

TEAEs were most common in the following SOCs: nervous system disorders (84%), gastrointestinal disorders (82%), and general disorders and administration site conditions

(78%).

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders.

Table 46 provides a summary of the per-patient incidence (PPI) of AEs by SOC for AE with a PPI of ≥ 10%.

Table 46: Adverse Events by Preferred Term ≥ 10% Incidence

Adverse Event	Entrectinib 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
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		

Adverse Event	Entrectinib N=355	
	All Grades (%)	Grade ≥ 3 * (%)
Increased Weight	25	7
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 hypoaesthesia, palmar-plantar erythrodysaesthesia, oral paresthesia, genital hypoaesthesia
[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
[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

Source: Modified draft label July 2, 2019 from applicant; package insert. Reviewers verified data from Datasets AAE from NDA Module 5.3.5.3 (ISS Analysis legacy datasets)

Clinical Reviewer Comment: composite terms that were negotiated with Genentech are defined in the footnotes to the above table.

Laboratory Findings

During the review, FDA requested additional information from Genentech to evaluate the cause of the high frequency of laboratory abnormalities in the laboratory dataset including both low and high values outside of the normal range (IR-23, 22 March 2019). Genentech performed a review of the abnormal laboratory values and stated that the majority of the apparent abnormal laboratory readings noted in the dataset occurred as a result of reporting variations in laboratory units, or transcription errors. Genentech additionally clarified that the majority of abnormal laboratory readings were discovered to be within the normal ranges provided by the site upon further investigation. A few patients with abnormal laboratory values had concomitant medications or comorbidities that could potentially have contribute to the abnormal laboratory values.

The majority of patients who experienced post baseline shifts in hematology parameters had shifts to Grade 1 or 2. Few patients had clinically relevant shifts (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) with the most common being Grade 3 anemia (9%) and Grade 3 neutropenia (7%).

The majority of patients who experienced post baseline shifts in chemistry parameters had shifts to Grade 1 or 2. Few patients had clinically relevant shifts (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) with the most common being Grade 3 hypophosphatemia (12%), Grade 3 hyponatremia (4%) and Grade 3 hypoalbuminemia (3%).

In the integrated safety population based on the adverse event dataset, hyperuricemia reported as an adverse event occurred in 9% (32/355) of patients. The majority of these events (26/32, or 81% of events) were Grade 1, meaning the patient had an elevation of uric acid with no physiologic consequence. No Grade 2 or Grade 3 hyperuricemia events were reported. Grade 4 elevation in uric acid was reported in 6 patients (1.7%), none of which were categorized serious events (although one case of Grade 4 hyperuricemia that can be reasonably attributed to entrectinib occurred in a patient with tumor lysis syndrome, who ultimately died). All except one Grade 4 hyperuricemia resolved at the time of the data cutoff date. The median time to increase in uric acid was 0.9 months (range: 1 day to 14 months). Among 32 patients with an adverse event of hyperuricemia, 34% (11/32) required interventions to reduce uric acid levels, 6% (2/32) required dose reduction, 6% (2/32) required dose interruption, and no patient discontinued entrectinib due to hyperuricemia. Hyperuricemia resolved in 73% of patients following initiation of uric acid-reducing medication without interruption or dose reduction of entrectinib.

The incidence of hyperuricemia as a laboratory abnormality per CTCAE v4.03 was reviewed by Genentech and FDA reviewers. Hyperuricemia was defined per CTCAE v4.0 and v4.03 as follows:

- Grade 1: uric acid > ULN -10 mg/dl (0.59 mmol/L) WITHOUT physiological consequences
- Grade 3: uric acid > ULN -10 mg/dl (0.59 mmol/L) WITH physiological consequences

- Grade 4: uric acid >10 mg/dl; >0.59 mmol/L; life-threatening consequences.

In order to differentiate Grade 3 elevations in uric acid (which require a physiologic consequence) from Grade 1 elevations in uric acid, Genentech reviewed the laboratory ALB dataset for hyperuricemia and cross referenced the adverse event AAE dataset and concomitant medications (ACM dataset) . Patients who had a peak post-baseline uric acid value of >ULN - 10 mg/dL (0.59 mmol/L) were considered to have a Grade 3 elevation of uric acid if both of the following criteria were met:

- Presence of a concurrent AE of "hyperuricemia" or "blood uric acid increased" reported with an onset date within +/- 30 days of lab abnormality
- Concomitant treatment with allopurinol within 30 days on or after the AE onset

At the data cutoff date for the NDA dataset (31 May 2018), there were 259 patients who had a baseline and post-treatment laboratory blood uric acid measurement. A total of 110 of 259 (42%) patients had a normal baseline uric acid level and at least one post-baseline uric acid level that was greater than the upper limit of normal but less than 10 mg/dL (0.59 mmol/L). Of these 110 patients, there were 11 patients reported as having an adverse event of "hyperuricemia" or "blood uric acid increased" in the AE dataset; all were non-serious events. Hyperuricemia was considered to have an adverse physiological consequence for 3 of the 11 patients with an adverse event of hyperuricemia due to initiation of treatment with allopurinol in response to the event; the remaining 8 patients did not require initiation of urate-lowering drugs or dosage modification of entrectinib. Therefore, Genentech defined 3 patients as having a Grade 3 change as the highest post-baseline increase in uric acid per CTCAE version 4.03 and 107 patients as having a Grade 1 elevation in uric acid levels as the highest post-baseline increase.

There were 17 patients (7%) with a normal uric acid level at baseline and at least one post-baseline uric acid value of >10 mg/dL (0.59 mmol/L), which is categorized as Grade 4 elevation of uric acid per CTCAE version 4.03. A total of 9 of these 17 patients had a concurrent adverse event of hyperuricemia recorded. In addition, there were 7 patients who had Grade 3 uric acid levels at baseline who developed Grade 4 elevation of uric acid on study. None of these events were serious or life threatening. Based on the above evaluation, there were 134/259 (52%) patients with hyperuricemia of any grade and a total of 27/259 patients (10%) that met the criteria for Grade 3 (n=3) or Grade 4 (n=24) hyperuricemia.

The majority of patients who experienced post-baseline shifts in liver laboratory parameters (AST increased, ALT increased, and bilirubin increased) had shifts to Grade 1 or 2. Few patients had clinically relevant shifts in liver laboratory parameters (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline). Grade 3 increase in ALT occurred in 3% of patients and Grade 3 increase in AST also occurred in 3%. The median time to onset of increased AST was 0.5 months (range: 1 day to 29.5 months). The median time to onset of increased ALT was 0.5 months (range: 1 day to 9.2 months). Increased AST leading to dose interruptions or reductions occurred in 10.5% and 1.8% of patients, respectively. Increased ALT

leading to dose interruptions or reductions occurred in 10% and 2% of patients, respectively. No patients discontinued ROZLYTREK due to increased AST or ALT. There were no Hy's Law cases identified among the 355 patients in the safety database.

Overall, the incidence of liver laboratory abnormalities reported as AEs was higher in the pediatric analysis set compared to the overall adult population, primarily driven by a higher rate of increases in AST and ALT. Five (1.4%) patients in the integrated safety population had concurrent elevations ALT or AST (>3x ULN) and elevated total bilirubin (>2x ULN). Upon medical review, baseline liver metastasis or other confounding factors (such as medical history of liver disease or disease progression with new liver lesions) were reported in all 5 patients; as such, none of the liver enzyme abnormalities observed was suggestive of drug-induced liver injury (i.e., met the criteria for Hy's Law).

Table 47: Laboratory Abnormalities (>20%) Worsening from Baseline in Patients Receiving Entrectinib in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG

Laboratory Abnormality	Entrectinib NCI-CTCAE Grade N= 355[1]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Anemia	67	9
Lymphopenia	40	12
Neutropenia	28	7
Chemistry		
Increased creatinine[2]	73	2.1
Hyperuricemia[3]	52	8
Increased AST	44	2.7
Increased ALT	38	2.9
Hypernatremia	35	0.9
Hypocalcemia	34	1.8
Hypophosphatemia	30	7
Increased lipase	28	10
Hypoalbuminemia	28	2.9
Increased amylase	26	5.4
Hyperkalemia	25	1.5
Increased alkaline phosphatase	25	0.9
Hyperglycemia[4]	NE[3]	3.8

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase
[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 111 to 346 patients.
[2] Based on NCI CTCAE v5.0
[3] Based on NCI CTCAE v4.03 using laboratory dataset (ALB), adverse event dataset (AAE) and concomitant medication dataset (ACM)
[4] NE=Not evaluable. Grade 1 and 2 could not be determined per NCI CTCAE v5.0, as fasting glucose values were not collected.

Source: draft package insert label 2 July 2019. Reviewers verified data with dataset 1lb in NDA Module 5.3.5.3

<u>Clinical Reviewer Comment</u>: Because of the need for monitoring and intervention, hyperuricemia was included in the Warnings and Precautions (W&P) section of the entrectinib product label. If the incidence of truly life-threatening reactions is 1%, the database was too small (259 patients with baseline and follow up uric acid levels) to ensure that a life-threatening adverse event of hyperuricemia would have been observed. Additionally, 34% of the 32 patients with hyperuricemia adverse reactions required medical intervention to reduce uric acid levels; while the mechanism by which entrectinib results in increased uric acid levels is not known, one patient died of tumor lysis syndrome accompanied by Grade 4 uric acid elevation.

Increased ALT and AST was observed in this safety experience. Because the overall incidence is high (44% increased AST and 38% increased ALT), hepatotoxicity is a known risk of drugs inhibit

the same target (TRK inhibitor; larotrectinib and ALK inhibitor; crizotinib), which have hepatotoxicity in the W&P sections of their respective product labels, and due to need for monitoring and potential dose medication, hepatotoxicity will also be included in the W&P section of the entrectinib product label.

Vital Signs

In the vital signs dataset, weight, body mass index, body surface area, height, heart rate, and blood pressure, both systolic and diastolic, were recorded. In the AE dataset, tachycardia, bradycardia, hypo- and hypertension, and weight increase and decrease were reported based on vital signs.

Clinically notable changes in vital signs included increased weight and hypotension, as discussed elsewhere in this review (Section 8.3.5 "**AESI**"). At the data cut- off date of May 31, 2018, AE of increased weight was reported for 25% (88/355) of patients. The majority of increases in weight were of Grade 2 severity (11% of patients), followed by Grade 1 (8% of patients). Increased weight increased of Grade 3 severity was reported in 6.5% of patients. Of the 88 patients with an AE of increased weight, most experienced increase in weight within 60 days of starting entrectinib. In the overall integrated safety population, 18% patients experienced AEs of hypotension, of which 3% experienced Grade 3 hypotension. SAEs of hypotension were reported in 1.7%. A total of 4.5% patients experienced AEs of hypertension, of which 5 patients experienced Grade 3 hypertension. All events of hypertension were non-serious.

Electrocardiograms (ECGs)

In Study STARTRK-2, ECGs were performed in triplicate and assessed by a central reader for all U.S. and Japanese sites. For all other sites, ECGs were performed locally and in singlicate. The protocols had baseline ECGs at screening. These ECG data could be collected up to 30 days prior to the first dose. The FDA reviewer examined the timing of ECG data collected at predose on Cycle 1 Day 1. The clinical reviewer confirmed that most predose samples were collected pre-dose and that the postdose samples were obtained ~4 h after dosing as planned per protocol. Overall, ECG data collected predose on Cycle 1 Day 1 could be used as the baseline for QT assessment.

QT

FDA's interdisciplinary review team for QT studies (QT-IRT) conducted a review of data. No large QTc prolongation effect (i.e., >20 ms) of entrectinib was observed in FDA's QT assessment of the ECG sub-study of patients (n=113) in Study STARTRK-2 (RXDX-101-02), an open-label, global Phase 2 study at the proposed therapeutic dose, 600 mg once daily (QD). The data was analyzed using a bytime central tendency analysis as the primary analysis, which did not suggest that entrectinib is associated with large mean increases in the QTc interval at times corresponding to $C_{max,ss}$ and $C_{trough,ss}$.

The data did not support an exposure response analysis because the exposure range is narrow and the PK/ECG sampling schedule could not be used to evaluate possible PK/PD hysteresis. One patient had QTcF > 500 ms and 4 patients had change in QTcF of > 60 ms. Genentech provided an integrated assessment of QTc categorical outliers across all 4 studies. Across these studies, patients were exposed to a range of doses from 100 mg to 2600 mg/day. According to Genentech's analysis, 11 of the 355 patients reported a maximum QTcF interval post-baseline >500 ms or maximum QTcF increase from baseline > 60 ms, as determined by single or triplicate measures. Genentech identified 2 patients (1.1%) who had a maximum QTcF interval post baseline >500 ms and a maximum QTcF increased from baseline > 60 ms. For both patients, no clinically relevant cardiac AEs were reported, serum electrolytes were within normal ranges, and they were not taking known QT prolonging medications. In addition, there was 1 patient who experienced grade 1 ventricular extrasystoles and had QTc prolongation >500 ms.

See "**QT Interval prolongation"** under Adverse Events of Special Interest for the clinical review of QT prolongation.

Immunogenicity

No safety issues related to immunogenicity were identified for entrectinib.

8.3.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest (AESI)

The selected AEs were defined on the basis of previous clinical experience, mechanism of action and safety profile from drugs with similar targets to provide a more comprehensive understanding of the safety profile of entrectinib.

AEs of special interest (AESI) were identified based on information from publications describing the neurobiology of TRK and predictions of potential toxicities with TRK inhibition, the preclinical toxicology program, and clinical experience with entrectinib. For an analysis of ALT/AST increases, anemia, and increased creatinine, see the Section above on Laboratory Findings.

Neurologic AESI

A broad spectrum of CNS adverse reactions can occur in patients receiving entrectinib, including impairment in cognitive function or mood, dizziness, and sleep disturbances. PTs combined to make up the composite term of cognitive impairment for inclusion in entrectinib product labeling were: amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, visual hallucination, memory impairment, mental disorder, mental status changes.

Among the 355 patients who received entrectinib across clinical trials, 96 (27%) experienced cognitive impairment; in 77% of these patients, symptoms occurred within 3 months of starting entrectinib. Cognitive impairment included cognitive disorders (8%), confusional state (7%), disturbance in attention (4.8%), memory impairment (3.7%), amnesia (2.5%), aphasia (2.3%), mental status changes (2%), hallucinations (1.1%), and delirium (0.8%). Grade 3 cognitive adverse reactions occurred in 4.5% of patients. Among the 96 patients with cognitive impairment, 13% required a dose reduction, 18% required dose interruption and 1% discontinued entrectinib due to cognitive adverse reactions. Table 48 submitted by Genentech in response to IR-25 (5 April 2019), provides a high-level overview of neurotoxicity by time to first onset of a CNS adverse reaction.

Table 48: Summary of Time to First onset of CNS Adverse Reaction

Time to first onset of CNS Adverse Reaction	Total adult (N= 338)	Pediatric (N = 17)	Total (N=355
Number of patients (n)	92 (100%)	1 (100%)	93 (100%)
< 3 months	70 (77%)	1 (100%)	71 (77%)
≥ 3months and < 6 months	11 (12%)	0	11 (12%)
≥ 6months and < 9 months	3 (3.3%)	0	3 (3.3%)
≥ 9 months and < 12 months	2 (2.2%)	0	2 (2.2%)
≥ 12 months +	5 (6%)	0	5 (5%)

Source: copied from IR-25 dated 5 April 2019. Verified with dataset AAE submitted to NDA Module 5.3.5.3 (ISS)

Among the 355 patients who received entrectinib across clinical trials, 36 (10%) experienced mood disorders. The median time to onset of mood disorders was 1 month (range: 1 day to 9 months). Mood disorders occurring in ≥1% of patients included anxiety (4.8%), depression (2.8%) and agitation (2%). Grade 3 mood disorders occurred in 0.6% of patients. One completed suicide was reported 11 days after the last dose of entrectinib. Among the 36 patients who experienced mood disorders, 6% required a dose reduction, 6% required dose interruption and no patients discontinued entrectinib due to mood disorders.

Dizziness occurred in 136 (38%) of 355 patients. Among the 136 patients who experienced dizziness, Grade 3 dizziness occurred in 2.2% of patients. Ten percent of patients required a dose reduction, 7% required dose interruption and 0.7% discontinued entrectinib due to dizziness.

Among the 355 patients who received entrectinib across clinical trials, 51 (14%) experienced sleep disturbances. Sleep disturbances included insomnia (7%), somnolence (7%), hypersomnia (1.1%), and sleep disorder (0.3%). Grade 3 sleep disturbances occurred in 0.6% of patients. Among the 51 patients who experienced sleep disturbances, 6% required a dose reduction and no patients discontinued entrectinib due to sleep disturbances.

The incidence of CNS adverse reactions was generally similar in patients with and without CNS metastases; however, the incidence of dizziness (38% vs. 31%), headache (21% vs. 13%), paresthesia (20% vs. 6%), balance disorder (13% vs. 4%), and confusional state (11% vs. 2%) appeared to be increased in patients with CNS metastases who had received prior CNS irradiation (N = 90) compared to those who did not (N = 48).

Neurotoxicity was largely reversible. At the time of the clinical cut-off date of May 31, 2018, 60% patients who reported neurotoxicity recovered and 4.3% patients were recovering from neurological AEs.

Neurotoxicity rarely led to withdrawal of treatment: 1 patient discontinued entrectinib due to neurotoxicity. This patient experienced Grade 1 hallucination early on during treatment, and his mental status progressively declined until he was diagnosed with Grade 3 cognitive disorder. Entrectinib was initially interrupted and later withdrawn due to the event per the treating physician's decision. This patient's narrative ((b) (6)), included in the STARTRK 2 CSR, was reviewed and confirmed.

Neurotoxicity requiring intervention was generally managed with dose interruption and/or dose reduction of entrectinib, and very few patients required other interventions, such as concomitant medications and neuro-oncology follow-up. Of the patients with neurotoxicity, 8% received concomitant medications to treat the adverse reaction.

<u>Clinical Reviewer Comment</u>: Neurotoxicity appears to be a class effect for TRK inhibitors and entrectinib had been shown to cross the blood:brain barrier in preclinical models. The Division of Neurology products (DNP) was consulted and provided advice regarding analysis of the CNS

adverse reaction data and appropriate language for describing these adverse reactions in the package insert, including the agreed upon PTs for the composite terms of cognitive impairment and mood disorders. The incidence of dose reductions and interruptions of entrectinib due to a CNS AE was 3.4% and 2.5%, respectively. Product labeling for entrectinib includes information in the Warnings and Precautions section advising patients and healthcare providers of these risks, and includes instructions that patients experiencing a CNS adverse reaction should not to drive or operate hazardous machinery. The dosage modification section of product labeling includes instructions for withholding entrectinib, followed by reintroduction at the same or reduced dose following resolution of the AE, or permanent discontinuation of entrectinib, based on severity.

Congestive Heart Failure

In the integrated safety population (N=355), congestive heart failure events were reported in 12 (3.4%) of patients, including Grade 3 (2.3%). An overview of congestive heart failure AEs by PT was undertaken and showed that ejection fraction (EF) was decreased in 4 patients (1.1%), with a Grade 3 EF decrease in 2 patients (0.6%). The PTs that were noted in the narratives included pulmonary edema (1.1%), cardiac failure and congestive cardiac failure (each 0.8%), acute right ventricular failure, cardiogenic shock and chronic ventricular failure (each 0.3%).

Most heart failure events were Grade 3 (2.3% of patients) in severity. Serious events were reported in 7 (2.0%) patients. All of the 7 patients who experienced serious events of congestive heart failure presented with dyspnea or fluid overload; 4 patients experienced a decrease in EF. Five of the 7 patients were treated with systemic diuretic therapy. Entrectinib was interrupted in 3 patients, reduced in 1 patient, and withdrawn in 3 patients. Five of 7 patients with serious congestive heart failure events recovered. Per the summary of clinical safety, of the 12 patients with congestive heart failure events, 7 patients had a past medical cardiac history at baseline and/or concurrent conditions that may have predisposed them to congestive cardiac failure events. Overall, congestive heart failure events were generally manageable with entrectinib dose interruption or reduction.

One Grade 5 adverse event of cardiogenic shock was reported in a patient with NSCLC (Patient (b) (6)) due to pericardial effusion and pericardial tamponade. The patient developed cardiogenic shock two days after starting entrectinib and died. It was noted that the patient had suspected pericardial, bilateral pleural, omental and peritoneal carcinomatosis at baseline, as well as diffused lung, liver, and bone metastases. This patient was not included in the analysis of cardiac events because Genentech did not consider the adverse event to be drug related, and instead attributed the AE to underlying disease.

One Grade 4 AE of eosinophilic myocarditis was reported in a 40 year old male (Patient (b) (6) STRTRK-1) with metastatic NSCLC after receiving treatment with one dose of entrectinib at 800mg/m^2. See Table **49** for patient narratives for further details.

Table 49**:** Patient Narratives for Cardiac Adverse Events of Special Interest

Patient ID Study ID	Date of Treatments	Narrative
(b) (6) ALKA	(b) (6) (D69)	52-year-old female with metastatic NSCLC treated with 600mg/m^2 of entrectinib was hospitalized on D69 with serious cardiac tamponade. Pericardiocentesis revealed malignant pericardial effusion.
(b) (6) STRTRK-1	(b) (6) (D2)	40-year-old male with metastatic NSCLC started treatment with 800mg/m^2 of entrectinib. On D1, EKG revealed possible Q waves in inferior leads, asymptomatic, troponin of 0.06ng/ml (N: 0-0.31). On D2 patient had diarrhea that resolved the same day. On D3, patient woke up with nausea, grade 3 vomiting, angina, and dizziness. EKG revealed ST elevation, troponin of 0.46ng/ml (range 0.31-0.64). Cardiac catheterization revealed no significant CAD and echo revealed grade 4 myocarditis, normal LVEF. Biopsy of right heart revealed eosinophilic myocarditis. Patient required pressors and a balloon pump, and high dose steroid with IV solumedrol. On D6 a cardiac MRI revealed EF of 72%. Patient recovered and was discharged from hospital on D7. Last dose of entrectinib was (b) (6).
(b) (6) STRTRK-2	(b) (6) (b) (6) (D15)	58-year-old male. On D14, Grade 2 peripheral edema occurred and the patient was treated with Lasix. Grade 3 hypotension was noted on the same day and the patient was hospitalized. On D15, pericardial effusion and grade 2 CHF was noted treated with Lasix, and pressors. On D16 study drug discontinued. On D21 the patient had Grade 1 cough. Echo revealed pericardial effusion with Normal EF. Pericardiocentesis did not have malignant cells. On D37 the patient developed grade 4 pneumonia, hospitalization continued. The patient died on D443. Cause of death was Grade 5 pneumonia.
(b) (6) STRTRK-2	(b) (6) (D43)	76-year-old male with NSCLC was diagnosed on D15 with Grade 3 pneumonia, treated and stabilized. D28 revealed PD. Patient was allowed to continue entrectinib. On D32 pneumonia resolved and was discontinued on D32. On D43 patient died at home due to grade 5 cardiopulmonary arrest. No Autopsy performed.
(b) (6) STRTRK-2	(b) (6) (D2)	57-year-old female with Squamous Cell Carcinoma. On D1 received one dose of 600mg. On D2 patient noted to have cardiopulmonary arrest (CPA) and transported to ER immediately. ECG asystole, PaO2 85%, 36C temp. CPR initiated, intubated. No response. Cause of death CPA.
(b) (6) STRTRK-2	(b) (6) (D264)	55-year-old male with anaplastic thyroid cancer, D22 Grade 3 dyspnea, Grade 3 pneumonia, admitted to ICU. D29: Bilateral pleural effusions and patchy infiltrates, mild hypotension. D30 dyspnea improved. Anemia treated with PRBCs. On D121 mild aphasia/ stroke. D121 Grade 2 dyspnea, cardiac MRI revealed cardiac metastases. D140 Grade 1 CHF, fluid overload. D216 worsening volume overload, SOB, orthopnea weight gain of 3 Kg, Grade 3 CHF on D217. 2D Echo on D218 normal EF, reduced right ventricle dilation and mass in right ventricle. Dose reduced to 400mg daily on D223. On D225 discharged from hospital and weight was 18 lbs lower than on admission. D263 presented to ER with Grade 3 dyspnea, Grade 4 acute respiratory failure. D265 patient died due to Grade 5 acute respiratory failure.

Patient ID Study ID	Date of Treatments	Narrative
(b) (6) STRTRK-2	(b) (6) (D141)	33-year-old female with NSCLC. D 37 had Grade 1 peripheral edema. D45 Grade 2 dyspnea, edema worsened to grade 2. Drug interrupted D45 and restarted D51. Dyspnea resolved D57, and edema Grade 1. D72 again grade 1 dyspnea, drug interrupted on D72. D86 dyspnea Grade 2 and chest pain Grade 2, edema Grade 2. Drug reduced to 400mg on D86. On D123 worsening dyspnea, D124 hospitalized Grade 3 cardiac failure. BNP 1014pg/ml. EF 35% with global hypokinesis. D126 G1 CHF discharged. D127 edema resolved. D135 entrectinib restarted 200mg. D141 scans revealed PD.
(b) (6) STRTRK-2	(b) (6) (D413)	60-year-old female with leiomyosarcoma developed Grade 2 chest pain, dyspnea on D352 and Grade 2 orthopnea, PND, Grade 1 peripheral edema on D352. Grade 3 pulmonary edema, BNP of 2603 pg/ml (N<100), ECHO EF 35-40% global hypokinesis, Grade 1 cardiomyopathy and luminal irregularities also occurred on D352. The events resolved on D352, and entrectinib was restarted. On D413 entrectinib was discontinued for pulmonary edema.
(b) (6) STRTRK-2	(b) (6) (D72)	66-year- old male with pancreatic adenocarcinoma, D4 experienced peripheral edema bilateral, D6 Grade 2 dyspnea, D7 Grade 2 orthopnea. Drug interrupted on D7. Hypoxia and troponin that were increased resolved with Lasix. D23 drug restarted at same dose and reduced to 400 mg on D28 for dyspnea and disturbance in attention. On D34 Grade 3 respiratory distress with EKG changes and troponin of 0.27 ng/ml (N: 0-0.04), BNP of 287pg/ml and D Dimer of 483ng/ml. D36 bilateral pleural effusions. ECHO EF of 45%, global hypokinesis and mild MR. On D37 discharged on 2L oxygen. D45 EF was 55-60%, severe MR, mod to severe left atrial enlargement, mild to mod LVH. On D46 restarted on entrectinib 400mg daily. D57 Grade 3 CHF and recommended percutaneous repair of MV. On D65 ECHO EF 55-60% and moderate LA enlargement, severe MR severe mitral regurgitation into the left atrial appendage due to degenerative mitral valve disease, systolic reversal of pulmonary vein inflow from the left lower pulmonary vein and significant systolic blunting in the three other pulmonary veins which was assessed to be likely due to lower systolic blood pressure. Treated medically. D74 presented with CHF Grade 3. Discontinued on D78 and resolved on D 80. Last day of entrectinib was D72. On D113 dyspnea improved to Grade 1. Patient was alive (b) (6) at last f/u and has received two intervening therapies.

Source: Reviewer generated table based on narratives to cardiac events submitted to CSR in NDA Module 5.3.5.2.

<u>Clinical Reviewer Comment</u>: Congestive heart failure (CHF) was added to the W&P section of the entrectinib product label because CHF is a serious adverse event. Although it is challenging to assess relatedness of cardiac events to entrectinib based on the single arm trials and most of the affected patients had a prior medical history of cardiac risk factors , it is unusual to observe clinically detected CHF at an incidence of 2.3% even in clinical trials enrolling patients with refractory cancers. Patient (b) (6) STRTRK-1, who developed Grade 4 myocarditis, had a biopsy consistent with eosinophilic myocarditis possibly related to entrectinib as this is an unusual adverse event for which no such events are expected in clinical trials. A post marketing

requirement (PMR) will be conducted by Genentech to further assess the contribution of entrectinib to cardiac risk and characterize cardiac adverse events. Genentech plans to conduct additional assessments for left ventricular ejection fraction (LVEF) at screening and Cycle 3 Day 1 in clinical trial(s) of entrectinib to better assess cardiac function prior to and during treatment.

Skeletal Fractures

DOP2 consulted the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding this safety concern identified late in the review cycle based on late-breaking reports of bilateral femoral neck fractures in pediatric patients presented at the annual American Society of Clinical Oncology meeting in June 2019 (Robinson et al.). The identification of these cases prompted a further investigation by FDA into fracture events across the entrectinib program. DBRUP provided assistance in interpretation of the events, recommendations on description of skeletal fractures and provided assistance in the design of the data to be obtained in a PMR to further characterize the fracture risk. See their review for full details.

The mechanism of action of entrectinib involves inhibition of the neurotrophic tropomyosin receptor 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), anaplastic lymphoma kinase (ALK), Janus kinase (JAK)2, and tyrosine kinase non-receptor 2 (TNK2). In addition to their known key role in nervous system development and maintenance, neurotrophins (e.g. nerve growth factor, NGF) and their receptors (e.g., TRKA, TRKB and TRKC) are also involved in skeletal tissue formation and healing. There are nonclinical models that suggested their involvement in chondrogenesis and osteogenesis (Su et al., 2017). A study by Tomlinson et al. (2017) demonstrated that communication between osteoblasts and sensory nerves through nerve growth factor-TRKA signaling is essential for load-induced bone formation in mice, suggesting a key role for TRKA in this process. Entrectinib, a TRKA, TRKB and TRKC inhibitor, may increase the risk of fractures.

In response to an information request by FDA, Genentech evaluated this fracture safety signal by conducting a cumulative review of the clinical trials and company drug safety databases to identify all events of fractures reported in entrectinib-treated patients. That review included patients who were not part of the NDA dataset (which had a cutoff of May 31, 2018) in order to provide a comprehensive analysis of the fracture risk. The search had a clinical cutoff date of March 8, 2019 for Studies STARTRK-1 and ALKA, March 31, 2019 for Studies STARTRK-2 and STARTRK-NG and May 3, 2019 for the company drug safety database. The analysis included a total of 528 patients (498 adults, 30 pediatric patients) whowere exposed to entrectinib across the 4 clinical studies. The composite term “fractures” used in the search for fracture events included the following MedDRA preferred term (PTs): humerus fracture, foot fracture, ankle fracture, femoral neck fracture, stress fracture, fibula fracture, fracture, rib fracture, spinal fracture, wrist fracture, femur fracture, pathological fracture, tibia fracture, lower limb fracture.

The search retrieved a total of 38 patients with reported events indicative of fractures from the clinical trial database. Upon review of the retrieved events, 4 were determined to be adverse events of joint dislocation (2), meniscus injury (1), and rotator cuff injury (1). These 4 events were therefore subsequently excluded from the fracture analysis.

Of the 34 patients (27 adults and 7 pediatric patients) identified from the cumulative search and review of retrieved events, 15 patients were from outside of the original NDA dataset (11 adults and 4 pediatric patients). Fracture events were considered serious in 15 of the patients (12 adults and 3 pediatric patients). Narratives are provided below.

Narratives submitted for these 34 patients are summarized as follows:

Pediatric Patients:

- 10 year old male patient with left proximal tibia fracture on study day 225 and second left proximal tibia fracture on study day 297 (unclear whether this was a recurrent fracture or new fracture)
- 10 year old female patient with 2nd right metatarsal fracture on study day 130
- 7 year old male patient with right lower limb fracture on study day 54
- 8 year old female patient with tibia fracture on study day 121
- 6 year old male patient with left femur fracture on study day 75 and second left femur fracture after a fall on study day 83 (appears to be a new fracture)
- 4 year old female with bilateral femoral neck fractures on study day 85 with no antecedent trauma
- 9 year old male patient with bilateral femoral neck fractures on study day 221

Adults:

- 22 year old woman with metatarsal fracture on study day 563
- 66 year old woman with ankle fracture on study day 53
- 23 year old woman with tibial stress fracture on study day 42 and additional/recurrent (unclear) tibial stress fractures on study days 100, 281, 366 and 574
- 53 year old woman with humerus fracture on study day 340
- 70 year old woman with bilateral jaw fractures (parasymphysial) on study day 253
- 68 year old woman with unspecified fracture on study day 104; noted to have osteoporosis
- 57 year old man with medial tibial plateau fracture on study day 117; no trauma noted
- 68 year old woman with left humerus fracture on study day 11 and 100 (unclear whether recurrent or new)
- 33 year old woman with left ankle fracture on study day 153
- 38 year old woman with right pathologic femoral neck fracture on study day 38
- 41 year old man with spine fracture on study day 74
- 29 year old man with right humerus fracture on study day 98
- 64 year old woman with rib fracture on study day 85

- 81 year old woman with spinal compression fracture on study 61; noted to have osteoporosis
- 54 year old man with left toe fracture on study day 185
- 72 year old woman with right hip stress fracture on study day 31 after fall; noted to have osteoporosis
- 80 year old woman with right hip stress fracture on study day 7 after mechanical fall; noted to have prior stress fracture of right hip
- 59 year old woman with wrist fracture on study day 114 after a fall
- 67 year old woman with left pathologic femoral neck fracture on study day 262 and right femoral neck fracture on study day 499 after a fall
- 67 year old woman with left ankle and fibula fracture on study day 163 after fall
- 64 year old woman with pathologic left femoral neck and shaft fractures on study day 48 after fall from bed and left proximal tibia stress fracture on study day 49
- 31 year old man with spinal fracture on study day 302
- 27 year old man with pathologic right femur shaft fracture on study day14 after fall
- 60 year old woman with pathologic right humerus fracture on study day 15 after injury; noted to have osteoporosis
- 80 year old woman with lumbar compression fracture on study day 91 after fall
- 51 year old woman with left bimalleolar ankle fracture on study day 121, left foot fracture on study day 138; noted to have osteoporosis
- 68 year old woman with right hip fracture on study day 380 after fall; noted to have avascular necrosis of right hip

In the safety population comprising 338 adult patients included in the adult safety population in the original NDA submission and data from the 30 pediatric patients provided in the updated fracture safety dataset who received entrectinib, 17 (5%) adult patients and 7 (23%) pediatric patients experienced fractures. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients, all fractures occurred in patients with minimal or no trauma. In general, there was inadequate assessment for tumor involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumor involvement were reported in some patients. In both adult and pediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). In a limited number of patients, bilateral femoral neck fractures occurred.

Among adult patients with fractures, median time to fracture was 3.8 months (range 0.3 to 18.5 months). Entrectinib was interrupted in 41% of patients and discontinued in none of the patients who experienced a fracture; in pediatrics, the median time of onset of fracture events was 3.98 months (range: 1.8 months - 7.4 months). By the time of data cut-off, 5 (71%) of pediatric patients and 17 (63%) of adults were reported to have complete healing of their fractures. Entrectinib was interrupted in 44% of patients and was not discontinued in any patient.

The W&P section of entrectinib product labeling will include a recommendation for initiation of an evaluation for fracture in all patients with clinical symptoms suggestive of fracture (e.g., pain, changes in mobility, deformity). The safety of resumption of entrectinib is not known in patients who experience fracture is not known; specifically, there are no data on the effects of entrectinib on healing of known fractures and risk of future fractures.

Clinical Reviewer Comment: Based on its mechanism of action, there is a biologic plausibility for a causal relationship for entrectinib in the occurrence of fractures due to the role of TRK in bone health/remodeling. The risk of fractures may be more pronounced in pediatric patients, since the reported fractures in pediatric patients appeared to occur in the absence of trauma and because there were 2 cases of bilateral femoral neck fractures (a 4-year-old female and 9-year-old male), an unusual event in pediatric patients. However, there were confounding factors in many of the cases of fracture, such as pre-existing osteopenia, concurrent steroids use, etc. According to the consult by DBRUP, most fractures did not appear to be due to tumor pathology at the fracture site but data was limited (among the 34 patients with fracture events, none were reported to have had bone biopsies to further evaluate the fracture event). Most patients who experienced a fracture did not appear to have significant underlying risk factors for fracture (only 5 of the adult patients with a fracture were reported to have a history of osteoporosis). While the 5% incidence rate of fractures observed in adults in the entrectinib clinical trials does not appear to exceed the background fracture incidence rate in adults with solid tumors (estimated to be as high as 18%), the 23% incidence rate of fractures observed in pediatric patients was unexpectedly high, as the corresponding estimated background rate is approximately 6%.). Of particular concern is that all fractures in pediatric patients were associated with minimal or no trauma, whereas most fractures in adults occurred in the setting of a fall or other trauma to the affected area. This suggests that entrectinib may have a differential effect on the growing versus mature skeleton. In some adult and pediatric patients, there appeared to be either recurrent or multiple events of fractures. These findings suggest not only a role of entrectinib in fracture, but potentially a detrimental effect of entrectinib on fracture healing.

The W&P section of product labeling for entrectinib will communicate the risk of fractures and Genentech has agreed to conducting a study(ies) to better characterize the risk of fractures in adult and pediatric patients and inform product labeling regarding mitigating this risk. DBRUP recommended the following additional studies:

Nonclinical

These recommended nonclinical studies could help to identify a potential adverse effect of entrectinib on bone metabolism, and perhaps provide information on the mechanism of action of such an effect.

- Conduct a short-term study in young growing rats to determine the effects of entrectinib on longitudinal bone growth and mineralization by static histomorphometry, e.g. in the proximal tibia. (refer to Schenk et al.,1986). Effects on the growth plate, bone and osteoid

volume, and trabecular parameters should also be determined in this study.

- Conduct a study of adequate duration (e.g. 2-3 months) to evaluate the effect of entrectinib on bone tissue in young adult rats using bone densitometry, static and dynamic histomorphometry and biomechanical strength testing. Because DXA and areal bone mineral density data may be confounded by entrectinib's potential effects on growth, quantitative computed tomography (QCT) of the long bones may be performed, also because this technique can provide data on both cortical and cancellous bone compartments. Bone mechanical tests should be performed of both cancellous and cortical bone sites, and data on both extrinsic and intrinsic strength parameters, which are independent of bone size, should be obtained. The correlation between bone mineral content (BMC) and bone strength parameters for control vs. treated groups may also provide relevant information.

Clinical Reviewer Comment: In consultation with the nonclinical review team, FDA decided not to require these animal studies because juvenile animal studies have already been performed and the risk of fracture has already been identified in clinical trials, so additional animal studies are unlikely to provide substantive new information that cannot be obtained in the clinical trials, including the PMR.

Clinical

The following assessments should be performed in the ongoing and planned trials of entrectinib in all adult and pediatric patients.

- Initial and serial assessments of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans. DXA should be performed every 6-12 months. The DXA scans should analyze areas where there are standardized DXA placement procedures and normative data available for assessment (i.e. lumbar spine, femoral neck, and total hip). Analyses should be based on scans with standard (supine) patient positioning. Adequate quality control measures should be established for DXA scans performed in the trials (as described by Faulkner et al., 1995). Serial DXA scans in patients who are continuing entrectinib therapy will not be as informative as those in patients who are initiating entrectinib therapy (since initiating patients will have a baseline BMD available for comparison). However, serial DXA scans in patients continuing entrectinib could still provide useful information regarding durability of a potential drug effect on BMD.
- Initial and serial serum bone formation and resorption markers (N-terminal propeptide of Type I Collagen [P1NP], osteocalcin, bone-specific alkaline phosphatase [BSAP] and carboxy-terminal cross-linked telopeptides of type 1 collagen [CTX-1]). Because levels vary with time of day and in response to meals, these markers should be measured in standardized conditions, preferably in the morning after an overnight fast. Similar to BMD, markers of bone turnover will be more informative in patients initiating entrectinib, but also may provide useful information regarding durability of a potential drug effect.
- Initial and serial measures of calcium metabolism markers (e.g. vitamin D, parathyroid

hormone) to evaluate a potential role of entrectinib in calcium metabolism and skeletal homeostasis.

Pediatric Patients:

- Assessment of linear growth at least every 6 months. Height measurements should be conducted according to recommendations in Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children.
- Assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays. With growth impairment, sclerotic lines, usually referred to as growth arrest or "Harris" lines, develop adjacent and parallel to growth plates (Park, 1964; Ogden, 1984). The appearance of these lines may be helpful in assessing possible growth plate effects of entrectinib. These lines typically are not apparent on X-ray until approximately 6 weeks following a triggering event (Jacobson et al., 2012). Therefore, for patients starting entrectinib therapy, initial X-rays should be performed 6 weeks following the entrectinib start date. X-rays should be performed at 6-month intervals and should use a consistent side (left or right) for all scans.
- If there continues to be uncertainty regarding the nature of entrectinib's effects on bone tissue after evaluation of adequate data from the abovementioned assessments, peripheral quantitative computed tomography (pQCT) of the distal radius and/or tibia should be considered, as this assessment would provide more specific information on bone geometry and differential effects on cortical versus trabecular bone compared to DXA. pQCT is not recommended as an initial assessment, however, given the additional burden, radiation exposure and expense associated with this procedure.

Clinical Reviewer Comment: the clinical review team will review the protocol for this PMR, when submitted by Genentech, to ensure that these assessments are incorporated into the study

Vision Disorders

In preclinical studies in rats, microscopic findings of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium were and are considered entrectinib-related. In all ongoing clinical studies, eye exams were required at screening, during treatment, at the end of treatment, and as clinically indicated. In the integrated safety population (n= 355), visual disturbances were reported in 21% of patients, including Grade 1 (82%), Grade 2 (14%) and Grade 3 (0.8%) severity.. The spectrum of AEs related to vision disorders included: blurred vision (9%), photophobia (5%), diplopia (3.1%), visual impairment (2%), photopsia (1.3%), vitreous floaters (1.1%), cataract (1.1%), vitreous detachment (0.8%), vitreous adhesions, blindness, corneal erosion, keratitis and retinal hemorrhage (each 0.3%). Periorbital edema and eyelid swelling also occurred. The majority of cases, patients were able to continue entrectinib.

Clinical Reviewer Comment: the Division of Anti-infective and Ophthalmology Drug Products was consulted for interpretation of visual disorders and to provide advice regarding the description

of these events to be included in the Warnings and Precautions Section of product labeling. The ophthalmology consultant advised the Division that severe visual disturbances were unlikely to be related to a direct effect on the eye, and were more likely to be related to CNS metastases or the effect of entrectinib on the CNS, as seen with drugs with an overlapping mechanism of action such as crizotinib. Given the known CNS effects of entrectinib, the temporal relationship between some of the visual disturbances, and positive dechallenge in some cases (described in ***Error! Reference source not found.*** *below) a causal relationship for entrectinib in many of the cases of visual disturbance is likely. Many of the ocular AEs are consistent with entrectinib causing dry eye syndrome, which can usually be treated with ocular demulcents (artificial tears). In addition, there are some ocular adverse events appeared to be related to allergic reactions (e.g., periorbital swelling). The ophthalmology consultant considered that the majority of the remaining ocular events could be attributed to the normal aging process (*Table 50*).*

Table 50: Vision Changes with Entrectinib and Plausible Cause

MedDRA Preferred Term	N=97	**Plausible Etiology**
EYE DISORDERS		
Total number of patients with an event	97	
Total number of events	171	
Vision blurred	31	Likely related to dry eye condition
Photophobia	18	Likely related to dry eye condition
Diplopia	11	Likely related to dry eye condition
Dry eye	10	Likely related to dry eye condition
Eye pain	9	Likely related to dry eye condition
Visual impairment	7	Likely related to dry eye condition
Cataract	4	Likely age related
Photopsia	4	Associated with vitreous detachments, likely age related
Vitreous floaters	4	Likely age related
Conjunctivitis allergic	3	Potential drug related allergic event
Periorbital oedema	3	Potential drug related event
Vitreous detachment	3	Likely age related
Conjunctival hyperaemia	2	Likely related to dry eye condition
Eye swelling	2	Potential drug related event
Eyelid oedema	2	Potential drug related event
Glaucoma	2	Unlikely to be related
Lacrimation increased	2	Likely related to dry eye condition
Asthenopia	1	Likely related to dry eye condition
Blindness	1	Attributed to radiation necrosis of a left parieto-occipital lobe lesion
Cataract cortical	1	Unlikely to be related
Chalazion	1	Unlikely to be related
Conjunctival haemorrhage	1	Unlikely to be related

MedDRA Preferred Term	N=97	Plausible Etiology
EYE DISORDERS		
Corneal erosion	1	Likely related to dry eye condition
Eye disorder	1	Unknown- single event
Eye irritation	1	Likely related to dry eye condition
Eye pruritus	1	Likely related to dry eye condition
Halo vision	1	Likely related to dry eye condition
Keratitis	1	Likely related to dry eye condition
Lacrimation decreased	1	Likely related to dry eye condition
Meibomian gland dysfunction	1	Likely related to dry eye condition
Metamorphopsia	1	Unknown- single event
Mydriasis	1	Unknown- single event
Pathologic myopia	1	Unlikely to be related
Presbyopia	1	Likely to be age related
Retinal haemorrhage	1	Unknown- single event
Strabismus	1	Unlikely to be drug effect on eye
Trichiasis	1	Unknown- single event
Vitreous adhesions	1	Likely to be age related
Xerophthalmia	1	Likely related to dry eye condition

Source: copied from Dr Wiley Chambers ophthalmology consult.

Table 51: Patient Narratives for Visual Disturbances

Patient ID Study ID	Date of Treatments	Narrative
(b) (6)	(b) (6)	67-year-old female with metastatic NSCLC started treatment with 600mg/day of entrectinib, dose reduced to 400mg/day for grade 1 gait disturbance on D 36 reported on D11. On D69, treatment was interrupted for grade 1 diplopia reported on D65. On D74 dose was further reduced to 200mg for persistent gait disturbance and fatigue. On D91 an eye exam was normal and dose was increased to 400mg. On D109 patient was hospitalized for Grade 3 diplopia and eye exam was normal. Entrectinib was held from D109 and diplopia resolved D110. On D113 the dose was reduced to 200mg with no recurrence of diplopia.
STRTRK-2	(D69)	

Patient ID Study ID	Date of Treatments	Narrative
(b) (6)	(D249)	61-year- old female with papillary thyroid cancer experienced Grade 1 dizziness on D10, Grade 3 muscular weakness. On D27 experienced Grade 1 blurred vision. Drug was interrupted and resumed on D35 at 400mg. On D51 was noted to have new brain lesions and allowed to continue entrectinib. On D163 s/p motor vehicle accident was noted to have Grade 3 blindness in right eye. CT and MRI showed stable left parieto-occipital lesion. Resumed treatment on D168 after Grade 3 blindness improved to Gr 2 blurred vision. D 211 Gr 1 blurred vision worsened to Gr 2. Drug was interrupted and restarted on D 231. On D 246 noted to have progression of disease and last dose of entrectinib was (b) (6). Cause of blindness was radiation necrosis per applicant.
(b) (6) STRTRK-1	(b) (6) (D37)	58-year-old male with metastatic melanoma was started treatment with 600mg/day of entrectinib developed grade 3 peripheral sensory neuropathy on D11 and dose was interrupted and resumed at 200mg/day on D22. On D22 patient experienced grade 1 blurred vision in both eyes and continued to have this 1-2 times a day. On D37 patient was hospitalized for Grade 1 blurred vision (intermittent) in both eyes frequency increasing. Dose was interrupted on D37. MRI revealed a subependymal lesion in the roof of his posterior right lateral ventricle, extending to corpus callosum had increased in size. On D38 symptoms of blurred vision improved. On D44 entrectinib was restarted at 200mg/day. The Grade 1 blurred vision and diplopia resolved on D169.

Source: Reviewer generated table from narratives submitted to CSR in NDA Module 5.3.5.2

QT Interval prolongation

Among the 355 patients who received entrectinib across the clinical trials, 2.8% of patients with at least one post-baseline ECG assessment experienced QTc interval prolongation of >60 ms after starting entrectinib and 1.7% had a QTc interval >500 ms. Based on the review done by FDA's QT-IRT team, in the QT substudy of STARTRK-2, of 113 patients receiving entrectinib 600 mg daily, there was no large increase in QTc change from baseline. Based on QT-IRT review, the data did not support an exposure-response analysis because the exposure range was narrow and the PK/ECG sampling schedule could not be used to evaluate a causal effect of entrectinib on QT prolongation.

Clinical Reviewer Comment: It was the opinion of the QT-IRT team that there is no clear signal that entrectinib causes prolongation of QTc due to limited data. The relevance of sporadic outliers in an uncontrolled study when the limited QT assessment does not support a large drug-effect is unclear. The narratives for 2 patients with both QTc >500 and dQTc >60 ms do not

indicate any confounders [e.g., QT prolonging medications, electrolyte abnormalities] that could explain the isolated QTc prolongation (refer to their review). The clinical studies were not designed to evaluate concentration-QTc relationship and even in their dedicated QTc assessment the data did not support such analysis. Nevertheless, to be conservative, the package insert will include language in Warnings and Precautions section indicating that patients should be monitored who already have or who are at significant risk of developing QTc interval prolongation, including patients with known long QT syndrome, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. QT interval and electrolytes should be assessed at baseline and periodically during treatment, adjusting frequency based upon risk factors such as congestive heart failure, electrolyte abnormalities, or concomitant medications known to prolong the QTc interval. Based on the severity of QTc interval prolongation, entrectinib should be withheld and resumed at the same or reduced dose, or permanently discontinued.

Dizziness

In the integrated safety population (N=355), adverse events of dizziness were reported in 38%. The cases of dizziness were reviewed with consideration to whether alternative etiologies or comorbid conditions present within 7 days of the reported dizziness event suggested an alternative neurologic or cardiovascular cause. Among patients with dizziness adverse events, 1.2% were possibly attributable to cardiovascular disease, 15% had potentially attributable to neurologic etiology, and 4.0% with a history of orthostatic hypotension. However, for the majority (80%), no alternative etiology was identified; thus, these events were probably attributable to entrectinib. The mechanism by which entrectinib may cause these events is unclear. There is biologic plausibility that entrectinib is responsible for these events given TRK receptors' involvement in neuronal development and maintenance of the central and peripheral nervous system neurologic.

Syncope

Adverse events of syncope were reported in 3.9% (14/355) of patients. Syncopal events were generally by rapid onset and were of short duration with a prompt recovery. Among the 14 patients who experienced syncope, four patients had concurrent co-morbid conditions of hypotension and/or dehydration and QT prolongation was a concurrent co-morbid condition in one patient. Relevant co-morbid cardiac disease was document in one patient who had a medical history of cardiac arrest and one patient who had medical history of Prinzmetal's angina.

Ataxia

In the integrated safety population (N=355), AEs of ataxia were reported in 17 (4.8%) patients. The majority of these events occurred contemporaneously with other AEs (e.g. fatigue, mental status change, mood change, memory impairment, dizziness, neuralgia, syncope, somnolence),

which suggests a neurologic etiology. In the context of the CNS penetrance of entrectinib and the identified risks of neurologic adverse events (e.g. syncope, cognitive disorders) with entrectinib, attribution of ataxia in the majority to entrectinib is plausible.

Clinical Reviewer Comment: Refer to DNP's full review of neurotoxicity, inclusive of ataxia.

Gait Disturbance

In the integrated safety population (N=355), AEs of gait disturbance were reported in 24 (7%) patients, overall. The majority of these patients' events were reported contemporaneously with other AEs (e.g. vertigo, insomnia, fatigue, cognitive disturbances, confusion). In the context of the CNS activity of entrectinib and the identified risk of neurologic adverse effects (e.g. syncope, cognitive disorders) with entrectinib therapy, a neurologic etiology of gait disturbance in the majority of the reported related cases is plausible.

Hypotension

In the integrated safety population (N=355), AEs of hypotension and orthostatic hypotension were reported in 63 (18%) patients, collectively. Most events of hypotension or orthostatic hypotension were reported concomitantly with other AEs. Of the 72 hypotensive events that were reported concurrently with other AEs, a majority were reported with AEs which may contribute to the development of hypotension, such as dehydration, diarrhea, vomiting, acute infections, and cardiac events. No single etiology of hypotension is suggested by the data.

Weight gain and Weight Loss

According to FDA nonclinical review team, in the 13-week study, entrectinib-treated male rats demonstrated increased food consumption, which is consistent with literature reporting hyperphagia and obesity in mice that express reduced amounts of TrkB (Xu et al, 2003) and in a human with a missense mutation in *NTRK2*, the gene encoding TrkB (Yeo et al., 2004). Paradoxically, dehydration and impaired weight gain was also observed in juvenile rats.

A consistent increase in food consumption and increased weight was not observed across 1-month and 3-month studies in rats and dogs at low and high doses. Findings may have been confounded by toxicity in some animals (animals that lost weight tended have CNS or GI toxicity). Therefore, the relationship between entrectinib exposure and food consumption or weight gain was less clear for entrectinib in animals. However, based on the mechanism of action, instances of clinical increased weight can reasonably attributed, at least in part, to entrectinib.

Increases in body weight were observed in patients treated with entrectinib. This observation is likely an on-target effect of entrectinib, since TRKB may be important in appetite control (Tsao et al. 2008). In patients who had adverse events of increased body weight, some were also

noted to have fluid retention or edema. Upon review of adverse events of increased weight in the integrated safety population (N= 355), approximately half of the patients had concurrent adverse events (within a 30-day time frame) of increased weight and fluid retention or edema. Based on this observation and available literature, it appears that both increased appetite and fluid retention/edema may potentially contribute to adverse events of increased weight.

At the data cut- off date of May 31, 2018, 25% patients (88/355) had an AE of increased weight. The majority of these AEs were Grade 2 (11% of patients) events, followed by Grade 1 (8% of patients). Grade 3 increased weight occurred in 6.5% of patients. Of the 88 patients who had an AE of increased weight, most experienced increased weight within 60 days of starting entrectinib.

Table 52, containing analyses submitted by Genentech, provides a high-level summary of the time to first onset of an adverse event of increased weight.

Table 52: Summary of Time to First onset of Increased Weight Adverse Events

Time to Onset of Adverse Event of Increased Weight	Total adult (N= 338)	Pediatric (N = 17)	Total (N=35)
	83 (100%)	5 (100%)	88 (100%)
0-30 days	34 (41.0%)	5 (100%)	39 (44.3%)
≥ 30 - <60 days	25 (30.1%)	0	25 (28.4%)
≥ 60- <90 days	10 (12.0%)	0	10 (11.4%)
≥ 90 - < 180 days	9 (10.8%)	0	9 (10.2%)
≥ 180 - < 365 days	5 (6.0%)	0	5 (5.7 %)
365+ days	0	0	0

Source: Table copied from IR-12 from 5 April 2019, and data verified from reviewer with dataset AAE

Among 88 patients with an AE of increased weight, 6% required dose reduction, 2.3% required dose interruption, and one patient (1.1%) permanently discontinued entrectinib.

<u>Clinical Reviewer Comment</u>: *Adverse events of increased weight gain were reported in 25% of entrectinib-treated patients. This is attributable to entrectinib, although more than one mechanism (fluid retention vs. increased food consumption) may be responsible for this adverse reactions, based on the role of TRKB in appetite control and the observed 15% incidence of "increased weight" reported in the product label for larotrectib (VITRAKVI), which also inhibits TRK.*

Impaired weight gain was seen in juvenile rats and adverse events of decreased weight were also reported in patients exposed to entrectinib. Adverse events of decreased weight were reported in 2.3% of patients. The weight changes may be attributable to entrectinib as the TRK pathway is involved in weight and thermal regulation; however, there are confounding factors such as underlying cancer and the catabolic nature of cancer that could also result in weight

loss. In some cases, due to the single arm nature of the studies, small sample size, and underlying cancer and comorbidities, it was difficult to assess the extent to which entrectinib was responsible for changes in weight. Refer to Section describing Grade 3-4 AEs for further details. The majority of AEs of decreased weight were of Grade 1 severity (1.1% of patients), followed by Grade 2 and Grade 3 (0.6% of patients each).

Dyspnea

Adverse events of dyspnea were reported in 30% of patients (106/355). The cases of adverse events of dyspnea were reviewed to evaluate the possible etiology of dyspnea, i.e., pulmonary, cardiac, or another etiology. In approximately half of the 106 cases, dyspnea could not be attributed to another comorbid condition because no alternative etiology or confounding factor could be identified; thus, these cases of dyspnea appeared to be related to entrectinib. In the remaining patients, comorbid conditions included concurrent pulmonary disorders (such as respiratory tract infection, pleural effusion, or pulmonary edema) in roughly 50%, cardiac disorders (such as heart failure, or arrhythmia) in 25%, and assorted conditions in the other 25% (e.g., anemia, anxiety, or hypotension).

Similar incidences of AEs reports as dyspnea were reported regardless of underlying diagnosis(i.e., NSCLC vs. other cancers), suggesting that the histologic cancer was not a risk factor for adverse events of dyspnea.

Clinical Reviewer Comment: AESI that were not included in the W&P section of the entrectinib product label included weight changes and clinically relevant adverse reactions occurring in <10% of patients such as dysphagia (10%), fall (8%), pleural effusion (8%), syncope (3.9%), pulmonary embolism (4%), and hypoxia (4%). After assessment of the narratives and review of Genentech's responses to multiple FDA IRs, the reviewers decided that inclusion of these adverse events in the W&P section was not warranted either because a causal relationship between the AE and entrectinib was unclear or inclusion in the W&P section was not necessary given that oncologists are typically skilled in managing a variety of adverse reactions to drugs, including those described above.

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

Not applicable.

8.3.7. Safety Analyses by Demographic Subgroups

Geriatric Patients

Of the 355 patients who received entrectinib across clinical trials, 25% were 65 years or older, and 5% were 75 years of age or older. Clinical studies of entrectinib did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger patients.

Pediatric patients

For the purposes of this review and product labeling, the pediatric population comprises patients less than 18 years of age. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients (n=30) compared to adult patients (n=338) were neutropenia (27% vs. 2%), bone fractures (23% vs. 5%), increased weight (20% vs. 7%), thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma-glutamyl transferase (7% vs 0%), and device-related infection (7% vs 3%). Three pediatric patients discontinued entrectinib due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis in one patient each). Due to the small number of pediatric patients, the modest size of the safety database in adults (n=338), the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors.

Clinical Reviewer Comment: An assessment of safety by other demographic subgroups (sex, ethnicity, age, RP2D vs entire efficacy population) did not show any safety signals. However, the data was difficult to interpret based on small sample size. Comparisons of AEs between adults and pediatric patients should be interpreted with caution due to the small sample sizes of these subpopulations.

In addition to the increased incidence of skeletal fractures, cytopenias, and elevated liver enzymes, infections appeared to be more common in the pediatric population; however, pediatric patients are prone to seasonal illnesses such upper respiratory infections and the symptoms that accompany them such as cough, nasal congestion.

As noted above, due to the small number of pediatric patients, the modest size of the safety database in adults (n=338), the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors.

There is insufficient pharmacokinetic and safety information to establish a safe and effective dose in pediatric patients less than 12 years of age, see Sections 1.3, 8.4, and 10 for further details.

8.3.8. Specific Safety Studies/Clinical Trials

There were no additional studies performed to evaluate any specific safety concerns.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted or required to support the use of entrectinib in the proposed indication. Entrectinib was aneugenic, but not mutagenic, in *in vitro* genotoxicity studies.

Human Reproduction and Pregnancy

No pregnancies have been reported in female patients exposed to entrectinib. One pregnancy was reported in the partner of a 47-year old male patient who was taking entrectinib. The pregnancy was voluntarily terminated at 5 weeks for unspecified personal reasons.

There were no reports of exposure to entrectinib in lactating patients; it is unknown whether entrectinib is excreted in human breast milk. However, because many drugs are excreted in human milk and because of the potential for serious adverse drug reactions in nursing infants, lactating mothers were not eligible for clinical studies with entrectinib.

Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of entrectinib in pediatric patients aged 12 years and older with solid tumors that have an *NTRK* gene fusion have been established. The effectiveness of entrectinib in adolescent patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumors harboring an *NTRK* gene fusion (ALKA, STARTRK-1, and STARTRK-2) and pharmacokinetic data in adolescents enrolled in STARTRK-NG; the pharmacokinetic profiles in adult and adolescent patients were comparable.

There is limited clinical experience with entrectinib in pediatric patients. The safety of entrectinib in pediatric patients 12 years of age and older was established through extrapolation of safety data in adults supported by safety data from 30 pediatric entrectinib-treated patients enrolled in STARTRK-NG. Of these 30 patients, 7% were < 2 years (n = 2), 77% were 2 to < 12 years (n = 23), 17% were 12 to < 18 years (n = 5); 57% had metastatic disease (n = 17) and 44% had locally advanced disease (n=13); and all patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were neuroblastoma (47%), primary CNS tumors (30%), and sarcoma (10%). The median duration of exposure for all pediatric patients was 4.2 months (range: 0.2 to 22.7 months).

Due to the small number of pediatric patients, limited number of adult patients, the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients (n=30) compared to adult patients (n=338) (using the database lock date of 31 May 2019) were neutropenia (27% vs. 2%), bone fractures (23% vs. 5%), increased weight (20% vs. 7%), thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma-glutamyl transferase (7% vs 0%), and device-related infection (7% vs 3%). Three pediatric patients discontinued entrectinib due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis in one patient each).

From the nonclinical studies, it is mechanistically plausible that entrectinib could have skeletal effects. According to Su et. al. Trk receptors has been observed in injured bone tissues, and neurotrophin may play a role in bone fracture healing (Su et. al. 2018). For pediatric patients on entrectinib in the safety database, there were 2 patients (a 9-year old and a 4-year old) with bilateral leg fractures.

There were no findings of fractures or tooth problems in the animal toxicology studies in entrectinib. There was dose-dependent fetal rat developmental toxicity, especially in bone, seen mainly at a top dose which is less than 3 times higher than the human exposure at the proposed marketing dose. There was delayed growth in juvenile rats including shorter bones, and impaired learning and memory in juvenile rats. See the nonclinical part of this review for further details (Section 5.5.4).

As described in the skeletal fracture subsection of the AESI section of this review, skeletal fractures appeared to occur at a higher incidence in pediatric patients compared to adult patients and occurred in the absence of a history of trauma, suggesting that pediatric patient may be at higher risk of developing fractures with entrectinib compared to adult patients. Genentech will conduct a PMR study to better characterize the risk of fractures in adult and pediatric patients and identify ways to mitigate this risk.

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

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

The safety and effectiveness of entrectinib in pediatric patients less than 12 years of age with solid tumors who have an *NTRK* gene fusion have not been established.
The safety and effectiveness of entrectinib in pediatric patients with *ROS1*-positive NSCLC have not been established.

Clinical Reviewer Comment: Given the small number of pediatric patients in the safety database, the limited duration of follow-up, and limitations inherent in interpreting longitudinal growth and development information in single arm trials, additional information is needed to better characterize the safety of entrectinib in pediatric patients, particularly because they may undergo treatment with entrectinib for months or years. Genentech is required to conduct a postmarketing requirement study to assess the long-term effects of entrectinib on pediatric growth and development. Given that entrectinib will be indicated for the treatment of pediatric patients 12 years of age and older with (b) (4) *metastatic cancer who have no satisfactory treatment options, the benefit:risk assessment favors use for use of entrectinib in the adolescent population despite the residual uncertainty regarding late effects of entrectinib, given the serious, life-threatening nature of the disease, based on the indication, and the lower risk of effects on growth and development than in younger patients.*

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There have been no reported cases of overdose in clinical studies with entrectinib. In the entrectinib clinical development program, the highest dose to which patients have been exposed is 2600 mg once daily. There is no information available on higher doses.

Genentech stated that available clinical evidence does not suggest a potential for abuse with entrectinib in a patient population with cancer and this reviewer agrees.

No AEs suggestive of withdrawal and rebound effects have been reported in clinical studies with entrectinib.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Entrectinib was approved in Japan in June of 2019; given the limited time on the market, no information regarding postmarket experience was available at the time of this review. Entrectinib has not been approved in any country other than Japan at the time of this review.

Expectations on Safety in the Postmarket Setting

The review teams determined that a REMS is not required to ensure safe and effective use of entrectinib. Entrectinib will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs. See Section for details regarding the postmarketing studies Genentech is required to conduct to further characterize and identify ways to mitigate the serious risks of cardiac toxicity and skeletal fractures, and to characterize potential serious risk of adverse long-term effects of entrectinib on the growth and development, including neurological outcomes, of pediatric patients 12 years of age and older.

8.3.11. Integrated Assessment of Safety

The above safety assessment incorporates data from four trials and is therefore integrated.

SUMMARY AND CONCLUSIONS

8.4. Statistical Issues

There was no major statistical issue that impacted the overall efficacy conclusions. However, because the efficacy of entrectinib is based on pooled data analysis from three non-randomized studies, ignoring the variability among the studies, the estimated treatment effect may be under or over estimated. The sources of heterogeneity included, but were not limited to, the study designs (e.g., difference in frequency of tumor assessments). Due to the rarity of the disease, pooling of data from several sources was considered acceptable in this case despite these limitations. In addition, in a single arm study time-to-event endpoints such as progression-free survival and overall survival, as well as patient reported outcomes, are not interpretable and no statistical inference can be made.

8.5. Conclusions and Recommendations

Based on the data from the 51 patients with *ROS1*-positive metastatic NSCLC who had not received prior treatment with a ROS1 TKI included in the primary analysis set, entrectinib demonstrates a large and clinically meaningful ORR associated with durable responses in this patient population. The estimated ORR as assessed by BICR was 78% (95% CI: 65%, 89%), with 70%, 55%, and 30% of the 40 responders having observed DOR of ≥9 months, ≥12 months, and ≥18 months, respectively.

The observed clinical safety profile in the subgroup of patients with *ROS1*-positive NSCLC was similar to that in patients with other *ROS1*-positive solid tumors and *NTRK* fusion-positive tumors enrolled on the same studies. The safety review consisted of data from 355 adult and pediatric patients from four single-arm studies: Study ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG. In general, the adverse reactions observed with entrectinib were consistent with the mechanism of action and toxicity observed in preclinical studies of entrectinib. The primary risks related to entrectinib are a variety of different neurotoxicities including cognitive, mood, and sleep disorders; congestive heart failure; skeletal fractures; hyperuricemia; transaminase elevation; QT prolongation; and vision disorders. These serious risks are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of entrectinib product labeling. The rate of permanent discontinuation of entrectinib due to AEs was 9% and most discontinuations were attributed to disease progression the underlying cancer. The adverse reaction profile is acceptable when assessed in the context of clinical benefit observed (ORR of 78% with at least half of the responses durable for 12 months) and the life-threatening nature of metastatic NSCLC (5-year survival <5%).

In the opinion of the reviewers, the submitted evidence meets the statutory evidentiary standard for regular approval and provides substantial evidence of the effectiveness of entrectinib as a single agent in patients with *ROS1*-positive metastatic NSCLC. The magnitude of the treatment effect on ORR of 78% and the durability of responses are clinically meaningful and establish the clinical benefit of entrectinib in the treatment of patients with metastatic *ROS1*-positive metastatic NSCLC.

The reviewers recommend granting regular approval of entrectinib for the following indication: "ROZLYTREK (entrectinib) is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive".

Primary Statistical Reviewer Xiaoping (Janet) Jiang, PhD	Statistical Team Leader Lisa Rodriguez, PhD
Primary Clinical Reviewer Shanthi Marur, PhD	Clinical Team Leader Erin Larkins, PhD

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this NDA to the Oncologic Drug Advisory Committee (ODAC) because the safety profile is acceptable for the treatment of the indicated population and the application did not raise significant public health questions regarding role of entrectinib for this indication. Outside expertise was not necessary as there were no controversial issues that could benefit from an ODAC discussion.

10 Pediatrics

Data in pediatric patients with *ROS1*-positive NSCLC were not submitted in the NDA and NSCLC, in general, is rare in the pediatric population. Based on the previous orphan drug designation for entrectinib, Genentech is exempt from the requirement to assess safety and effectiveness of entrectinib for the claimed indication in all pediatric age categories under 21 CFR 314.55(d), Exemption for Orphan Drugs.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

On March 11, 2019, FDA sent an information request to Genentech requesting that Genentech incorporate the labeling information for NDA 212725 and NDA 212726 into a single integrated label and address additional format and content issues. Table 53 below summarizes changes to the proposed prescribing information for the integrated labeling submitted on March 29, 2019. See the final approved prescribing information for ROZLYTREK (entrectinib) accompanying the approval letter for final labeling.

Table 53: Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
Highlights		
General	Format was not consistent with Selected Requirement of Prescribing Information (SRPI).	Revised format in accordance with SRPI.
Indications and Usage	…	Modified based on changes made to Indications and Usage (1).
Dosage and Administration	…	Modified based on changes made to Dosage and Administration (2).
Warnings and Precautions (W&P)	Included W&P for congestive heart failure, QT interval prolongation, cognitive disorders and embryo-fetal toxicity.	Broadened cognitive disorders to central nervous system (CNS) effects, removed syncope, and added vision disorders, skeletal fractures, hepatoxicity and hyperuricemia based on changes made to W&P (5).
Drug Interactions	…	Modified based on changes made to Drug Interactions (7).
Full Prescribing Information		
Indications and Usage, *ROS1*-Positive Non-Small Cell Lung Cancer	...	Specified “adult patients” as recommended in Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry.
Dosage and	Included general statement	Revised to recommend

Section	Proposed Labeling	Approved Labeling
Administration, Patient Selection	that an FDA-approved test was not available and referred to section 14 for information on tests used in the trial.	selecting patients for treatment based on presence of *ROS1* rearrangements in tumor specimens and to state that an FDA-approved test for the detection of *ROS1* rearrangements in NSCLC is not available for treatment with entrectinib.
Dosage and Administration, Recommended Dosage	(b) (4)	Included a separate subsection for each indication based on recommendations in Content and Format of the Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products regarding drugs with multiple indications.
Dosage and Administration, Dosage Modifications for Adverse Reactions	Included a table describing (b) (4) (b) (4) (b) (4) dose reduction based on body surface area. Included a table describing the recommended dosage modifications for congestive heart failure, QT interval prolongation, cognitive disorders, syncope and anemia or neutropenia.	Simplified table to only include first and second dose reduction based on recommended dosage. Broadened dosage modifications for cognitive disorders to CNS effects, removed dosage modifications for syncope, and added dosage modifications for hyperuricemia, hepatotoxicity, and vision disorders based on changes made to W&P.
Warnings and Precautions		Reordered based upon frequency and potential severity of outcomes as recommended in Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and

Section	Proposed Labeling	Approved Labeling
		Format. Revised the W&P to describe the incidence in the safety population across clinical trials.
Warnings and Precautions, Central Nervous System Effects	(b) (4)	Expanded W&P to include cognitive impairment, mood disorders, dizziness and sleep disturbances based on FDA analysis of safety population.
Warnings and Precautions, Vision Disorders	Not included.	Added because clinically significant vision disorders occurred in patients, including blurred vision, photophobia, diplopia and visual impairment
		(b) (4)
Warnings and Precautions, Skeletal Fractures	Not included.	Added because clinically significant fractures occurred in adult and pediatric patients.
Warnings and Precautions, Hepatotoxicity	Not included.	Added because clinically significant elevations in AST and ALT requiring dosage modification occurred in the safety population.
Warnings and Precautions, Hyperuricemia	Not included.	Added because clinically significant hyperuricemia occurred in the safety population.
Warnings and Precautions, Embryo-Fetal Toxicity	Based recommendations on animal studies and mechanism of action. Included recommendations for females of reproductive potential to use contraception during treatment and for (b) (4) (b) (4) after last dose.	Based recommendations on animal studies, mechanism of action and human data. Lengthened recommendation based on guidance document (see discussion about subsection 8.1 in this table) and added recommendation for males with female partners of reproductive potential.
Adverse Reactions	…	Revised list of clinically significant adverse reactions

Section	Proposed Labeling	Approved Labeling
		based on changes to W&P.
Adverse Reactions, Clinical Trials Experience	Included a description of the safety population. … … (b) (4)	Revised description of safety population to indicate that the safety population described in Clinical Trials Experience is the same population used to describe the adverse reactions in the W&P and minimize description of pediatric population. Revised the list of serious adverse reactions (including fatal adverse reactions) and the list of adverse reactions that led to dose reduction and permanent discontinuation based on FDA analysis of available safety data. Added a description of grade 3-4 adverse reactions and adverse reactions that lead to dose interruption. (b) (4) Revised adverse reaction table to include columns for all grades and grades 3 to 5, list categories in decreasing frequency based on the rates for the adverse reactions listed in each category and list adverse reactions in each category in decreasing order, added additional terms, and redefined composite terms based 21 CFR 201.57 and FDA analysis of the safety

Section	Proposed Labeling	Approved Labeling
	(b) (4)	population. Modified list of less common clinically relevant adverse reactions to include other adverse reactions that occurred in <10% of the safety population based on FDA analysis of the safety population. Modified laboratory abnormality table to include additional laboratory abnormalities based on FDA analysis of safety population and list categories in decreasing frequency based on the rates for the abnormalities listed in each category and list abnormalities in each category in decreasing order based on 21 CFR 201.57 and FDA analysis of the safety population.
Drug Interactions	(b) (4)	Simplified recommendations and referred to Dosage and Administration for specific recommendations.
Specific Populations, Pregnancy	Not included.	Added human data summarizing the effects of mutations in TRK pathway from published literature.
Specific Populations, Lactation	Recommended discontinuing breastfeeding during treatment and for 14 days after the final dose.	Modified recommendations based on entrectinib elimination half-life.
Specific Populations, Females and Males of Reproductive Potential	Recommended using effective contraception during treatment and for (b) (4) after the final dose.	Modified recommendation based on Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry.

Section	Proposed Labeling	Approved Labeling
Specific Populations, Pediatric Use	Summarized the data supporting the safety and effectiveness of ROZLYTREK in pediatric patients with *NTRK* gene fusion-positive solid tumors without including required pediatric use statements.	Included pediatric use statements pediatric patients with *ROS1*-positive NSCLC as required by 21 CFR 201.57.
Specific Populations, Renal Impairment	Stated that no dose adjustment was needed for mild and moderate renal impairment and provided a definition of mild to moderate renal impairment.	Added method used to measure renal function to include sufficient information needed to evaluate renal function and determine need for dosage modification.
Specific Populations, (b) (4) Impairment	Stated that ROZLYTREK has not been studied in patients with hepatic impairment.	Revised dosage modifications based on degree of hepatic impairment and added definition for hepatic function based on FDA analysis.
Clinical Pharmacology, Pharmacokinetics	Included multiple subheadings to describe pharmacokinetics in specific populations.	Consolidated under heading "Specific Populations" based on recommendations in Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products - Content and Format
(b) (4)		(b) (4)
Clinical Studies, *ROS1*-Positive Non-Small Cell Lung Cancer	(b) (4)	Replaced (b) (4) (b) (4) with percent of patients with a response at select timepoints, (b) (4) (b) (4)

Section	Proposed Labeling	Approved Labeling
	(b) (4)	The statistical and clinical review teams recommended including the percentages of responders with observed duration of response at least 9, 12, and 18 months using the data cut-off date of October 31, 2018 to provide more mature information. Agreement reached to also include the range of DOR.
	Described clinical outcomes in patients with brain metastases	Revised description of outcomes in patients with brain metastases to limit BICR-confirmed assessment in the 7 patients with measurable disease and without confounding factors (radiotherapy within the preceding 2 months) for attribution of IC-ORR to entrectinib.
	(b) (4)	
Patient Counseling Information	Included information for congestive heart failure, QT interval prolongation, cognitive disorders, embryo-fetal toxicity, lactation, administration and missed dose.	Added information for new W&P and drug interactions.

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team does not recommend a risk evaluation and mitigation strategy (REMS) be required to ensure safe and effective use of entrectinib for the indicated population. Recommendations for the safe and effective use of entrectinib are made in labeling and a Patient package insert. There are no additional risk management strategies required beyond the recommended labeling. Although entrectinib can cause severe/serious toxicity, it will be prescribed by oncologists who, by training, understand how to monitor and manage such serious toxicities.

13 Postmarketing Requirements and Commitment

Genentech has agreed to the following postmarketing requirements (PMR) and postmarketing commitments (PMC):

Clinical Pharmacology PMR

Complete a pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of entrectinib compared to subjects with normal hepatic function in accordance with the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*," available at: https://www.fda.gov/media/71311/download.

Final Protocol Submission: 08/2019
Trial Completion: 06/2021
Final Report Submission: 12/2021

Nonclinical PMR

Determine functional activation or inhibition of off-target receptors, transporters, and/or channels that, at concentrations of 10 µM, showed greater than 50% inhibition by entrectinib or M5 in the secondary pharmacology studies submitted to NDA 212725 and 212726. As part of an integral safety assessment, include EC50 or IC50 data for target receptors, transporters, and channels that are still significantly affected at a concentration less than 1 µM, particularly those involved in suicidal intent and behavior, as described in Muller et al., 2015.

Final Protocol Submission: 08/2019
Study/Trial Completion: 04/2020
Final Report Submission: 09/2020

Clinical PMR

Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the cardiac risks and sequelae in patients exposed to entrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification and monitoring. The design of the trial should include sufficient cardiac monitoring to achieve these objectives.

Draft Analysis Plan Submission: 06/2020
Final Analysis Plan Submission: 09/2020
Trial Completion: 06/2021
Final Report Submission: 06/2022

Clinical PMR
Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the risk of fractures and its sequelae in patients exposed to entrectinib with reasonable precision; to identify risk factors for development of these sequelae; and to support labeling recommendations to mitigate the risk of skeletal fractures. The design of the trial should include sufficient bone monitoring to achieve these objectives, including but not limited to initial and serial assessment of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans, and markers of bone formation, bone resorption, and of calcium metabolism.

Draft Analysis Plan Submission: 06/2020
Final Analysis Plan Submission: 09/2020
Trial Completion: 03/2024
Final Report Submission: 03/2025

Clinical PMC
Submit a report, including datasets, of clinical studies that further characterize the clinical benefit of entrectinib for the treatment of adult patients with *ROS1* fusion-positive metastatic NSCLC by providing a more precise estimation of the BICR-assessed overall response rate (ORR) and duration of response (DOR) in the 92 ROS1 TKI-naive patients with *ROS1*-positive NSCLC and measurable disease enrolled across the ALKA, STARTRK-1 [NCT02097810] and STARTRK-2 [NCT02568267] studies.

Provide updated DOR results for the 40 responders in the efficacy evaluable population of 51 patients (primary analysis population) and for the additional 27 responders among the 41 additional patients with *ROS1*-positive NSCLC with measurable disease as of the original data cut-off date for the NDA. This report will be submitted after all responders have been followed for at least 18 months from the date of initial response.

Trial Completion: 09/2020
Final Report Submission: 06/2021

Clinical PMC
Commit to providing adequate analytical and clinical validation results from clinical trial data to support labeling of the F1CDx test to detect *ROS1* rearrangements for identifying patients who may benefit from entrectinib. The analytical validation should consist of precision, limit of detection, and accuracy studies for the ROS1 indication. The clinical validation should be supported by a clinical bridging study comparing F1CDx and the clinical trial enrollment assays.

sPMA submission: 12/2019

14 Division Director (DHOT)

John Leighton, PhD
Director, Division of Hematology, Oncology, and Toxicology

15 Division Director (OCP)

Nam Atiqur Rahman, PhD
Director, Office of Clinical Pharmacology

16 Division Director (OB)

Rajeshwari Sridhara, PhD
Director, Office of Biometrics

17 Division Director (Clinical)

I concur with the recommendations of the review team, cited here and in the Quality review, that the application should be approved for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive, based on the demonstration of an effect on overall response rate that is large in magnitude [ORR 77% (95% CI: 64%, 88%)] and durability [56% of the 41 responders with DOR ≥ 12 months and 29% with DOR ≥ 18 months], providing substantial evidence of a clinically meaningful effect on ORR, which is similar to that observed with crizotinib and exceeds (based on the lower limit of the 95% confidence interval for the point estimate of ORR which is 64%) that of platinum-based combination therapy that includes an anti-PD-(L)1 antibody. Anti-tumor activity was also observed in previously treated CNS metastases; however, the clinical experience is very limited (7 patients evaluable for response); thus, no conclusions can be drawn regarding relative activity in the CNS compared to other drugs. Considering that *ROS1*-positive NSCLC constitutes only 1 -2% of the estimated 228,150 new cases of lung cancer projected to be diagnosed in the U.S. in 2019[1], the conduct of randomized clinical trials to demonstrate improvements in survival are not feasible in this population. The benefits of durable responses in this population with a serious and life-threatening disease outweigh the serious risks of entrectinib, which include congestive heart failure, a variety of neurocognitive impairment, mood disorders, and other central nervous system (ataxia, dizziness, dysesthesia,) effects, skeletal fractures, hepatotoxicity, QT prolongation, a variety of effects impairing vision, and hyperuricemia requiring medical intervention, as well as common (≥ 20%) but less serious toxicities of fatigue, constipation, dysgeusia, edema, diarrhea, nausea, weight gain, cough, vomiting, pyrexia, and arthralgias.

The major scientific issues with this application were the limited number of patients studied and short follow-up such that the treatment effect is imprecisely characterized, particularly with regard to the durability of responses. Additionally, at the time of approval, there is no FDA-approved companion diagnostic test for identification of patients for whom entrectinib is indicated. Although FDA generally requires contemporaneous approval of a companion diagnostic test, the nature of the mutation (gene fusion) increases the likelihood that the risk of false positive tests is low. Furthermore, studies are underway to analytically validate a companion diagnostic assay for this purpose. Given the unmet need for this population for effective therapies, the low risk of a false positive result with tests performed in CLIA-certified laboratories that, in accordance with CLIA, analytically validate their assays, and consistent with the approach taken with the approval of crizotinib for this same patient population, I concur that entrectinib be approved for this indication while development of a companion

[1] https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics.html accessed August 12, 2019.

diagnostic test for *ROS1*-positive NSCLC is ongoing.

The other major issue with this application was the poor quality of the application, which included numerous mis-statements and poor data presentation and required more than 70 requests for clarification of data across both NDAs (212275 and 212276) which were linked by cross-referenced data; the apparent lack of familiarity of the Genentech team with the data included in the application, such that initial responses to information requests were often inaccurate, requiring duplicative follow-up by FDA to obtain clarification on the information presented in the NDA; and the failure of Genentech to provide timely updates on important safety data (risk of skeletal fractures). Additionally, Genentech's failure to submit complete data for the required financial disclosure information diverted staff time and attention from review of the primary data, that required multiple internal and external meetings, review of additional submissions describing corrective actions as well as new data submissions over the course of several months to adequately address this deficiency. Given these major deficiencies in application content and quality, the review of this application from a clinical standpoint required excessive time and delayed the time to final action on this application.

I concur with the requirement for additional post-marketing studies to further characterize the adverse reaction of congestive heart failure; to further characterize the adverse reaction of fractures; to evaluate the effects of moderate and severe hepatic impairment on the pharmacokinetics of entrectinib; and to further characterize the possible off-target effects of entrectinib or its major metabolite.

Finally, I concur with agreed-upon commitments to identify at least one analytically validated commercial assay(s) that will accurately identify the presence of *ROS1* gene fusions in NSCLC tumor specimens to identify patients for whom entrectinib is indicated; to obtain additional data on the durability of responses observed in the population supporting this approval; and to further characterize the anti-tumor activity of entrectinib in patients with *ROS1*-positive metastatic NSCLC who have received no prior systemic therapy and progressed more than 6 months following completion of an adjuvant platinum-based chemotherapy regimen.

Patricia Keegan, MD
Director, Division of Oncology Products 2

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of entrectinib (Rozlytrek) was also assessed by Drs. Erin Larkins and Shanthi Marur and I concur with their recommendation to approve this drug. My signature below also represents an approval recommendation for the clinical portion of this application under CDER.

_____

Gideon Blumenthal, MD
Deputy Center Director, Oncology Center for Excellence

19 Appendices

19.1. References

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19.2. Financial Disclosure

During the filing review, the review teams noted that there was a substantial proportion (12%, 32%, and 54%) of missing financial disclosure forms (FDFs) in three of the four studies evaluating safety and efficacy.

Relevant dates for applications:

- Genentech-Ignyta merger: effective February 8, 2018
- Transfer of INDs to Genentech: June 12, 2018
- Change of Sponsor letters issued on August 10, 2018 under IND 120500 and on December 4, 2018 under IND 135124

Genentech's "Note to File" in the original NDA documented the following reasons that FDFs were not collected:

- Investigator did not respond to contacts
- Genentech was not required to obtain FDFs for investigators who discontinued study participation more than one year prior to Genentech's acquisition of Ignyta.

The Division chose to file the NDAs despite the missing FDFs. Multiple requests (January 3, 2019 information request [IR]; February 8, 2019 IR, March 1, 2019 March 1, 2019 Filing letters; and March 14, 2019 teleconference) were made by the Division for information on the missing FDFs, including evidence of due diligence and Genentech's ability to obtain the missing FDFs. DOP2 also requested that Genentech provide justification as to why the absence of the required financial disclosure forms for a substantial proportion of clinical investigators does not impact the reliability of the clinical information submitted to the NDA due to potential bias due to undisclosed relationships.

On February 1, 2019, in response to FDA's request for additional information, Genentech provided a 300+ page PDF document that included line listings of investigators for each trial indicating the FDF status for Ignyta (no disclosable interests, disclosable interests, or missing/unable to obtain). These line listings were of little utility. FDA concluded that the response was inadequate.

On March 15, 2019 and March 29, 2019, Genentech submitted amendments describing:

- procedures for collection of Ignyta and Genentech FDFs
- summary-level information regarding the status of FDF documentation.

Genentech acknowledged that Ignyta did not maintain records of their due diligence to obtain missing FDFs.

Genentech stated that, based on the FDA *Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators* which states "If a clinical investigator did not participate in the entire study, information collected should be for the period of time he or she participated in the study and for one year following the end of his or her participation," Genentech prioritized obtaining financial disclosure information for Roche/Genentech for investigators who participated on study within a year of the merger (June 2018).

The tables below summarize the updated financial disclosure information provided by Genentech in the March 15, 2019 and March 29, 2019 amendments.

Table 54: Summary of Financial Disclosure Information for NDA 212725/6

STUDY	Total Number of Investigators to Date	Ignyta		Genentech	
		FDFs collected n	FDFs missing n	FDFs collected n	FDFs missing n
ALKA	38	27	11	26	12
STARTRK1	149	139/140*	1	70	79**
STARTRK2	1996***	1240/1273*	33	1031	965****
STARTRKNG	144	129/129*	0	141	3

(Updated FDF collection status dated March 15, 2019)
*****Denominator differs from the total number of investigators to date because additional investigators were added following the Genentech-Ignyta merger.
******Genentech states 64 investigators ended their participation in this study more than a year prior to Roche/Genentech-Ignyta merger; therefore, Genentech considers FDFs to be missing for 15 investigators.
*******Genentech assumes only 1357 investigators from this study contributed to the NDA, FDFs were collected for 1017 of these investigators and FDFs were missing for 340.
********Per Genentech 73 of the 1357 investigators who contributed data to the NDA ended their participation in this study more than a year prior to Roche/Genentech-Ignyta merger; therefore, Genentech considers FDFs to be missing for 267 investigators.

A summary of the FDF obtained by Ignyta and Genentech by investigator across the four studies limited to sites that enrolled patients are provided in Table 55 and Table 56.

Table 55: Summary of Ignyta Financial Disclosure Information by Investigator

	Disclosable Interest	Non Disclosable Interest	Missing Financial Disclosure Information	Total
Total Number of Investigators	4*	1520	57	1581
Number of investigators who enrolled patients with an Objective Response	1	814	22	837
Number of Investigator who enrolled patients with at least one dose	4*	1520	57	1581

* Since performing this analysis we have confirm that 2 of these investigators submitted a positive disclosure in error (see above).

Source: copied from IR response 29 March 2019

Table 56: Summary of Genentech Financial Disclosure Information by Investigator

	Disclosable Interest	Non Disclosable Interest	Missing Financial Disclosure Information	Total
Total Number of Investigators	3	1112	573	1688
Number of investigators who enrolled patients with an Objective Response	1	642	290	933
Number of Investigator who enrolled patients with at least one dose	3	1112	573	1688

Source: copied from IR response 29 March 2019

A summary of the financial disclosure information by patient across the four studies for sites that enrolled patients included in NDAs 212725 and 212726 for Ignyta and Genentech are provided in Table 57 and Table 58.

Table 57: Summary of Ignyta Financial Disclosure Information by Patient

	Disclosable Interest	Missing FDF
Number of patients with objective response (assessed by BICR) enrolled at site with	1	18
Number of patients enrolled into safety population at site with	12	108
Number of patients enrolled into NTRK efficacy evaluable population at site with	4	18

Source: copied from IR response 29 March 2019

Table 58: Summary of Genentech Financial Disclosure Information by Patient

	Disclosable Interest	Missing FDF	
		Investigator Left Study One Year Prior to Merger	Other
Number of patients with objective response (assessed by BICR) enrolled at site with	2	52	0
Number of patients enrolled into safety population at site with	8	241	13
Number of patients enrolled into NTRK efficacy evaluable population at site with	2	40	0

Source: copied from IR response 29 March 2019

Genentech asserted that bias related to the assessment of efficacy is mitigated by use of BICR for assessment of the key efficacy endpoints of ORR and duration of response; Genentech noted that ORR by BICR and Investigator assessment for both NDAs was similar.

To assess for bias in safety reporting, Genentech compared adverse event reporting in patients enrolled at sites without missing financial disclosure information and disclosable financial interests and adverse event reporting in patients enrolled by sites with disclosable interests or missing financial disclosure information for Ignyta and Genentech (Table 59 and Table 60). For the purposes of this analysis, the assumption was made that investigators with non-disclosable interests would not have any alterations in reporting behavior and therefore these investigators served as a “control” group. Genentech concluded that the patterns of reporting were consistent over time between the two groups irrespective of reporting status.

Table 59: Adverse Event Reporting Patterns Based on Ignyta Financial Disclosure Status

	Disclosure Status (n=355)	
	Enrolled at Site with NoDisclosable Interests (n=241)	Enrolled at Site with Disclosable Interest or Missing Financial Disclosure Information (n=114)
Patients with an AE reported while on treatment for < 3 months	240 (99.6%)	113 (99.1%)
Patients with an AE reported while on treatment ≥ 3 month and <6 months	146 (60.6%)	58 (50.9%)
Patients with an AE reported while on treatment ≥ 6 months and < 9 months	107 (44.4%)	41 (36.0%)
Patients with an AE reported while on treatment ≥ 9 months	71 (29.5%)	31 (27.2%)

AE=Adverse Event; Data source: ah_sa1898_t_ae_fdis_ign_SE

Source: copied from IR response 29 March 2019

Table 60: Adverse Event Reporting Patterns Based on Genentech Financial Disclosure Status

	Disclosure Status (N=355)	
	Non-Disclosable Interests* (n=100)	Disclosable Interest or Missing Financial Disclosure Information* (n=242)
Patients with an AE reported while on treatment for < 3 months	99 (99.0%)	242 (100%)
Patients with an AE reported while on treatment ≥ 3 month and <6 months	63 (63.0%)	140 (57.9%)
Patients with an AE reported while on treatment ≥ 6 months and < 9 months	41 (41.0%)	107 (44.2%)
Patients with an AE reported while on treatment ≥ 9 months	28 (28.0%)	74 (30.6%)

AE= Adverse Event; Data source: ah_sa1898_t_ae_fdis_ro_SE
*There are 13 patients in the safety population excluded as they were enrolled at sites where the investigator left one year prior to the acquisition by Roche and therefore not represented in this analysis. (source: t_fin_dis_pat_roche)

Source: copied from IR response 29 March 2019

Based upon these analyses, the clinical reviewers concluded that there did not appear to be a pattern of underreporting of adverse events at sites with disclosable interests for Ignyta or Genentech.

The Office of Regulatory Policy (ORP) and the review teams met on April 18, 2019. ORP clarified that financial disclosure (FD) information should be obtained for all investigators or sub-investigators who were directly involved in the treatment or evaluation of research subjects or documentation of due diligence should be provided. ORP confirmed that if a clinical investigator did not participate in the entire study, information collected should be for the

period of time he or she participated in the study and for one year following the end of his or her participation. 21CFR 54.4(b) requires investigators to provide information on financial interests and arrangements during the "course of the study and one year after completion of the study." For the purposes of determining the time period for obtaining FD information, FDA considers the completion date for both NDAs to be October 31, 2018, which is the data-cutoff date used for follow-up data for duration of response that was submitted to the NDAs on March 4, 2019. In addition to the relevant time period for Ignyta FD information, Genentech FD information should be obtained for investigators and sub-investigators who were directly involved in the treatment or evaluation of research subjects from the date of the merger (February 8, 2018) through the completion date (October 31, 2018) and will need to be updated for a year following the completion of the study.

In an information request sent May 7, 2019, FDA conveyed to Genentech that more than one attempt at contacting an investigator and more than one method of contact should be attempted in order to demonstrate due diligence. Genentech was further advised that all attempts to contact the investigator should be documented (e.g., email, letter, telephone calls, written memos, and certified mail or reliable courier service that provides notice of recipient's receipt), along with the date that these attempts were made (which should be separated by a reasonable interval of time in order to reach investigators that may be traveling, on leave, etc.). If an investigator is no longer at the institution where the study was conducted, FDA recommended that Genentech make a reasonable attempt to locate the investigator, for example by conducting an internet search, contacting professional associations, or requesting contact information from the institution. For those investigators that are no longer employed by the enrolling institution, Genentech was advised to indicate whether they were able to obtain current contact information, and, if not, how they attempted to obtain this information.

In reviewing the information provided by Genentech on May 22, 2019 (dated May 21, 2019) and June 7, 2019 in response to this request, FDA reviewers focused on clinical study sites with the largest number of patients enrolled and the number of attempts made by Genentech to obtain missing FDFs, the methods of contact (email, phone, mail), and the dates in which the attempts were made. In some cases, an investigator was on maternity or medical leave, had left the hospital/was no longer employed (most investigators in this category had left in 2017), or there was an upcoming site visit (June 2019) in which Genentech would attempt to contact the investigator again. In many cases, Genentech attempted to contact an investigator to obtain a FDF up to 10 times. Overall, the reasons cited for failing to obtain FDFs seemed reasonable and the FDA reviewers concluded that Genentech demonstrated due diligence in attempting to obtain the missing FDFs.

Clinical Reviewer Comment: Based on the review of the responses to the multiple requests for information from FDA, Genentech demonstrated due diligence in attempting to contact investigators for whom FDFs were missing. Relevant tables from this submission are provided below.

Table *61*: *Summary of Financial Disclosure Information*

Description	Sub-Total (if applicable)	Total
Grand Total Number of All Investigators/ Sub-Investigators		Ignyta: 1604[1] Roche/Genentech: 1682[1]
Total Number of Investigators/ Sub-Investigators Certified Regarding the Absence of Financial Interests and/or Arrangements for Ignyta		1597
Total Number of Investigators/ Sub-Investigators Certified Regarding the Absence of Financial Interests and/or Arrangements for Genentech/Roche		1381
Total Number of Investigators/ Sub-Investigators Not Certified for Ignyta		5
Total Number of Investigators/ Sub-Investigators Not Certified for Roche/Genentech		296
Total Number of Investigators/ Sub-Investigators Who Hold Financial Interests and/or Arrangements with Ignyta Requiring Disclosure	• Significant Payments of Other Sorts n= 1 • Unknown n=1	2
Total Number of Investigators/ Sub-Investigators Who Hold Financial Interests and/or Arrangements with Genentech/Roche Requiring Disclosure	• Compensation n= 3 • Equity Interest n= 1 • Significant Payments of Other Sorts n= 1	5

Source: IR 42 submitted 7 June 2019

This tabular summary includes investigators at sites that enrolled ≥1 patient into the NDA dataset and sites that enrolled ≥1 patient included in the Second Update Report for Study STARTRK-NG (data cut 31 March 2019). A table of all clinical investigators/sub-investigators not certified for Ignyta and Genentech, and the due diligence attempts made to obtain the missing information for Ignyta and Genentech were submitted with Genentech's June 7, 2019 response to FDA's IR-42 which was adequate and demonstrated due diligence in attempting to collect missing financial disclosure forms.

Covered Clinical Study (Name and/or Number): ALKA

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 38		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2*		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

There were no disclosable financial interests for this trial and Genentech demonstrated adequate due diligence in collecting financial disclosure forms.

Covered Clinical Study (Name and/or Number): STARTRK1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 149		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6*		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

The clinical reviewers determined that the disclosed financial interest was unlikely to have a material impact on the integrity of the data provided from this trial and that Genentech demonstrated due diligence in collecting financial disclosure forms.

Covered Clinical Study (Name and/or Number): STARTRK2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1996		
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): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Unknown: 1* Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4 forms missing for Ignyta and 308 forms missing for Genentech; FDA reviewers determined that due diligence was exerted to collect these missing FDFs.**		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Per Genentech, this investigator marked both the "yes" and "no" box on the financial disclosure form but did not provide details on the disclosure. This investigator is no longer at the site and attempts to contact the investigator for clarification were unsuccessful.*
***Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

The clinical reviewers determined that the disclosed financial interests/arrangements were unlikely to impact the integrity of the data from this trial and that Genentech exerted due diligence in their attempts to collect the missing financial disclosure forms.

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 144		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 for Ignyta and 1 for Genentech Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 financial disclosure forms were missing for Ignyta and 26 were missing for Genentech. FDA reviewers determined that due diligence was exerted to collect these missing FDFs.*		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

The clinical reviewers determined that the disclosed financial interests/arrangements were unlikely to impact the integrity of the data from this trial and that Genentech exerted due diligence in their attempts to collect the missing financial disclosure forms.

19.3. Nonclinical Pharmacology/Toxicology

No additional information.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

See primary Clinical Pharmaoclogy Review for NDA212726.

19.5. Additional Clinical Outcome Assessment Analyses

The QLQ-LC13 includes questions assessing lung cancer-associated symptoms such as dyspnea and cough that are the two clinical interested symptoms of patients with NSCLC. Figure 25 displays the statistical reviewer's plot of percentage of patients who reported cough extent up to cycle 10.

Figure 25: Percentage of Patients Who Reported Cough Extent by Cycle

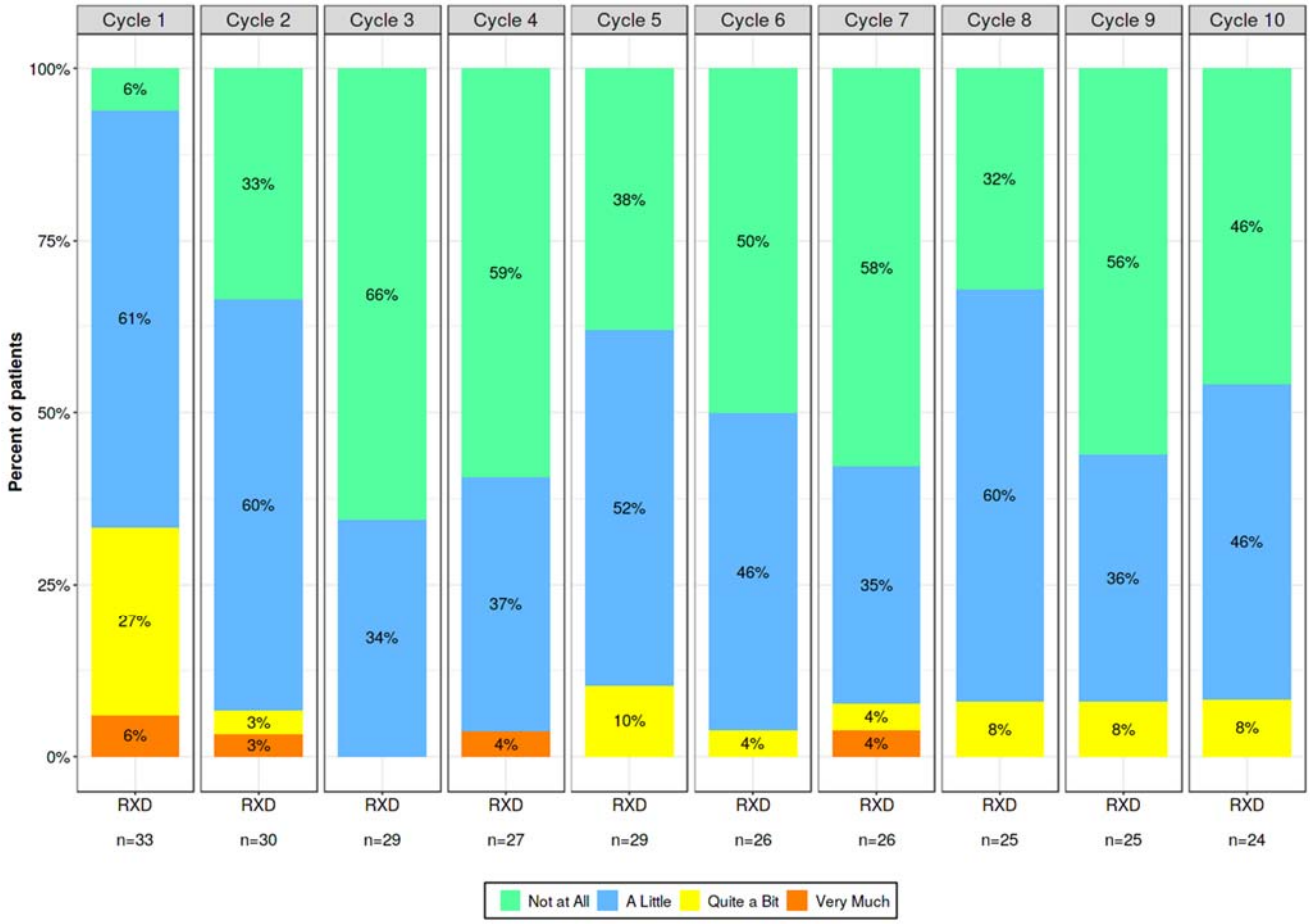


Figure 26 displays the statistical reviewer's plot of percentage of patients who reported cough up blood from cycle 1 to cycle 10 (cycle 1 assessment is the baseline assessment).

Figure 26: Percentage of Patients Who Reported Cough up Blood by Cycle

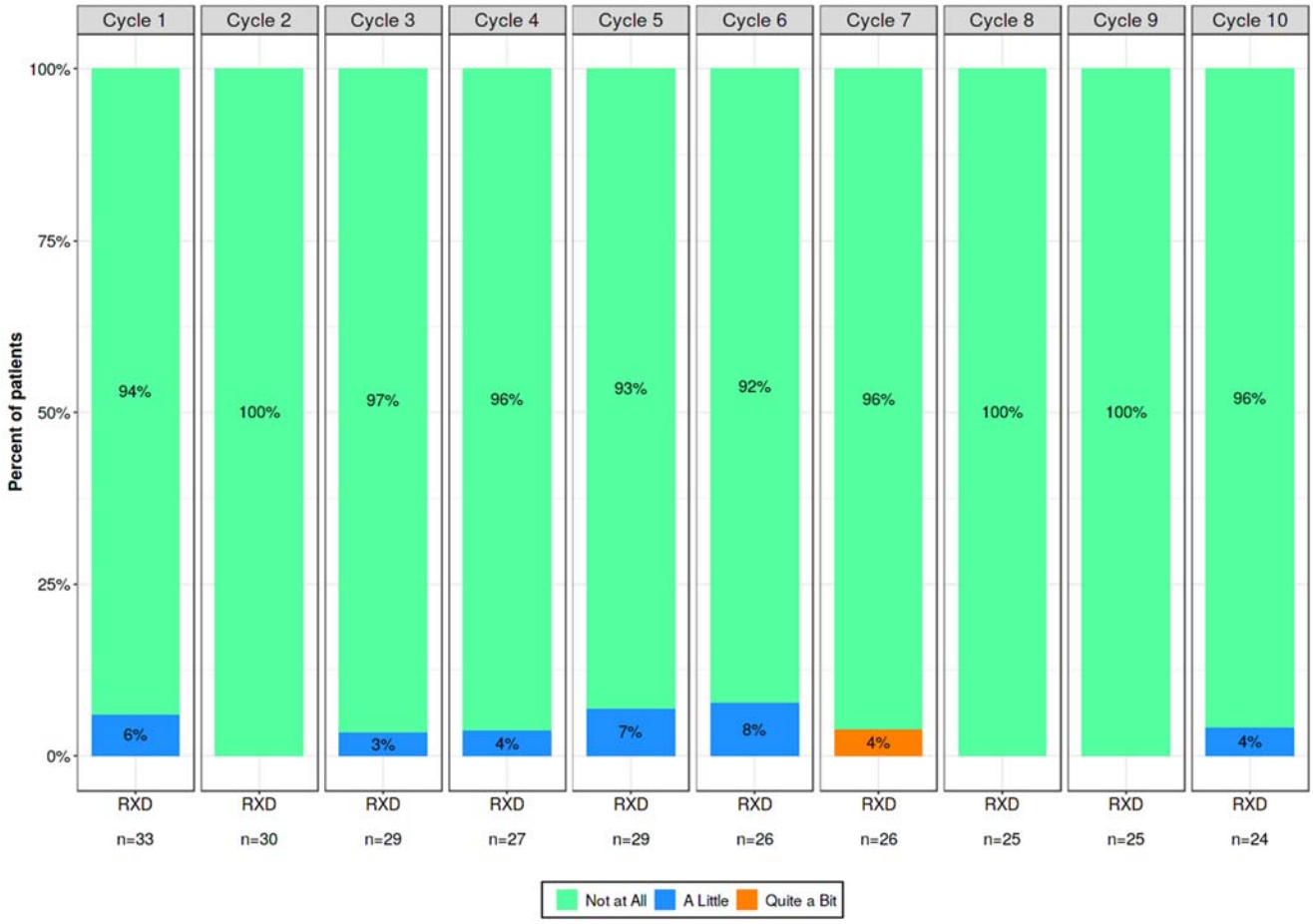


Figure 27 displays the statistical reviewer's plot of percentage of patients who reported short breath when rested from cycle 1 to cycle 10.

Figure 27: Percentage of Patients Who Reported Short Breath When Rested by Cycle

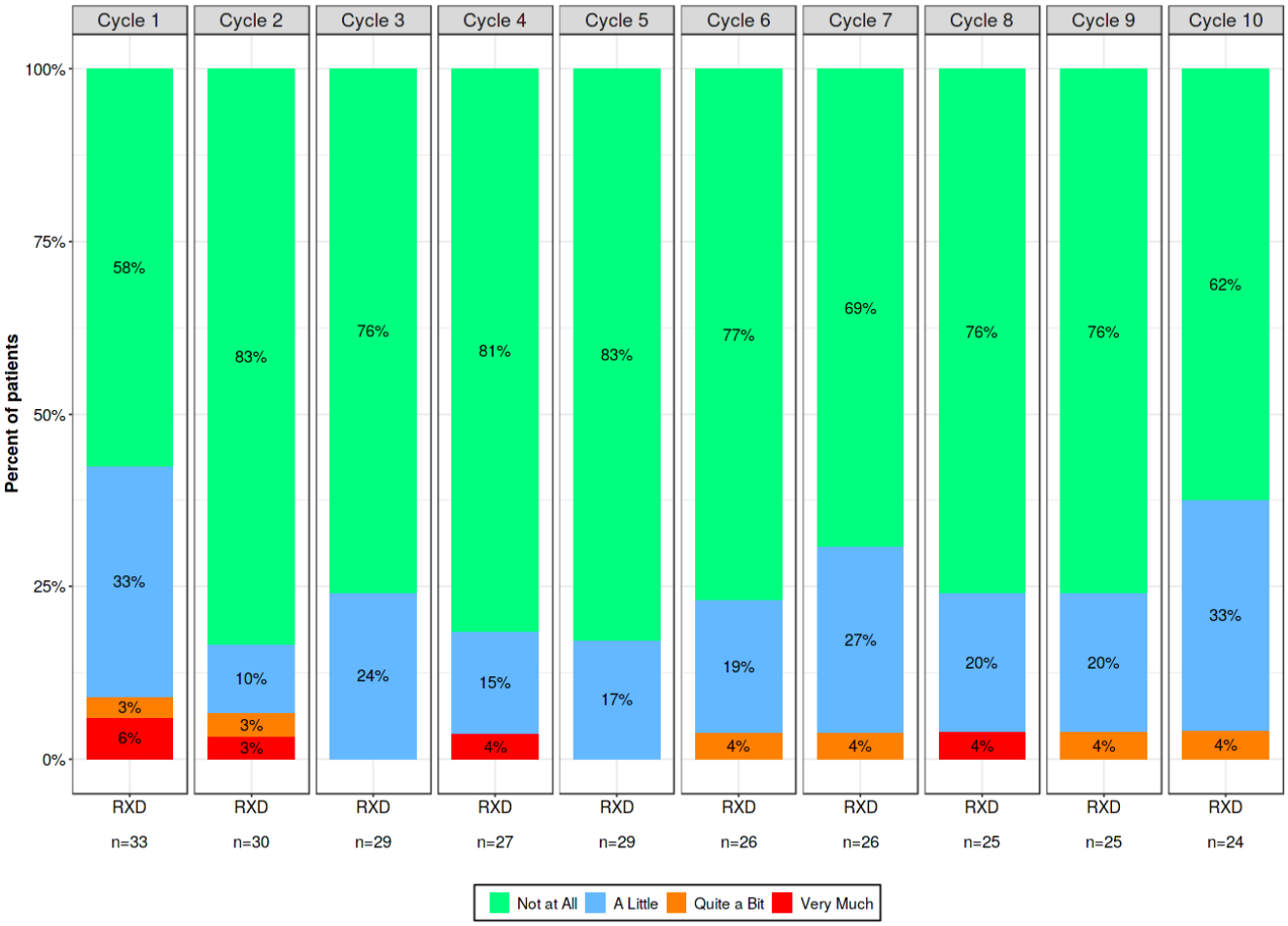
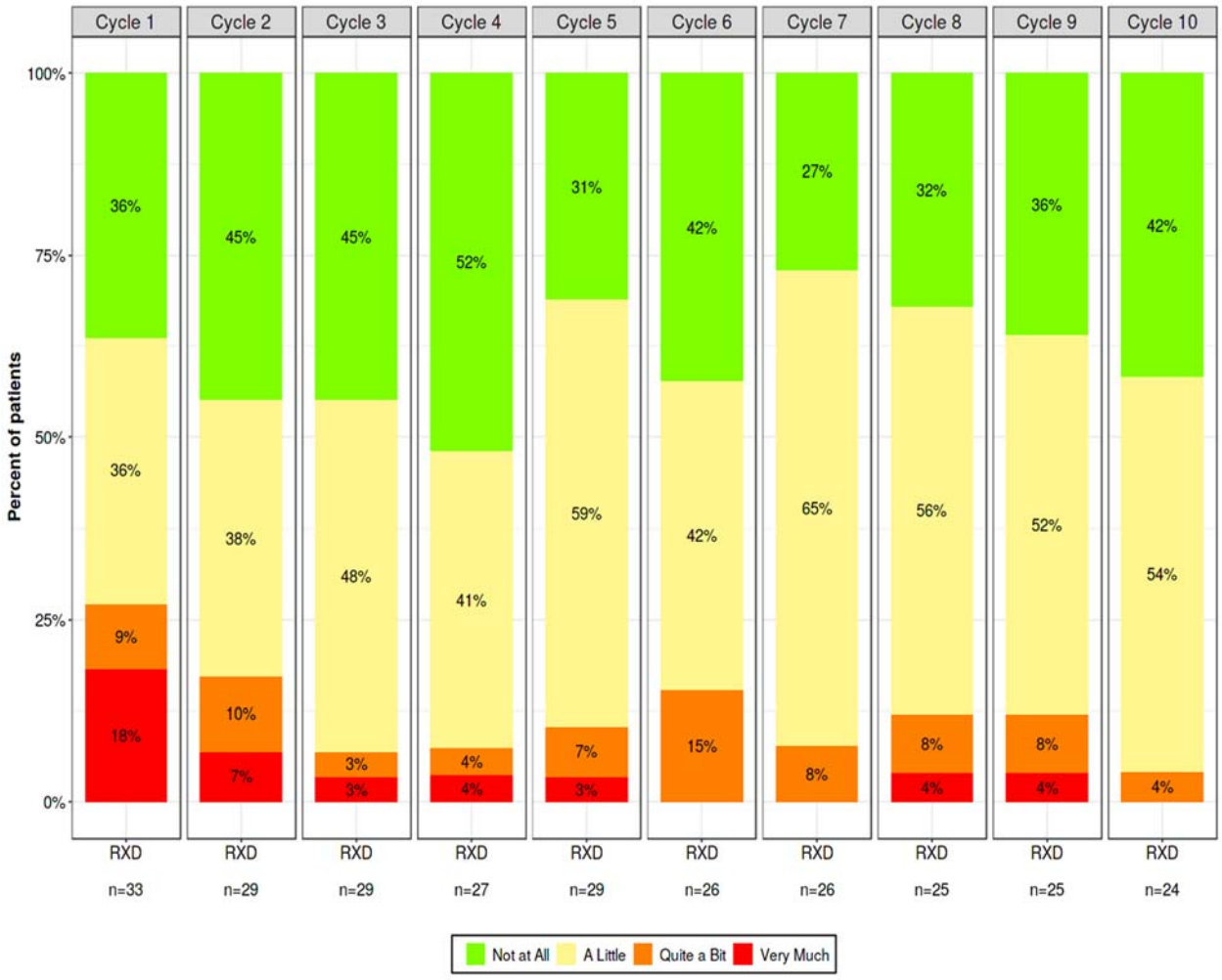


Figure 28 displays the statistical reviewer's plot of percentage of patients who reported short breath when walked from cycle 1 to cycle 10.

Figure 28: Percentage of Patients Who Reported Short Breath When Walked by Cycle



19.6. Description of Relevant Individual Trials Supporting the NDA

19.6.1. ALKA-372-001

Trial Design

Study ALKA-372-001 (GO40783), entitled, "A Phase 1, Dose Escalation Study of Entrectinib (RXDX-101) In Adult Patients With Advanced/ Metastatic Solid Tumors" was a first-in-human, open-label, single arm, nonrandomized, multicenter, dose escalation study in sequential cohorts of adult patients with advanced or metastatic solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK*-positive genetic alterations, which may include any type of molecular alteration, inclusive of fusions.

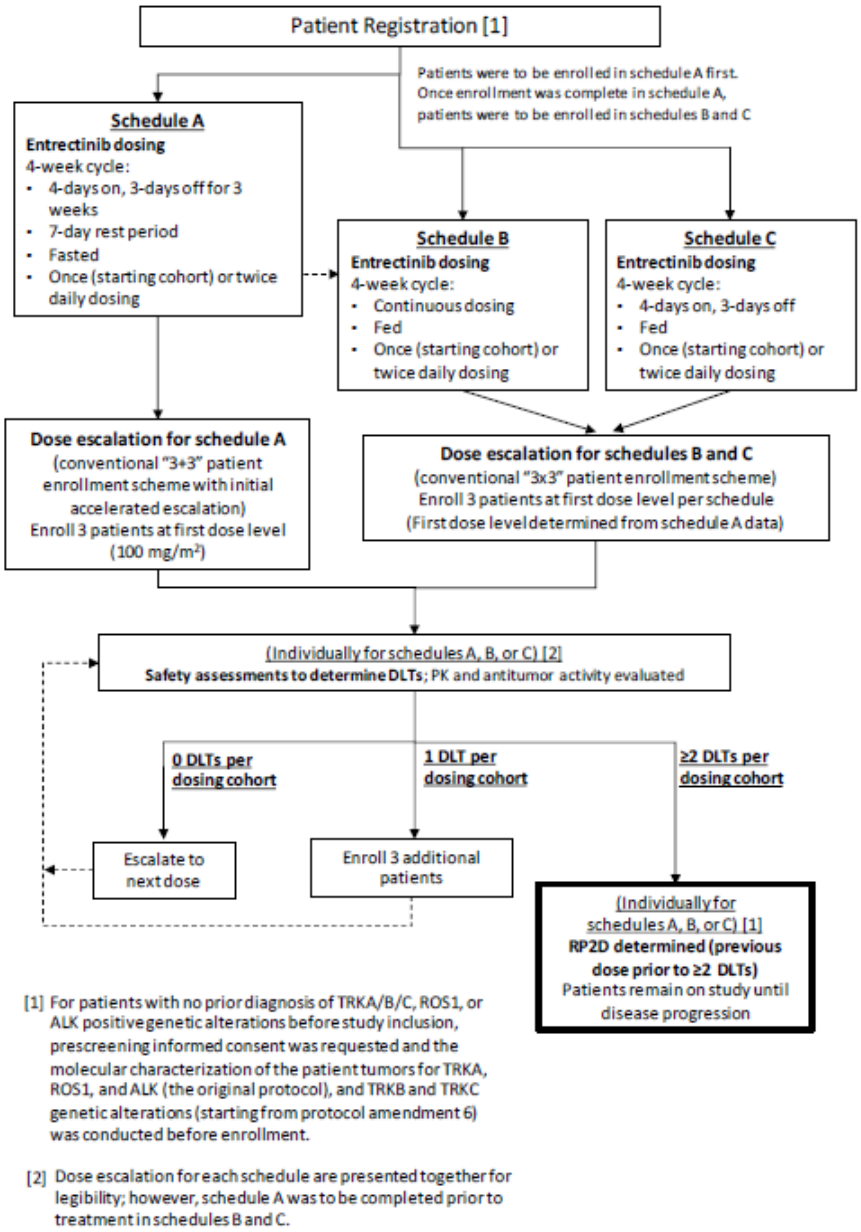
The following dose schedules were investigated in this study:

Schedule A: 100, 200, 400, 800, 1200, or 1600 mg/m^2 once daily (fasted) 4-days on, 3-days off schedule x 3 weeks followed by 7-day rest in a 4-week cycle
Schedule B: 200, 400 mg/m^2 or 600 mg continuous once daily (fed) in a 4-week cycle
Schedule C: 400 or 800 mg/m^2 once daily (fed) in a continuous 4-days on, 3-days off schedule in a 4-week cycle

The dose level and dose schedule for each patient was assigned by the sponsor at the time of patient registration. All patients had to be observed for 1 cycle before subsequent patients were enrolled at the next higher dose level. The study had an initial 100% accelerated escalation phase until a predetermined level of toxicity was encountered. At that point, escalation was to follow a modified Fibonacci scheme.

The design of the study was dose escalation and a standard "3+3" scheme was used to evaluate all the dose schedules and determine the RP2D. Figure 29 presents the dose escalation schema used in this study.

Figure 29: Dose Escalation Schema for ALKA-372-001



Source: Protocol submitted to Module 5.3.5.2

Key Eligibility Criteria

Consenting adult (age ≥ 18) patients with histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumors with *ALK*-positive alterations (per original protocol) or *ALK*-negative patients with TRKA, TRKB, TRKC, or ROS1 genetic alterations (*ALK*-negative patients with TRKA or ROS1 genetic alterations only up to protocol amendment 5) in patients for whom

no alternative effective standard therapy was available, standard therapy was considered unsuitable, or had been refused (per protocol amendment 8), were eligible for the study.

Other main selection criteria included:

- ECOG performance status ≤2
- Life expectancy of at least 3 months
- Baseline laboratory data indicating acceptable hematologic status, liver and renal function, and resolution of any acute toxic effects (excluding alopecia) of any prior anticancer therapy (NCI CTCAE [version 4.03] grade ≤ 1 or to the baseline laboratory values)
- Patients with controlled asymptomatic CNS involvement, in absence of therapy with anticonvulsant (up to protocol amendment 7) or in presence of therapy with non-enzyme-inducing anti-epileptic drugs (per protocol amendment 8) or requiring steroids at stable dose (≤ 4 mg/day dexamethasone or equivalent) for at least 2 weeks were also eligible.

Study Endpoints

The primary objective of this study was to determine the first cycle dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of entrectinib administered orally in three different dosing regimens: schedule A (4-days on treatment, 3 days off schedule for 3 weeks, followed by a 7-day rest period in a 4-week cycle; fasted condition; once daily dosing); schedule B (continuous daily dosing in a 4-week cycle; fed condition; once daily dosing); or schedule C (4 days on treatment, 3-days off schedule in a 4-week cycle; fed condition; once daily dosing) in adult patients with advanced/metastatic solid tumors with tropomyosin receptor kinases (TRK)A, TRKB, TRKC, tyrosine kinase ROS Proto-Oncogene 1 (ROS1), or anaplastic lymphoma kinase (ALK) positive genetic alterations.

The secondary objectives were to define the safety profile of entrectinib, to evaluate the pharmacokinetics of entrectinib in plasma, and to document any antitumor activity of entrectinib.

Dose Modification and Management Algorithms

A dose level –1, corresponding to 60 mg/m^2/day, dose de-escalation was required in patients receiving the starting dose level of 100 mg/m^2/day. No more than one intra-patient dose de-escalation was allowed. Doses reduced for drug-related toxicity were not be re-escalated, even if there was minimal or no toxicity with the reduced dose according to Table 62.

Table 62: Dose Modification for Entrectinib Based on the Worst Grade (as Per NCI CTCAE Version 4.03)

Toxicity since last dose	During treatment cycle	After recovery from toxicity* at the start of subsequent cycle
Hematological Toxicities		
Grade ≤2 Neutropenia (ANC <1500-1000/mm^3) and/or Thrombocytopenia (PLT <75000-50000/mm^3)	If occurs during treatment, maintain daily dose level	Maintain dose level
Uncomplicated Grade 3 Neutropenia (ANC <1000-500/mm^3)	If occurs during treatment, decrease daily dose by one dose level	Maintain dose level
Uncomplicated Grade 3 Thrombocytopenia (PLT < 50,000-25,000/mm^3) or Grade 3 associated to Grade ≥ 2 bleeding	If occurs during treatment, interrupt treatment	Decrease one dose level
Febrile neutropenia : ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38 °C for >1 hour	If occurs during treatment, interrupt treatment	Decrease one dose level
Neutropenic infection: Grade ≥3 infection documented clinically or microbiologically with Grade ≥3 neutropenia	If occurs during treatment, Interrupt treatment	Decrease one dose level
Grade 4 hematological toxicity of any duration	If occurs during treatment, Interrupt treatment	Decrease one dose level
Nausea and/or Vomiting		
Grade ≤2 (in absence of antiemetics)	If occurs during treatment, maintain daily dose level and add antiemetics, if needed. If occurs during rest period, add antiemetics, if needed	Maintain dose level with antiemetics§
Grade ≤2 (in presence of antiemetics)	If occurs during treatment, decrease the daily dose by one dose level, adjust antiemetics, as needed If occurs during rest period, adjust antiemetics, as needed	Maintain dose level with adjusted antiemetics§
Grade ≥3 (in absence of antiemetics)	If occurs during treatment, interrupt one day the drug administration, if needed, decrease the daily dose by one dose level, add antiemetics. If occurs during rest period, add antiemetics	Maintain dose level with antiemetics§
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease one dose level ‡
Diarrhea		
Grade ≤2 (in absence or presence of management of the event §)	If occurs during treatment, maintain daily dose level, add/adjust antidiarrheal treatment, if needed. If occurs during rest period, add/adjust antidiarrheal treatment, if needed	Maintain dose level
Grade ≥3 in absence of management of the event	If occurs during treatment, maintain daily dose level, add antidiarrheal treatment If occurs during rest period, add antidiarrheal treatment	Maintain dose level with antidiarrheal support or if persistent, decrease one dose level
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease one dose level
CNS Toxicities / Neurologic		
Grade ≤1 or no worsening compared to baseline	Maintain dose level	Maintain dose level
Grade 2	If occurs during treatment, decrease the daily dose by one dose level	Decrease one dose level
Grade ≥ 3	If occurs during treatment, interrupt	Decrease one dose level or

Source: protocol submitted to NDA Module 5.3.5.2

After a maximum of a 2-week delay, all toxicities (except for alopecia) were Grade ≤1 or recovered to baseline value, then proceeded with treatment as outlined in Table 62 above. If

toxicities did not allow re-treatment after the 2-week delay, an increased delay >2 weeks was discussed between the Investigators and the Sponsor.

Monitoring Plan

For efficacy, the antitumor activity of entrectinib was assessed by the investigator, using RECIST v1.1. Tumor response was assessed every even (per protocol amendment 1) or odd cycle (per protocol amendment 6), every 3 cycles for patients who continued on treatment for 12 cycles or more (per protocol amendment 6), and at the end of last treatment cycle, if more than 4 weeks had passed from last tumor imaging.

Safety assessments including adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, eye examinations, and chest X-rays) were performed at baseline and during the treatment period at different time points, depending on the parameter and on the schedule tested, and/or at the end of treatment. Patients were followed for AEs from the first dose up to 28 days after the last dose of study treatment or until all drug-related toxicities had resolved or an alternative anticancer therapy was started.

Adverse Event Collection

A DLT was defined as an AE occurring during the first treatment cycle that fulfilled prespecified criteria and grading (generally grades ≥3 in severity) and for which causal relationship to entrectinib could not be excluded; failure to recover (excluding alopecia) after delaying the initiation of next treatment administration by a maximum of 14 days, and failure to complete the first cycle treatment with at least 75% of the planned doses because of a drug related toxicity also met the criteria for a DLT. If a DLT was based on laboratory values alone, then, at a minimum, the laboratory test had to be repeated within 24 hours to confirm DLT. Grading of DLTs was according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

Sample Size Considerations

Initially, an overall sample size of approximately 40 treated patients was anticipated. Since the trial design foresaw that sequential dose-escalation steps applied to cohorts of 3 to 6 patients up to the identification of the MTD, the total number of patients who would be enrolled and treated would have possibly varied, depending upon the toxicity observed and the resulting influence on cohort size and number of dose levels tested. A total of 76 patients were enrolled. For patients enrolled up to and including November 30, 2017 with a clinical data cutoff date of May 31, 2018, 58 patients were enrolled at 2 investigative sites; 57 received study drug treatment. Patient enrollment was completed on 20 Mar 2018.

Analysis Sets

All patients who receive at least one dose of entrectinib will be displayed in the study outputs. The anti-tumor activity of entrectinib will be assessed by considering the objective tumor responses defined according to the RECIST criteria (version 1.1). The data includes patients enrolled up to and including 30 Nov 2017 with a clinical data cutoff of 31 May 2018.

Protocol Amendments

During the course the study, 10 protocol amendments were implemented. Substantial protocol and SAP amendments that were implemented are summarized below:

Original Protocol: (Date: 23 Jan 2012)

Amendment No. 1: (Date: 05 Mar 2012)
Modified the criteria reported in the dose escalation sections that permitted, in the first and second dose level, the simultaneous treatment of the first two patients per dose level.

Amendment No. 2: (Date: 14 Mar 2013)
Manufacturing changes to additional dose form 50mg capsules.
Inclusion criterion permitting prior therapy with ALK inhibitors other than crizotinib previously excluded, and permitting, for patients with CNS involvement, therapy with corticosteroids at stable doses (≤ 4 mg/day dexamethasone or equivalent) for at least 2 weeks.

Amendment No. 3: (Date: 05 Dec 2013)
To switch to treatment in fed condition, and introduction of a new schedule (once daily for 28 consecutive days, q4wks, Schedule B in fed condition) in addition to the current dose escalation (Schedule A, 4 days on/3 days off for 3 consecutive weeks followed by one week of rest, 4-week cycles, fasting condition), and addition of an additional schedule (Schedule C, 4 days on/3 days off, 4-week cycles, fed condition).

Amendment No. 4: (Date: 21 Jan 2014)
To implement an optional twice-daily dosing regimen in Schedule A of the protocol. Schedule A (4-week cycle) is comprised of 3 sequential weeks of 4 days on treatment (administered in fasting condition) followed by 3 days off treatment, with a one-week rest on the fourth week. This optional dosing regimen (administered in fasting condition) is being added to decrease the number of capsules that patients need to take at one time.

Amendment No. 5: (Date: 24 Jun 2014)
To allow the reduction of the intensity of laboratory assessments (hematological and blood chemical assessments) for patients under treatment for a long period of time.

To specify that brain MRI will be performed in glioblastoma patients.

Amendment No. 6: (Date: 14 Nov 2014)
An option has been introduced in the study to evaluate entrectinib when administered as a twice daily dosing regimen, in addition to the once daily dosing regimen, and for enrolling additional patients into a future dose level.
Clarification of DLT: If a DLT is based on lab values alone, then, at a minimum, a repeat value needs to occur within 24 hours to confirm DLT.
To clarify that in all schedules if a patient fails to receive at least 75% of complete first cycle of treatment, for reasons other than treatment-related toxicities, an additional patient must be enrolled at the same dose level.
Inclusion criteria: To allow the inclusion in the trial also of patients with TrkB and TrkC positive genetic alterations.

Amendment No. 7: (Date: 26 Feb 2015)
No clinical changes noted.

Amendment No. 8: (Date: 14 Jun 2016)
Enrollment criteria amended to align with global study: modified to enroll other types of TrkA/B/C, ROS1, or ALK molecular alterations that are of scientific exploratory interest. Only patients with a confirmed molecular alteration of interest will be allowed to enroll, based on agreement between the Investigators and the Sponsor of the study. To allow for retrospective (ongoing patients) and prospective (newly enrolled patients) blinded independent central review of imaging studies by a third-party imaging laboratory.

Amendment No. 9: (Date: 22 Aug 2016)
To modify the protocol to address the nonclinical embryo-fetal and ocular toxicities findings as described on the Dear Investigator Letter.

Amendment No. 10: (Date: 11 May 2017)
To modify the patient information, informed consent form, and protocol due to changes to the Reference Safety information in the new IB version 7.0.

Data Quality and Integrity

Upon further clarifications from Genentech in response to FDA's IRs, the reviewer was able to:
- Validate Genentech's analysis dataset and analysis results from legacy dataset
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy analyses

Compliance with Good Clinical Practices

The study has been conducted according to ICH-GCP E6 and (b) (4) SOPs in agreement with the sponsor. Independent external audits were conducted by (b) (4) and an external third party conducted by the sponsor. The study site could have also been subject to review by the independent ethics committee (IEC), to quality assurance audits performed by sponsor, and/or to inspection by appropriate regulatory authorities to assure compliance with proper study conduct.

Financial Disclosure

Study ALKA-372-001, entitled, "A Phase I Dose Escalation Study of Entrectinib (RXDX-101) in Adult patients with Advanced/Metastatic Solid Tumors" was conducted in Italy and was not submitted to an IND. There were major deficiencies regarding collection of financial disclosure forms (FDFs), including missing forms for up to 12 (32%) investigators. See Section 19.2 for full discussion of financial disclosure.

19.6.2. RXDX-101-01/STARTRK-1

Trial Design

STARTRK-1, entitled, "A Phase 1, Multicenter, Open-label Study of Oral Entrectinib (RXDX-101) in Adult Patients with Locally Advanced or Metastatic Cancer Confirmed to be Positive for *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, or *ALK* Molecular Alterations" is a dose-finding, multicenter, open-label study evaluating the safety and efficacy of entrectinib in adult patients with any locally advanced or metastatic solid tumor. The study is comprised of 2 segments, a dose escalation segment and a dose expansion segment. No dose expansion patients were enrolled as of the enrollment cutoff of 30 November 2017. The enrollment cutoff date was set to ensure that patients had approximately 6 months of follow-up at the data cutoff date of 31 May 2018. In the dose escalation segment, a molecular alteration in *NTRK1/2/3*, *ROS1*, or *ALK* was not a requirement for patient eligibility. As of the data cutoff date of 31 May 2018, 11 centers in the United States, Spain, and South Korea had enrolled patients.

This study segment was performed in sequential cohorts of eligible patients receiving entrectinib orally. Each cycle consisted of treatment for 28 consecutive days in repeated 4-week cycles. Dose escalation continued until a DLT was observed in 2 of 3 or 2 of 6 patients in cycle 1. If 2 of 3 patients experienced a DLT, then enrollment into the cohort stopped. A DLT was defined as an AE occurring during the first treatment cycle that fulfilled prespecified criteria of interest and grading (generally grades ≥3 in severity) and for which causal relationship to entrectinib could not be excluded; failure to recover from the AE within 28 days of onset also met the criteria for a DLT.

During dose escalation, a standard "3+3" patient enrollment scheme was followed with an accelerated titration design. The starting dose was 100 mg/m^2 once daily in the fed condition (entrectinib was administered within 60 minutes following a meal). Dose escalation began with an accelerated phase in which the dose was doubled in successive cohorts until 1 patient experienced a DLT in the first cycle; or 2 patients experienced AEs at least possibly related to entrectinib that were grade ≥2 severity, but not considered to be DLTs and occurred during the first cycle, whichever came first. Once this predetermined toxicity level was met, escalation was planned to be followed by a modified Fibonacci scheme (50%, 40%, or 33% increments). The MTD was the dose level at which 0/6 or 1/6 patients experienced a first-cycle DLT, and at least 2 of 3 or 2 of 6 patients experienced a first-cycle DLT at the next higher dose level (effectively, the MTD was the highest dose associated with a first-cycle DLT in <33% of patients). The RP2D determination was to be based on available safety, tolerability, PK and PD data from different dose levels and schedules tested. Once the RP2D by body surface area (BSA) was established, administration of a flat dose was to be considered in a subgroup of patients if PK and safety data supported the decision.

In the ongoing dose expansion segment, eligible patients are required to have molecular tumors with *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, or *ALK* molecular alterations. Patients are screened for the presence of molecular alterations by assays available to each clinical site (e.g., NGS, qPRC, FISH, immunohistochemistry). Patients are receiving entrectinib orally for 28 consecutive days in repeated 4-week cycles at the RP2D determined during the dose escalation segment (refer to Summary of Results; the RP2D was determined to be a fixed dose of 600 mg once daily for 28 consecutive days in repeated 4-week cycles). Eligible patients are enrolled into molecularly-defined cohorts under a Simon's 2-stage (minimax) design determined by the type of molecular alteration harbored by the patient's tumor.

Antitumor activity was evaluated by tumor assessment and response determined by RECIST v1.1. Patients had tumor assessments performed by CT or magnetic resonance imaging (MRI) at the end of cycle 1 and approximately every 8 weeks thereafter and at the end-of-treatment visit (if more than 4 weeks passed from the time of previous tumor imaging). The same imaging method was to be used to evaluate the tumors throughout the entire study. For patients with responding tumors (CR or PR), response confirmation was required to be performed at least 4 weeks after the first documentation of response. For patients with stable disease, tumor measurements were required to meet stable disease criteria of ≥35 days after first administration of entrectinib per the statistical analysis plan (SAP).

Per the protocol, alternate entrectinib formulations at an equivalent dose with similar or improved bioavailability were introduced into the study: during dose escalation, formulations F1 and F2A were used. Blood and urine samples were collected at various time points during the study for PK and PD assessments. Safety was monitored by AEs, laboratory assessments, physical examinations (including height), vital signs (including temperature, systolic/diastolic blood pressure, heart rate, weight, and BSA), ECGs, Eastern Cooperative Oncology Group (ECOG) performance status, and eye examinations. AE monitoring began upon first

administration of entrectinib and continued through 30 days after the last administration of entrectinib.

Patients remained on study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. In cases of progressive disease, after discussion with the sponsor, the patient could have continued treatment if the investigator believed that the patient might continue to derive clinical benefit.

Key eligibility criteria

Adult patients (age ≥18) with a histologically or cytologically confirmed diagnosis of relapsed or refractory locally advanced or metastatic solid tumors for whom no alternative effective standard therapy was available or for whom standard therapy was considered unsuitable or intolerable were enrolled.

Dose Escalation Segment:
A molecular alteration in *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, or *ALK* was preferred, but not a requirement for patient eligibility.

Dose Expansion Segment:
Eligible patients are required to have locally advanced or metastatic solid tumors harboring the following types of molecular alterations:

1. *NTRK* gene rearrangements (fusions) previously treated with other tropomyosin receptor kinase (TRK) inhibitors
2. *ALK* gene rearrangements with 1198 resistance single-nucleotide polymorphism (SNP)
3. ALK alternative transcription initiation (ALK^{ATI})
4. NTRK/ROS/ALK overexpression >6 (via RNA)
5. Activating splice variants
6. Other molecular alterations of interest, depending on biological rationale and after discussion with the sponsor

Study Endpoints

Primary Endpoint

Dose Escalation Segment: determine the first cycle DLTs, MTD, and a biologically effective and RP2D of entrectinib administered orally.
Dose Expansion Segment (ongoing): assess ORR, defined as the proportion of patients with complete response (CR) or partial response (PR).

Secondary endpoint

Dose Escalation Segment:

• Safety profile of entrectinib as characterized by AE type, severity, timing, and relationship to study drug, as well as electrocardiogram (ECG) and laboratory abnormalities in the first and subsequent treatment cycles
• Pharmacokinetics (PK) of entrectinib (and its potential metabolites) in plasma
• Antitumor activity of entrectinib as measured by tumor response (ORR) and duration of response (DOR) as well as PFS and overall survival (OS)
• Assay methods to detect molecular alterations (as defined in biomarker assessments), and identify appropriate analytical cutoffs and other relevant biomarker parameters that predict antitumor activity of entrectinib
• Pharmacodynamics (PD) of entrectinib on molecular targets in tumor and surrogate tissue
Dose Expansion Segment (ongoing):
• PFS defined as time from first dose of entrectinib to tumor progression or death due to any cause
• OS defined as time from first dose of entrectinib to death due to any cause
• Disease control rate (hereafter referred to as clinical benefit rate) defined as the proportion of patients with a confirmed CR, PR, or stable disease >6 months
• DOR as defined from the first date a response is identified (either CR or PR) until the date of disease progression
• Intracranial tumor response in patients with central nervous system (CNS) disease
• Safety and tolerability of entrectinib as characterized by AE type, severity, timing, and relationship to study drug, as well as ECG and laboratory abnormalities
• Assay methods to detect molecular alterations (as defined in biomarker assessments), and identify appropriate analytical cutoffs and other relevant biomarker parameters that predict antitumor activity of entrectinib
• PD of entrectinib on molecular targets in tumor and surrogate tissue
• PK of entrectinib (and its potential metabolites) in plasma

Dose Modification and Management Algorithms

All dose reductions were based on the most severe toxicity observed that was attributable to the study drug. At a starting dose level of 100 mg/m^2/day, no dose reduction was anticipated. If unacceptable toxicity presents, then the patient was instructed to stop treatment. No more than 1 intra-patient dose reduction was allowed. Doses reduced for drug-related toxicity should not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Recommended dose modifications during Phase 1 treatment cycles are shown in Table 63.

Table 63: Dose Modification Based on the Worst Toxicity Grade (as Per NCI CTCAE, Version 4.03) Observed During Phase 1

Toxicity since last dose	During treatment cycle	After recovery from toxicity at the start of subsequent cycle
Hematological Toxicities		
Grade ≤2 Neutropenia (ANC <1500-1000/mm^3) and/or Thrombocytopenia (PLT <75000-50000/mm^3)	If occurs during treatment, maintain daily dose level	Maintain dose level
Uncomplicated Grade 3 Neutropenia (ANC <1000-500/mm^3)	If occurs during treatment, decrease daily dose by 1 dose level	Maintain dose level
Uncomplicated Grade 3 Thrombocytopenia (PLT < 50,000-25,000/mm^3) lasting >7 days or Grade 3 associated to Grade ≥ 2 bleeding	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Febrile neutropenia : ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38 °C for >1 hour	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Neutropenic infection: Grade ≥3 infection documented clinically or microbiologically with Grade ≥3 neutropenia	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Grade 4 hematological toxicity of any duration	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Nausea and/or Vomiting		
Grade ≤2 (in absence of antiemetics)	If occurs during treatment, maintain daily dose level and add antiemetics, if needed.	Maintain dose level with antiemetics§
Grade ≤2 (in presence of antiemetics)	If occurs during treatment, decrease the daily dose by 1 dose level, adjust antiemetics, as needed	Maintain dose level with adjusted antiemetics§
Grade ≥3 (in absence of antiemetics)	If occurs during treatment, interrupt 1 day the drug administration, if needed, decrease the daily dose by 1 dose level, add antiemetics.	Maintain dose level with antiemetics§
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease 1 dose level ‡
Diarrhea		
Grade ≤2 (in absence or presence of management of the event §)	If occurs during treatment, maintain daily dose level, add/adjust antidiarrheal treatment, if needed.	Maintain dose level
Grade ≥3 in absence of management of the event	If occurs during treatment, maintain daily dose level, add antidiarrheal treatment	Maintain dose level with antidiarrheal support or if persistent, decrease 1 dose level
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease 1 dose level
CNS Toxicities / Neurologic		
Grade ≤1 or no worsening compared to baseline	Maintain dose level	Maintain dose level
Grade 2	If occurs during treatment, decrease the daily dose by 1 dose level	Decrease 1 dose level
Grade ≥ 3	If occurs during treatment, interrupt treatment	Decrease 1 dose level or **Discontinue study treatment**‡
Other Non-Hematological Toxicities (except alopecia)		
Grade ≤1	Maintain daily dose level	Maintain dose level
Grade 2	If occurs during treatment, maintain or decrease the daily dose by 1 dose level, if clinically indicated	Maintain dose level
Grade ≥ 3	If occurs during treatment, interrupt treatment	Decrease 1 dose level‡
Grade ≤ 2 hypersensitivity reaction suggestive of anaphylactic reaction	Investigator to discuss with Sponsor before proceeding	
Grade ≥ 3 hypersensitivity reaction suggestive of anaphylactic reaction‡	Treatment discontinuation	Treatment discontinuation
Failure to recover		
Failure to recover to grade ≤ 1 toxicity (except alopecia) or to baseline values, if grade 2 is allowed at study entry, after delaying the initiation of next cycle by > 2 weeks	Monitor until resolved to grade ≤1	Decrease 1 dose level ‡
§For prophylaxis and management of the events, see details in Supportive Care section of the study ‡ Investigator to discuss with Sponsor before proceeding **Abbreviations:** ANC = absolute neutrophil count; PLT= platelet count		

Source: protocol submitted to NDA Module 5.3.5.2

Adverse Event Collection

Grading of DLTs was according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. An AE is any untoward medical occurrence in a study patient administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. New signs and symptoms of underlying disease, or signs and symptoms of emerging disease must be recorded as AEs. AE monitoring for patients will begin upon first administration of entrectinib and will continue through the follow-up telephone contact 30 days following the last administration.

Sample Size Considerations

The accrual goal for each of the previously identified dose-escalation cohorts was 20 patients using a Simon's two-stage (minimax) design: 6 patients were enrolled to the first stage. A total of 14 patients were enrolled if ≥1 objective response was observed in the first 6 treated patients. The accrual goal for the dose expansion segment was approximately 50 patients.

Analysis Sets

The analysis sets for the dose escalation and dose expansion segments were defined as follows:
• DLT (dose escalation segment only): Patients (1) who experienced a DLT during cycle 1 after at least 1 dose of study drug and (2) who did not experience a DLT, completed cycle 1, and who were compliant with entrectinib treatment administration, having taken a minimum of 80% of study drug doses expected during cycle 1.
• Safety: Patients who received at least 1 dose of entrectinib. Patients who were replaced for evaluation of DLT were still to be included in the safety analysis set if they received at least 1 administration of entrectinib. No patients were replaced for evaluation of DLT.
• Efficacy: Patients who received at least 1 planned dose of entrectinib and who had measurable disease at baseline tumor assessment according to RECIST v1.1. Patients who experienced early discontinuation for any reason prior to the first planned tumor assessment were also included in the efficacy analysis set and were classified with the best response of not evaluable.
• PK: Patients who received at least 1 dose of entrectinib and had evaluable PK data.

Protocol Amendments

During the course the study, 6 protocol amendments were implemented. Substantial protocol and SAP amendments that were implemented are summarized below:

Original Protocol Version 1.0: (Date 25 Feb 2014)

Version No. 2.0: (Date 26 Mar 2014)
This version incorporates FDA comments related to patient safety. The main procedural change concerns the Phase 1 Dose Escalation Segment. The duration of Cycle 1 was changed to 6 weeks instead of 4 weeks. All subsequent cycles are 4 weeks.

Version No. 3.0: (Date 16 April 2014)
This version incorporates changes for clarification concerning study personnel, Phase 1-Cycle 1 timing, visit windows, dose modifications, concomitant medications, recording/reporting of adverse events, table footnotes, and study visit section headings.

Version No. 4.0: (Date 8 Oct 2014)
The requirement for patients to have tumors that harbor molecular alterations of TrkA/B/C, ROS1, or ALK has been removed for patients enrolling in the dose escalation segment of the study. An option has been introduced in the Phase 1 segment of the study to evaluate entrectinib when administered as a twice daily dosing regimen, in addition to the once daily dosing regimen included in Version 3.0 of the Protocol. Asymptomatic non-hematological laboratory changes (except renal and liver laboratory values) that can be successfully supplemented (i.e., hypokalemia) have been excluded from the definition of a DLT. The requirement has been removed for suspending dose escalation once systemic exposure is within 90% of that observed at the MTD dose level with the intermittent dose schedule evaluated in the FIH study. Patients with tumors expressing TrkB and TrkC with associated molecular alterations will be enrolled into separate expansion cohorts as opposed to being combined into one cohort. The criteria for enrollment into the 2 ALK cohorts has been changed from prior experience with 1 ALK inhibitor to ALK inhibitor-naïve and from prior experience with ≥ 2 ALK inhibitors to prior experience with ≥ 1 ALK inhibitors. Radiological tumor assessments are to be performed at the end of Cycle 1, then approximately 8 weeks thereafter (i.e., during each odd cycle). In Version 3.0, the tumor assessments were to be performed during each even cycle.

Version No. 5.0: (Date 23 Apr 2015)
The length of Cycle 1 in the Phase 1 segment was reduced from 42 days to 28 days for all patients. Phase 2a cohorts were modified to the below to support a signal-seeking, exploratory dose expansion cohorts:
• Cohort #1: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor an *NTRK1* rearrangement.

• Cohort #2: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor an *NTRK2* rearrangement.
• Cohort #3: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor an *NTRK3* rearrangement.
• Cohort #4: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding CRC, that harbor an *ALK* rearrangement. Patients with locally advanced or metastatic NSCLC will be excluded from this cohort, except in countries where patients do not have access to approved ALK inhibitors for the treatment of NSCLC.
• Cohort #5: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor a *ROS1* rearrangement.
• Cohort #6: Approximately 50 patients with locally advanced or metastatic solid tumors that express TrkA, TrkB, TrkC, ROS1, or ALK with an associated non-fusion, molecular alteration to one of the genes encoding these proteins, which include *NTRK1* (encoding TrkA), *NTRK2* (encoding TrkB), *NTRK3* (encoding TrkC), *ROS1* (encoding ROS1), *ALK* (encoding ALK), *NGF* (encoding NGF), *BDNF* (encoding BDNF), *NTF3* (encoding NT-3), *NTF4* (encoding NT- 4), and *NGFR* (encoding p75).
Thus, the total sample size was increased from N=120 to 150, efficacy endpoints were modified, along with statistical considerations, which was reviewed by the agency and adequate.

Version No. 6.0: (Date 26 Aug 2016)
Due to new nonclinical findings of ocular toxicities, eye exams including at least the visual acuity and slit-lamp tests to monitor for corneal-related visual disturbances during treatment with entrectinib, at Screening, on study, at the End of Treatment, and as clinically indicated to monitor for potential corneal related-visual disturbances.
Added retrospective BICR of tumor scans.

Data Quality and Integrity: Sponsor's Assurance

According to the CSR Section 9.6 submitted to Module 5.3.5.2 RXDX-101-01 “Legacy Clinical Study Report” under Part A “All data quality assurance steps described were used for the dose escalation segment of the study. These same steps will be followed for the dose expansion segment and described in a subsequent CSR when the segment is complete. By signing the protocol, the investigator granted permission to personnel from Ignyta or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.”

Upon further clarifications from Genentech in response to FDA’s IRs, the reviewer was able to:
- Reproduce Genentech’s analysis dataset and analysis results from legacy dataset
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA’s major efficacy analyses

Compliance with Good Clinical Practices

Within the text of the protocol was the statement: "The Investigator agrees that the study will be conducted according to the protocol, the US Code of Federal Regulations (CFR), Good Clinical Practice (GCP) (E6) and the ethical principles that have their origin in the Declaration of Helsinki and the ICH guidelines. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities."

Financial Disclosure

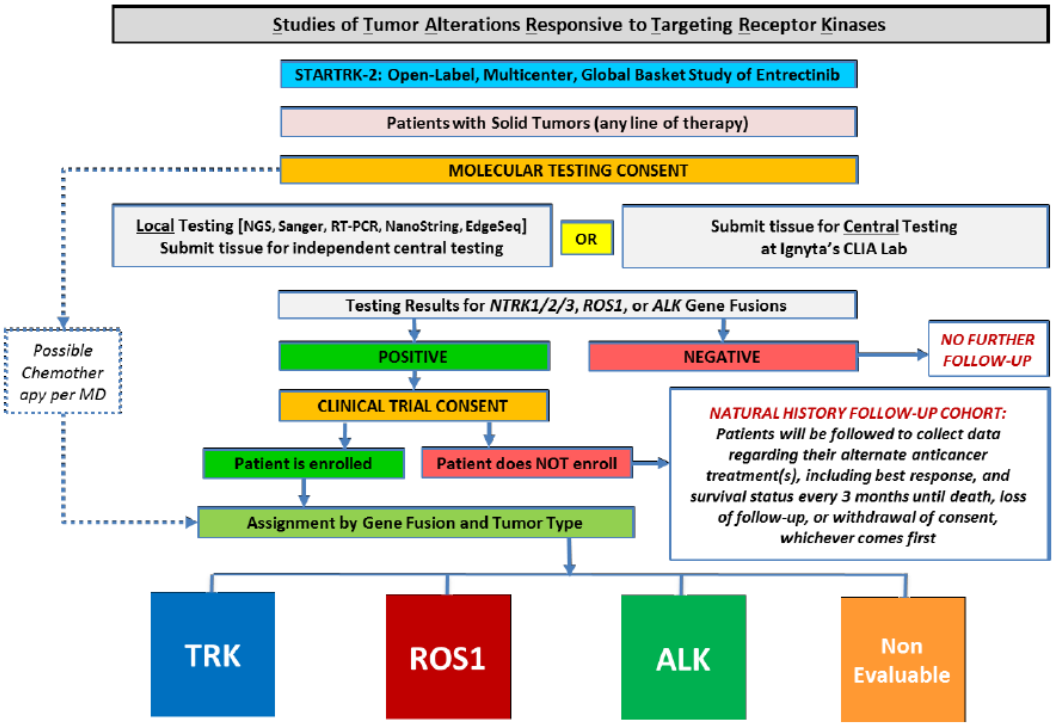
Study STARTRK-1 (RXDX-101-01, GO40784) entitled, "A Phase 1, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients with Locally Advanced or Metastatic Cancer Confirmed to be Positive for *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, or *ALK* Molecular Alterations" was conducted in South Korea, Spain, and the United States and was submitted to IND 120500. See Section 19.2 for full discussion of financial disclosure.

19.6.3. RXDX-101-02/STARTRK-02

Trial Design

STARTRK-02, entitled "An Open-Label, Multicenter, Global Phase II Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements," is an antitumor, global, open-label, multicenter, basket study in adult patients with advanced or metastatic solid tumors that harbor an NTRK1/2/3, *ROS1*, or *ALK* gene fusion. *NTRK1*, *2*, and *3* gene fusions were treated as a combined *NTRK*1/2/3 gene fusion basket. Figure 30 provides the schematics of study design. The primary objective of the study was to determine the ORR of entrectinib, as assessed by BICR, in each patient population basket of solid tumors. The secondary objectives include determining DOR as assessed by BICR in each patient population basket. The patients enrolled into baskets of *NTRK* fusion-positive solid tumors and *ROS1*-positive NSCLC had a data cut off of 31 May 2018. The study and patient enrollment are ongoing as of this date.

Figure 30: STARTRK-2 Basket Study Schema



Source: protocol submitted to NDA module 5.3.5.2

Key eligibility criteria

- Histologically- or cytologically-confirmed diagnosis of locally advanced or metastatic solid tumor that harbors an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement that is predicted to translate into a fusion protein with a functional TrkA/B/C, ROS1, or ALK kinase domain, respectively, without a concomitant second oncodriver (e.g., EGFR, KRAS) as determined by Ignyta's CAP/CLIA laboratory or by any nucleic acid-based diagnostic testing method performed at a local CLIA-certified or equivalently-accredited diagnostic laboratory.
- Measurable disease as assessed locally using RECIST v1.1.
- Patients with CNS involvement, including leptomeningeal carcinomatosis, which is either asymptomatic or previously-treated and controlled, are allowed.
- Prior anticancer therapy is allowed (excluding approved or investigational Trk, ROS1, or ALK (non-NSCLC patients only) inhibitors
- Prior radiotherapy is allowed if more than 14 days have elapsed since the end of treatment. Patients who received brain irradiation must have completed whole brain radiotherapy at least 14 days prior and/or stereotactic radiosurgery at least 7 days prior to the start of entrectinib treatment.
- Age ≥ 18, ECOG 0-2.
- Peripheral neuropathy Grade ≥ 2.
- History of non-pharmacologically induced prolonged QTc interval

Study Endpoints

Primary Endpoint:

To determine the ORR of entrectinib, as assessed by BICR, in each patient population basket of solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement

Secondary Endpoints:

- To determine the DOR, time to response (TTR), and clinical benefit rate (CBR) of entrectinib, as assessed by BICR, in each patient population basket of solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement
- To determine the intracranial tumor response of entrectinib and CNS progression-free survival (CNS-PFS) in patients presenting with measurable CNS disease at baseline, as assessed by BICR using RANO or RANO-BM, as applicable
- To estimate the PFS and OS of patients with solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement treated with entrectinib
- To evaluate the safety and tolerability of entrectinib when administered at the RP2D in patients with solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement
- To assess the population PK of entrectinib and to explore correlations between PK, response, and/or safety findings in patients with *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangements
- To evaluate the effect of entrectinib on ventricular repolarization
- To assess treatment-related symptoms and general health status using validated instruments of patient reported outcomes

Dose Modification and Management Algorithms

If toxicities that are possibly related to entrectinib are not easily managed or corrected, and are not tolerable to the patient, or if there are AEs that are not acceptable in the Investigator's judgment, the patient should have study treatment interrupted until the AE resolves to Grade ≤ 1. If study treatment is interrupted, dose reduction (if mandated) should occur when study treatment is resumed. All dose reductions should be based on the most severe toxicity observed that is attributable to entrectinib. If needed, dose reductions may occur in decrements of 200 mg and no more than 2 dose reductions will be allowed; therefore, the possible daily doses of entrectinib are listed in Figure 31:

Figure 31: Schema of Dose Reduction for Toxicity

Dose Level	Dose (mg QD)
RP2D	600
- 1	400
-2	200

Copied from protocol submitted to NDA Module 5.3.5.2

Entrectinib treatment may be interrupted for a maximum of 28 days to allow sufficient recovery from any toxicity if the patient is still deriving clinical benefit in the judgment of the Investigator.

For patients with CNS disease who have been on study for at least 2 cycles of treatment (i.e., 8 weeks) with a best response of SD per RECIST v1.1 and without treatment-related Grade ≥ 2 adverse events, dose escalation to 800 mg daily will be allowed as per Investigator's discretion after discussion with the Sponsor.

Dose modifications for toxicities are described in Figure 32.

Figure 32: Dose Modifications for Entrectinib-Related Adverse Events

Toxicity*	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at same dose level	Continue at same dose level For prolonged or intolerable CNS toxicity, withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment; or discontinue treatment as per the Investigator's discretion
Hematologic	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then resume treatment at the same dose level or reduce by 1 dose level as per the Investigator's discretion Grade 3 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then reduce the dose by 1 dose level and resume treatment Grade 4 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption
Prolonged QTc	Continue at same dose level	Interrupt entrectinib until recovery to baseline Assess and correct electrolytes and concomitant medications Continue at same dose level	Interrupt entrectinib until recovery to baseline Assess and correct electrolytes and concomitant medications. Reduce dose by 1 dose level and resume treatment. If an alternative cause for QTc prolongation is found and corrected, resume at same dose level	Discontinue treatment permanently
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Withhold dose until toxicity is Grade 0, then resume treatment at same dose Discontinue treatment permanently if pneumonitis recurs	Withhold dose until toxicity is Grade 0, then resume treatment at same dose Discontinue treatment permanently if pneumonitis recurs	Discontinue treatment permanently	Discontinue treatment permanently

*dose modifications to be based on worst toxicity grade as per NCI CTCAE v4.0

Copied from protocol submitted to NDA Module 5.3.5.2

Monitoring Plan:

Figure 33: Schedule of Assessments

	Screening [a]	Cycle 1		Cycles 2-3 (+/- 2d)		Cycle 4+ (+/- 2d)	End of Treatment [c]	Safety Follow-Up [d]	Survival Follow-Up
Treatment Day	-30 to -1	1 [a]	15	1	15 [b]	1	~ 7 days after last dose	~ 30 days after last dose	~ Every 3 months
Baseline Assessments									
Molecular testing informed consent [1]	No time limit								
Tumor biopsy [2]	(X)						(X)		
Clinical trial informed consent [3]	X								
Eligibility assessment [3]	X								
Physical examination [4]	X	(X)	X	X	(X)	X	(X)	(X)	
Eye exam [5]	X			C2			(X)		
Serum pregnancy test [6]	X			X		X	(X)		
Laboratory Studies									
US: Triplicate ECGs [7]	X	X		X		X	(X)		
JPN: Triplicate ECGs [8]	X	X		X		X	(X)		
ROW: Single ECG [9]	X	X		X		X	(X)		
Clinical laboratory assessments [10]	X	(X)	X	X	(X)	X	(X)	(X)	
Coagulation and lipid panel [10]	X								
PK samples [11]		X		X		X	(X)		
a. **JPN**: PK Sub-Study [12]		X		X		X	(X)		
PD samples [13]		X		X		X	(X)		
Tumor Markers [14]	X	(X)		X		X	(X)		
Imaging Assessments (+/- 7 days) [15]									
CT/MRI brain	X			(C2)		(q8w)	(X)		(q8w)
CT/MRI chest, abdomen, (pelvis)	X			C2		q8w	(X)		(q8w)
Bone scan	(X)			(C2)		(q8w)	(X)		(q8w)
Other Clinical Assessments									
ECOG, body weight, and vital signs [16]	X	(X)	X	X	(X)	X	(X)	(X)	
Adverse events and conmeds [17]	X	X	X	X	(X)	X	(X)	X	
Entrectinib compliance assessment			X	X	(X)	X	(X)		
Entrectinib dispensing and dosing [18]		X		X		X			
Post-study survival status [19]									X
Patient Reported Outcomes									
Quality of life questionnaires [20]		X		X		X	(X)		

Footnotes

(X) = optional or as applicable

1. **Molecular Testing Informed Consent:** Pre-study participation consent to detect *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangements (test performed at Ignyta's CAP/CLIA laboratory in San Diego, California, USA, or alternatively, local testing using any nucleic acid-based diagnostic testing method that relies on direct assessment of gene rearrangements and is performed at a CLIA-certified or equivalently-accredited diagnostic laboratory will be accepted) in order to determine eligibility to proceed to the clinical trial consent process. Local or central determination of gene rearrangements to determine eligibility can be performed in advance with no time limit, and molecular testing does not trigger the Screening window. For patients enrolled via local molecular testing, submission of patient tumor sample (archival or fresh tissue, unless medically contraindicated) is required for independent central molecular testing at Ignyta's CAP/CLIA laboratory.
2. **Tumor Biopsy:** Biopsies may be performed during Screening for patients who enrolled via local molecular testing but do not have enough leftover tumor tissue to submit to Ignyta. Also, if clinically feasible and patient has consented to the biopsy, additional tissue at the time of progression will be collected to gain insights into potential mechanisms of resistance.
3. **Clinical Trial Informed Consent and Eligibility Assessment:** Following central determination of an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement, patients can proceed to consent to the main study and perform Screening assessments, including a thorough review of their prior medical and oncologic history.
4. **Physical Examination:** During Screening, a complete physical examination of major body systems, including known and suspected sites of disease, should be performed. During subsequent visits, abbreviated physical exams will be sufficient.
5. **Eye exam:** Ophthalmologic exams including at least the visual acuity and slit-lamp tests (which may be performed by an optometrist) will be required at Screening, Cycle 2 Day 1, at the End of Treatment, and as clinically indicated.
6. **Serum Pregnancy Test:** To be performed in all female patients of child-bearing potential during Screening, Day 1 of every cycle, at the End of Treatment, and as clinically indicated.
7. **ECG (US):** Three consecutive 12-lead ECGs performed approximately 2 minutes apart will be collected during Screening, on Days 1 of Cycles 1-3 pre-dose and 4 hours (+/- 15 minutes) post-dose, only pre-dose on Days 1 of each treatment cycle thereafter, at the End of Treatment, and as clinically indicated.
8. **ECG (JPN):** In the same patients participating in the JPN PK Sub-Study[12], three consecutive 12-lead ECGs performed approximately 2 minutes apart will be collected during Screening, on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 pre-dose and 4 hours (+/- 15 minutes) post-dose coinciding with the PK samples; thereafter, triplicate ECGs need to be collected only pre-dose on Days 1 of each treatment cycle, at the End of Treatment, and as clinically indicated.

   After the required number of patients have been enrolled in the Japan PK Sub-Study, all subsequent newly enrolled patients will only require triplicate ECGs performed approximately 2 minutes apart during Screening, pre-dose on Days 1 of each treatment cycle, at the End of Treatment, and as clinically indicated. The Sponsor will communicate appropriately when the Japan PK Sub-Study is completed.
9. **ECG (ROW):** A single 12-lead ECG should be performed during Screening, on Days 1 of Cycles 1-3 pre-dose and 4 hours (+/- 15 minutes) post-dose, only pre-dose on Days 1 of each treatment cycle, at the End of Treatment, and as clinically indicated.
10. **Clinical laboratory Assessments:** Hematology, biochemistry, and urinalysis assessments will be performed during Screening, on Days 1 and 15 of Cycle 1, Day 1 of each subsequent treatment cycle thereafter, at the End of Treatment, and as clinically indicated.

    Standard coagulation and lipid panels will be required at Screening and as clinically indicated on-study.

    All laboratory assessments will be performed locally at each institution.
11. **PK Samples:** Blood samples for determination of population PK will be collected pre-dose on Day 1 of each treatment cycle and at the End of Treatment. Additionally, if clinically feasible, a PK sample should be obtained at the time of any serious and/or unusual adverse events that may be causally related to the study drug.

	US: After each set of triplicate ECGs collected on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1, an additional PK blood sample will be collected at 4 hours (+/- 15 minutes) post-dose to match the time of the post-dose ECGs. **ROW:** After each set of ECGs are collected on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1, an additional PK blood sample will be collected at 4 hours (+/- 15 minutes) post-dose to match the time of the post-dose ECGs
12.	**Japan PK Sub-Study:** In at least 6 patients (3 male, 3 female), blood samples will be collected at 0 (pre-dose), 0.5, 1, 2 hours (+/- 5 minutes), 4 (**prior to blood sample collection, record triplicate 12-lead ECGs approximately 2 minutes apart**), 6, 8 hours (+/- 15 minutes), and 24 hours (+/- 1 hour) post-dose on Cycle 1 Day 1 and on Cycle 2 Day 1. At Cycle 3 Day 1, an additional PK blood sample will be collected at 4 hours (+/- 15 minutes) post-dose to match the time of the post-dose ECGs. Thereafter, starting with Cycle 4, only pre-dose samples will be collected on Day 1 of each subsequent treatment cycle and at the End of Treatment. **After the required number of patients have been enrolled in the Japan PK Sub-Study, all subsequent newly enrolled patients** will only require pre-dose PK samples on Day 1 of each treatment cycle and at the End of Treatment. The Sponsor will communicate appropriately when the Japan PK Sub-Study is completed.
13.	**PD Samples:** Blood and urine samples for exploratory biomarker analyses will be collected along with the clinical laboratory samples on Day 1 of each treatment cycle and at the End of Treatment.
14.	**Tumor Markers:** Blood and urine samples should be collected as per Standard of Care (SOC) for each patient's particular tumor type and recorded in the eCRF at Screening, on Day 1 of each treatment cycle, at the End of Treatment, and as clinically indicated.
15.	**Imaging Assessments:** CT or MRI of the brain, chest, abdomen, +/- pelvis (depending on tumor type), as well as a bone scan* (if applicable) should be performed during Screening according to the standard of care for each particular tumor type, e.g., for NSCLC patients, only CT or MRI scans of the brain, chest and abdomen are expected. * Sodium fluoride (NaF) PET scan may also be performed; FDG PET or PET/CT can be used in NSCLC patients and other patients with PET-avid tumors, but the CT potion of a PET/CT may not be used in lieu of a diagnostic CT, unless it is performed with IV contrast. Please consult with the Imaging Manual for further details on required scans per tumor type. On treatment scans are to be performed at the end of Cycle 1 (Cycle 2 Day 1 +/- 2 days), then approximately every 8 weeks thereafter (+/- 7-days) and at End of Treatment (if more than 4 weeks have passed since the last imaging assessment). Tumor assessments may also be performed outside of the protocol-defined time points at the discretion of the Investigator. Patients with responding tumors (CR or PR) must have response confirmed at least 4 weeks after the first documentation of response. All anatomical areas that were scanned during Screening should be assessed at every on-study time point using the same imaging modality in order to determine tumor response as per RECIST v1.1. In addition to submitting all scans for BICR within 1 week of collection, local assessment of tumor response should also be performed by the Investigator.
16.	**Vital Signs:** Blood pressure and pulse can be assessed either in the supine or seated position. Body weight should be collected at every clinic visit, while height is only required at Screening.
17.	**Adverse Events and Concomitant Medications/Treatments:** Patients must be followed for adverse events from the first day of study treatment until at least 30 days after the last dose of study drug, or until all serious or study drug-related toxicities have resolved or are deemed "chronic" or "stable", whichever is later. Only serious adverse events related to study procedures need to be reported from the time of the main informed consent. Concomitant medications and concurrent treatments should be documented at Screening and at every clinic visit.
18.	**Entrectinib Dispensing and Dosing:** Entrectinib bottles will be dispensed at the start of each new cycle of treatment. Entrectinib will be self-administered orally at home (except on clinic days), on a continuous daily dosing regimen at a dose of 600 mg per day (three 200-mg capsules per day). On Day 1 clinic visit days, entrectinib should be taken at the clinic after all the pre-dose assessments have been conducted, at the direction of the study research nurse. On Day 15 and other visits (e.g., imaging days), entrectinib should be taken at home according to the patient's daily routine.

19.	**Post-Study Survival Status:** Patients discontinuing study treatment due to documented radiographic progression will enter the survival follow-up period, where survival status and subsequent anticancer therapy information (including best response) will be collected every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first. Survival can be collected via telephone call or medical chart review. Patients discontinuing study treatment prior to documented radiographic progression will also enter the survival follow-up period, where they will continue to have schedule disease assessments approximately every 8 weeks until documentation of radiographic progression, the start of a subsequent anticancer therapy, or decision to no longer treat (e.g., supportive care), whichever is first. At that time, survival status (and subsequent anticancer therapy information, including best response, if appropriate) will be collected every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first.
20.	**Patients Reported Outcomes:** All patients will complete the QLQ-C30 and EQ-5D quality of life questionnaires at the clinic **PRIOR to any other clinical activity** on Cycle 1 Day 1, Day 1 of each subsequent treatment cycle thereafter, and at the End of Treatment. **NSCLC** and **mCRC** patients enrolled across all baskets will also complete the lung cancer and colorectal cancer specific modules, QLQ-LC13 and QLQ-CR29, respectively, along with the other 2 questionnaires.
a.	**Cycle 1 Day 1 Assessments:** Assessments in parenthesis (X) do not need to be completed if they have been performed during the Screening period within the past 7 days.
b.	**Day 15 Assessments:** These safety visits will be performed during Cycles 1-3 and are optional at Cycles 2 and 3 as per Investigator's discretion. Starting at Cycle 4, patients will be seen in the clinic once a month, at the start of each new cycle of treatment.
c.	**End of Treatment Assessments:** Assessments in parenthesis (X) do not need to be completed if they have been performed within the past 7 days (within the last 2 weeks for patient reported outcomes and 4 weeks for tumor assessments, respectively).
d.	**Safety Follow-Up:** Patients should be evaluated in clinic approximately 30 days after the last dose of study drug. Physical examination (including ECOG and vitals) and clinical laboratory assessments should be performed as clinically indicated. Adverse events should be followed until all serious or study drug-related toxicities have resolved or are deemed "chronic" or "stable", whichever is later.
e.	**Screening Assessments:** Assessments that have been performed as part of standard of care, **prior to obtaining informed consent AND** that are within the past 7 days of Screening **AND** within 30 days of the first dose of study drug, may be used for Screening and do not have to be repeated.

Source:Protocol submitted to NDA Module 5.3.5.2

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Seizure prophylaxis with non-enzyme-inducing anti-epileptic drugs (non-EIAEDs) is allowed during the study for patients with controlled asymptomatic CNS involvement. Treatment with antidiarrheal drugs was outlined by Grade in the protocol. Prophylactic use of G-CSF or initiation of erythropoietin may be instituted according to the American Society of Clinical Oncology guidelines in patients who are having difficulty with severe neutropenia or anemia.

For treatment compliance, see Section 8.2 for pooled data from all registration studies.

Adverse Event Collection
An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a medicinal product, regardless of causal attribution. An AE can therefore be any of the following:

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition),
Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)
Assessment of adverse events will include type, incidence, severity (graded by the NCI CTCAE, v4.0), timing, seriousness, and relatedness. Adverse events will be assessed at every clinic visit.

Sample Size Considerations

For the basket of *ROS1* fusion-positive patients, up to 62 patients would be enrolled to Part A. with 90 additional patients treated at the RP2D to Part B, this would provide at least 80% power to rule out a BICR-assessed ORR of <=50% (null) when the true ORR is at least 65% at significance level of 0.025 (one-sided).

Analysis Sets

Each basket cohort of patients would be treated as its own separate patient population with the following definitions:

- Natural History Follow-Up Cohort: All gene rearrangement positive patients who were screened and were not enrolled into the study
- Safety Analysis Population [SA]: All eligible patients who enroll into a defined basket and have received at least one dose of entrectinib would be the primary population for evaluating patient characteristics, treatment administration, and safety endpoints for each particular basket
- Efficacy Analysis Population [EA]: The response-evaluable patient population was defined as all patients in the SA who had measurable disease at baseline per investigator. The EA population would be used for the primary efficacy analyses

- CNS Response Population [CRP]: CNS response population would be defined as all patients in the EA who had measurable CNS disease at baseline
- Patient Report Outcomes Population [PRO]: All patients in the SA who completed the QLQ-C30 and EQ-5D questionnaires on Cycle 1 Day 1 and answered at least one question on an on-study time point thereafter
    - For NSCLC or mCRC baskets, the PRO population would include all NSCLC or mCRC patients who also completed the QLQ-LC13 or QLQ-CR29 questionnaires, respectively, on Cycle 1 Day 1 and answered at least one question on an on-study time point thereafter, in addition to the QLQ-C30 and EQ-5D questionnaires as described above
- Population Pharmacokinetics Populations [POP-PK]: All patients in the SA who have at least one PK sample collected during the study

Protocol Amendments

Original Protocol Version 1: (Date 30 July 2015)

Version 2: (Date 2 Nov 2015)

- Allow local molecular testing for enrollment into the study
- Allow patients with non-measurable disease (evaluable disease only) to also be enrolled into the study, to contribute to safety and pharmacokinetics (PK); this basket will not be assessed for the primary endpoint.
- Revise other inclusion and exclusion criteria to maximize enrollment of these rare patient
- Including blood cell count restrictions removed as there were not hematologic toxicities at that point, and bilirubin and creatinine clearance thresholds were increased as entrectinib had not been shown to affect hepatic or renal function.
- Add post-dose ECGs and time-matched post-dose PK samples for patients enrolled outside the US and Japan
- Add precautionary language on the concomitant use of acid-reducing agents
- For the master Clinical Trial Informed Consent Form (version 03 August 2015), additional information was provided with regards to alternative treatments for NSCLC patients in the "What other choices…" section

Version 3: (Date 9 Sept 2016)

- Due to new nonclinical findings of embryo-fetal and ocular toxicities, the amendment and Dear Investigator letter included a reinforcement of the existing pregnancy restrictions and contraceptive precautions with additional mandatory monthly serum pregnancy tests in all female patients of childbearing potential, and to add ophthalmologic exams (Screening, Cycle 2 Day 1, at the End of Treatment, and as clinically indicated), including at least the visual acuity and slit-lamp tests to monitor for corneal-related visual disturbances during treatment with entrectinib.

- Appendix 1 (Molecular Testing) was updated based on the FDA/CDRH approval of the Ignyta Trailblaze Pharos™ assay as an investigational device for use in STARTRK-2 under IDE G160133. With this approval, the Ignyta *NTRK1/2/3*, *ROS1*, *ALK* Gene Rearrangements Assay was changed from a 2-step test using immunohistochemistry (IHC) followed by next generation sequencing (NGS) to just one step using NGS. All references to the 2-step test were changed accordingly throughout the protocol.
- In an effort to maximize the enrollment of these rare patients, the "non-measurable disease" basket was renamed "non-evaluable for the primary endpoint" basket, to allow for the protocol eligibility criteria, e.g., ECOG performance status > 2, dual primary cancers where one cancer's mutation status is unknown, or dual oncogenic drivers, e.g., *ALK* fusion and *EGFR* mutation. Patients with non-measurable disease will continue to be enrolled to this basket.
- Recognizing that CNS metastases are common in many solid tumors and that recent data with tyrosine-kinase inhibitors suggest that dose intensification may be necessary to overcome incomplete target inhibition in the CNS, intra-patient dose escalation in patients with CNS disease who have been on study for at least 2 cycles of treatment with a best response of Stable Disease (SD) per RECIST v1.1 AND without treatment-related Grade ≥ 2 adverse events will be allowed as per Investigator's discretion after discussion with the Sponsor.
- To efficiently assess whether entrectinib has anticancer activity in other (non-NSCLC and non-mCRC) solid tumors, the statistical analysis methodology for all evaluable baskets (NSCLC, including CNS-only progression post crizotinib, mCRC, other solid tumors) was harmonized to one single statistical design based on a 2-stage sequential testing design. While the original statistical assumptions for the main baskets (a true response rate of 20% or less is considered insufficient to warrant further study, whereas a true response rate of 40% or more is considered worthy of further study) were preserved, the number of patients evaluated in each stage and the minimum number of responders needed to meet the primary endpoint were re-calculated based on a sequential testing technique with at least 80% power and 1-sided alpha=0.025.

Version 4: (Date 3 Aug 2017)
The protocol was revised to expand the *ROS1* fusion-positive, ROS1 inhibitor-naïve NSCLC basket size to include an additional 90 patients by adjusting the statistical assumptions for this patient population relative to crizotinib.

Data Quality and Integrity

Section 14.3 in the protocol states, "After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented."

Upon further clarifications from Genentech in response to FDA's IRs, the reviewer was able to:

- Reproduce Genentech's analysis dataset and analysis results from legacy dataset
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy analyses

Compliance with Good Clinical Practices

Section 15 of the protocol states, "This study will be conducted in accordance with the U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

Financial Disclosure

Study STARTRK-2 (RXDX-101-02, GO40782) entitled, "An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements" was conducted in Australia, Hong Kong, Japan, Singapore, South Korea, Taiwan, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Switzerland, United Kingdom, and the United States and was submitted to IND 120500 and IND 135124. A signed financial disclosure form (FDF) was not obtained for 573 (31.8%) investigators in Study STARTRK-2, and 2 PIs that enrolled patients in the *NTRK* efficacy population. Many IRs were sent to the applicant and teleconferences to attempt to reconcile the FDFs or show due diligence. See Section 19.2 for full review of the pooled data regarding missing FDFs.

Of the investigators who responded, disclosable financial interests were recorded by 2 out of 1801 (<1%) of investigators in Study STARTRK-2, as in Table 64 below:

Table 64: Investigators With a Positive Financial Disclosure

Study Protocol	Roche Site Number	Ignyta Site Number	Number of Patients Enrolled at Site	Investigator Name	Investigator Type	Disclosure
STARTRK-2	(b) (6)				Principal Investigator	Payment received from Roche/GNE greater than $25,000 for speaking/ consultation fees
STARTRK-2					Sub-Investigator	(b) (6) is a Genentech employee and holds significant equity interests in Roche/GNE that exceeds $50,000

Source: Response to IR dated 7 June 2019

See Section 19.2 for full discussion of financial disclosure.

19.6.4. RXDX-101-03 / STARTRK-NG

Trial Design

STARTRK-NG, entitled "A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, with or without TRK, ROS1, or ALK Fusions" is a 5-part, multicenter, open-label dose escalation study in pediatric subjects with relapsed or refractory extracranial solid tumors (Phase 1; Part A), with expansion cohorts (Phase 1b) in subjects with primary brain tumors harboring NTRK1/2/3, *ROS1*, or *ALK* molecular alterations (Part B), neuroblastoma (Part C), and other non-neuroblastoma, extracranial solid tumors harboring *NTRK*1/2/3, *ROS1*, or *ALK* gene fusions (Part D). In addition, an exploratory cohort (Part E) will enroll subjects who are otherwise eligible but unable to swallow capsules.

<u>Dose escalation:</u>

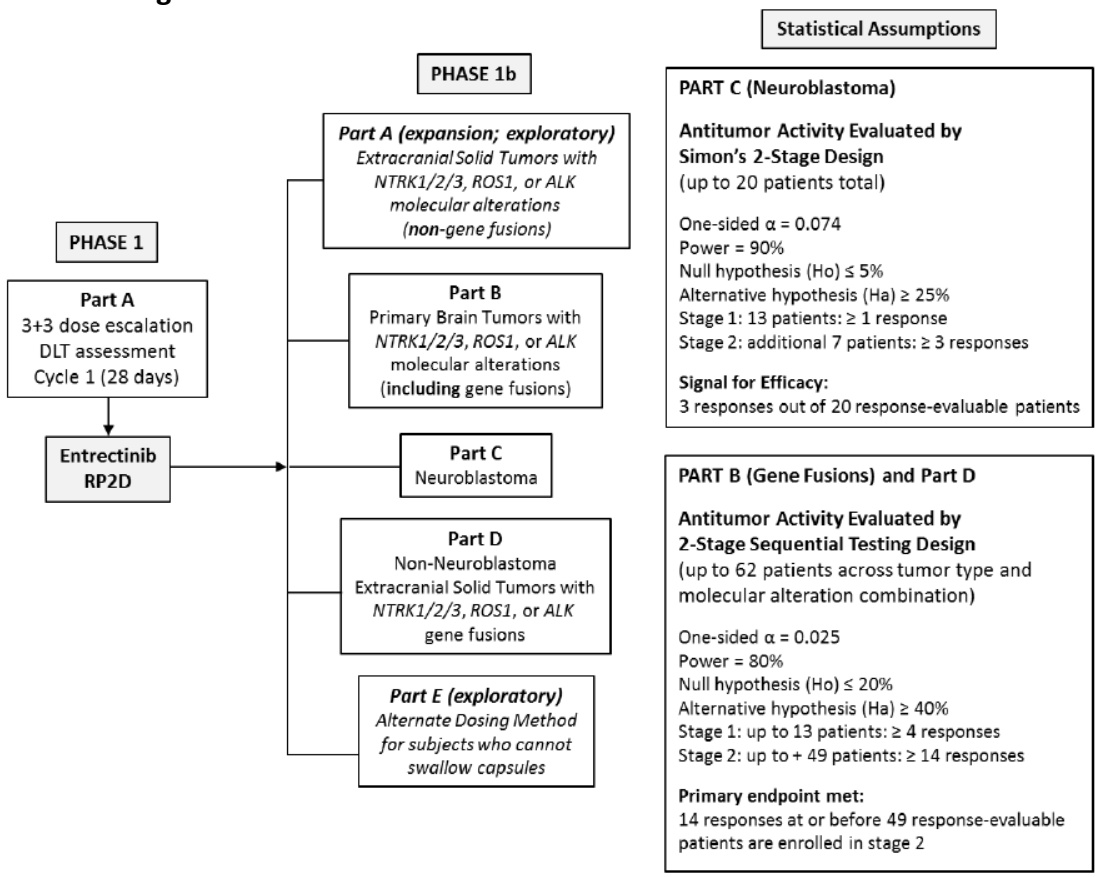
Entrectinib was administered orally with food, QD, in repeated 4-week cycles. The starting dose in Part A was 250 mg/m^2 on a continuous daily dosing regimen. Up to four dose levels were evaluated. A "3+3" patient enrollment scheme was followed during the dose escalation.

The RP2D was planned to be determined from DLT(s) derived from clinical and laboratory observations in the first treatment cycle (28 days). The MTD was defined as the dose level immediately below the dose level at which ≥ 2 patients from a cohort of 3 to 6 patients experienced a DLT. After MTD was established, based on the DLT assessment and an overall acceptable safety profile at the MTD, this dose was selected as the RP2D for evaluation in the Phase 1b portion of the study.

Dose expansion:

Phase 1b was designed to enroll additional patients with specific tumor types and molecular alterations. All patients in Phase 1b were planned to receive entrectinib at the pediatric RP2D, except for Part E, who were to initially receive entrectinib via alternative dosing methods at the -1 dose level de-escalation from the RP2D.

Figure 34. Design of STARTRK-NG



Copied from STARTRK-NG CSR Module 5.3.5.2

For DLT evaluation, toxicity will be graded according to the NCI CTCAE; Version 4.03. Peripheral motor and sensory neuropathy will be graded according to the pediatric specific grading criteria. The DLT evaluation period will start from the Cycle 1 Day 1 and end on Cycle 1 Day 28. Tumor assessments included magnetic resonance imaging (MRI) or computed tomography (CT) scans, metaiodobenzylguanidine (MIBG) scans, with/without bone marrow aspirates and biopsies. Tumor responses in patients were evaluated using RECIST version 1.1, Curie score, or RANO, depending on the tumor type.

Patients were allowed to continue entrectinib until clinical, laboratory or radiographic evidence of disease progression, development of unacceptable toxicity, or discontinuation at the discretion of subject/parent/guardian or Investigator.
The study is ongoing.

Key eligibility

- Children, adolescents, and young adult patients with relapsed or refractory extracranial solid tumors (Phase 1; Part A), with additional expansion parts (Phase 1b) in children, adolescents, and young adult patients with primary brain tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations (Part B), neuroblastoma (Part C), and other non-neuroblastoma, extracranial solid tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions (Part D).
- In addition, an exploratory cohort (Part E) enrolls patients who were otherwise eligible but unable to swallow capsules.
- Patients ≥2 years and <22 years of age were eligible for Part A through Part D, and patients from birth to <22 years of age were eligible for Part E.

Study Endpoints

Primary objective: to determine the MTD or RP2D of entrectinib in pediatric patients (children and adolescents) with relapsed or refractory solid tumors.

Secondary objectives:

1. To describe the safety profile of entrectinib as characterized by AE type, severity, timing and relationship to entrectinib treatment, as well as electrocardiogram (ECG) and laboratory abnormalities in the first and subsequent treatment cycles
2. To characterize the PK of entrectinib in plasma
3. To determine the ORR, DOR, TTR, CBR, and PFS in all enrolled patients (Parts A [expansion], C, and D) receiving entrectinib at the RP2D, using RECIST v1.1 and the Curie Scale, as applicable
4. To determine the intracranial tumor response, DOR, TTR, and CNS-progression free survival (CNS-PFS) in Parts B and D patients receiving entrectinib at the RP2D and presenting with measurable CNS primary or secondary disease at baseline, using RANO or RANO-BM, respectively.

Dose Modification and Management Algorithms

Up to 2 dose reductions due to treatment-related toxicity will be permitted in individual participants.
Definitions and dose modifications related to prolonged QTc were written into the protocol.

For dose-limiting somnolence or cognitive disturbance:
• If the toxicity resolves to Grade < 2 or baseline within 14 days (≤ 14 days) of drug discontinuation, the subject may resume treatment with a dose reduction
• If the toxicity does not resolve to Grade < 2 or baseline within 14 days of drug discontinuation, the subject must be removed from protocol therapy
For all other non-hematologic dose-limiting toxicity:
• If the toxicity resolves to Grade ≤ 2 or baseline within 14 days (≤ 14 days) of drug discontinuation, the subject may resume treatment with a dose reduction
• If the toxicity does not resolve to Grade ≤ 2 or baseline within 14 days of drug discontinuation, the subject must be removed from protocol therapy.
• Two dose modifications for toxicity are permitted. If DLT recurs or new DLT is observed after 2 dose reductions, the subject must be removed from protocol therapy. This includes subjects who have had their dose increased by intra-subject dose escalation.
• Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

Adverse Event Collection

Safety was evaluated on an ongoing basis through a list of assessments including monitoring of AEs per CTCAE v3, laboratory evaluations, vital signs, and performance status throughout the study. Other assessments including PK and molecular testing were performed.

Analysis Sets

- Enrolled Population: All patients enrolled in this study with a cut-off date of 31 Nov 2017
- Safety population: All enrolled patients who received at least one administration of entrectinib. The phase 1 dose escalation efficacy analysis was conducted using this safety population.
- DLT-Evaluable population: Patients who had received at least 75% of the prescribed dose during Cycle 1 (≥ 21 of 28 days) or experienced DLT at any time within 28 days after receiving the first dose or who discontinued study drug due to toxicity within 28 days after receiving the first dose. Patients who discontinued entrectinib treatment due to progressive disease or other reason not related to toxicity were replaced if they had not received 75% of the prescribed dose during Cycle 1.

Pharmacokinetic Evaluable Population: All patients who received any dose of entrectinib and who had at least one quantifiable post-baseline PK sample available.

Protocol Amendments

Original Submission: (Date: 5 Nov 2015)

Version 2: (Date: 18 Nov 2015)
Revised to clarify the dose modification criteria threshold to resume study drug treatment for DLTs, specifically, entrectinib-related DLTs of somnolence or cognitive disturbance.

- Somnolence and cognitive disturbance were added as exceptions to the rule for defining dose-limiting toxicities that are due to failure to recover to Grade ≤ 2 or baseline.
- The dose modification rules for dose-limiting toxicities were revised to point out specific rules for prolonged QTc, somnolence, and cognitive disturbance

Version 3: (Date: 30 Nov 2016)

- To expand the Phase 1b portion of the study beyond neuroblastoma, as a way to more efficiently assess whether entrectinib has anticancer activity in pediatric cancers which harbor TRK, ROS1, or ALK molecular alterations, especially gene fusions. Antitumor endpoints and statistical methods were added accordingly. In addition, retrospective blinded independent central review of tumor assessments will be performed for a select group of subjects, e.g., gene fusion-positive subjects and neuroblastoma responders.
- To move Part B (Primary Brain Tumors) to the Phase 1b portion of the study; all subjects enrolled in Part B will receive entrectinib at the RP2D determined in Part A without the need to confirm that dose in a mini dose escalation.
- A separate cohort (Part E) was created to accommodate subjects ages ≥ 2 years and < 22 years who are unable to swallow capsules and all subjects < 2 years who otherwise meet all other eligibility criteria for the other parts. Alternative dosing methods will be applied.
- Due to new nonclinical findings of embryo-fetal and ocular toxicities (Dear Investigator Letter, August 2016), the protocol was amended:
    - To reinforce the existing pregnancy restrictions and contraceptive precautions with at least 2 methods of contraception and to extend the restriction to at least 90 days following the last dose of study drug
    - To add ophthalmologic exams (i.e., visual acuity test), in the Schedule of Assessments (Screening, Cycle 2 Day 1, at the End of Treatment, and as clinically indicated) to monitor for corneal-related visual disturbances during treatment with entrectinib
- Planning for the upcoming introduction of a pediatric-specific formulation, additional collection of blood samples was added to better understand the pharmacokinetics of entrectinib in pediatric subjects receiving the current adult formulation (capsules) versus future formulation(s).

Version 4: (Date: 24 March 2017)

1. Amended to establish a PK bridge between intact capsules vs. capsule contents mixed with a small amount of food to ensure a safe starting dose in patients treated in Part E:
2. Since the effect of fat content and food volume on entrectinib administered using alternative dosing method (e.g., capsule content mixed with a small amount of food) is unknown, a meal with a standardized fat content and volume in Part E will be used

3. For patients who do not require seizure prophylaxis therapy with enzyme inducers, a table was added to counsel providers and patient savoid the co-administration of strong or moderate CYP3A inhibitors and inducers.

Data Quality and Integrity

Described in Section 13 of the protocols within the CSR submitted in Module 5.3.5.2.

Compliance with Good Clinical Practices

Per Section 3.4 of the protocols within the CSR submitted in Module 5.3.5.3, "This study was conducted in accordance with GCP, and investigators were trained according to applicable Sponsor SOPs."

Financial Disclosure

Study STARTRK-NG (RXDX-101-03, CO40778) entitled, "A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, with or without TRK, ROS1, or ALK Fusions" was conducted in the US and was submitted to IND 120500. A signed financial disclosure was not obtained for 34 (12%) investigators in Study CO40778 (STARTRK-NG). A positive FDF was received for the one investigator: (b) (6) had received payment from Roche/GNE greater than $25,000 in a calendar year for speaking fees. See Section 19.2 for full discussion of financial disclosure.

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/

KELIE M REECE
08/14/2019 11:55:08 PM

CLAIRE E MYERS
08/15/2019 08:49:07 AM

WHITNEY S HELMS on behalf of STEPHANIE L AUNGST
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YOUWEI N BI
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JIANG LIU
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YUCHING N YANG
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GUOXIANG SHEN
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HONG ZHAO
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I concur.

NAM ATIQUR RAHMAN
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I concur.

XIAOPING JIANG
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LISA R RODRIGUEZ
08/15/2019 09:54:53 AM

RAJESHWARI SRIDHARA
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PATRICIA KEEGAN
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NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212726
Priority or Standard	Priority
Submit Date(s)	December 18, 2018
Received Date(s)	December 18, 2018
PDUFA Goal Date	August 18, 2019
Division/Office	DOP2/OHOP
Review Completion Date	August 13, 2019
Established Name	Entrectinib
(Proposed) Trade Name	Rozlytrek
Pharmacologic Class	Kinase inhibitor
Code name	RO7102112; formerly known as RXDX-101 and NMS-1191372
Applicant	Genentech, Inc.
Formulation(s)	Capsule: 100 mg, 200 mg
Dosing Regimen	Adults: 600 mg orally once daily Pediatric patients 12 years and older: recommended dosage is body surface area (BSA) based as shown below: • BSA greater than 1.50 m^2: 600 mg orally once daily • BSA 1.11 to 1.50 m^2: 500 mg orally once daily • BSA 0.91 to 1.10 m^2: 400 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and adolescent patients with (b) (4) (b) (4) metastatic solid tumors that are neurotrophic tyrosine receptor kinase (*NTRK*) fusion-positive who have either progressed (b) (4) (b) (4). This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	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 is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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Reviewers of Multi-Disciplinary Review and Evaluation

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Pharmacometrics Reviewer	Youwei Bi, PhD
Pharmacometrics Team Leader	Jiang Liu, PhD
PBPK Reviewer	Xinyuan Zhang, PhD
PBPK Team Leader	Yuching Yang, PhD
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Clinical Pharmacology Team Leader	Hong Zhao, PhD
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Division Director (OHOP)	Patricia Keegan, MD
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Additional Reviewers of Application

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Other: Ophthalmology Consult (DTOP)	Wiley Chambers, MD
Other: Bone Consult (DBRUP)	Jacqueline Karp, MD/Theresa Kehoe, MD (TL)

DBRUP=Division of Bone, Reproductive and Urologic Products
DEPI=Division of Epidemiology I
DMEPA=Division of Medication Error Prevention and Analysis
DNDBE=Division of New Drug Bioequivalence Evaluation
DNP=Division of Neurologic Products
DPVII=Division of Pharmacovigilance II
DRISK=Division of Risk Management
OPE=Office of Pharmacovigilance and Epidemiology
OPDP=Office of Prescription Drug Promotion
OPQ=Office of Pharmaceutical Quality
OSE=Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
OSIS=Office of Study Integrity and Surveillance

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

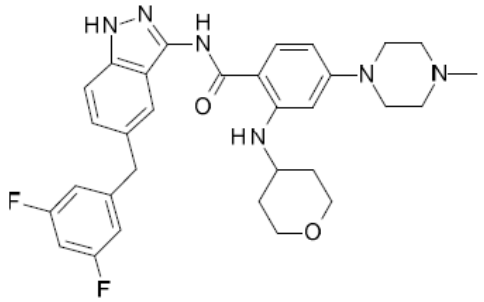
On December 18, 2018, Genentech Inc. (Genentech) submitted the original New Drug Application (NDA) 212726 under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) seeking approval of Rozlytrek (entrectinib) for the treatment of adult and pediatric patients with (b) (4) metastatic solid tumors harboring an *NTRK* gene fusion. On the same day, Genentech submitted original NDA 212725 seeking approval of entrectinib for the treatment of *ROS1*-positive metastatic non-small cell lung cancer (please see the separate multidisciplinary review for additional details regarding this application).

Entrectinib (RO7102112; also referred to as RXDX-101 and as NMS-1191372) is an 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). Gene rearrangements (fusions) in each of the genes encoding these target kinases have the potential to be oncogenic drivers, tend to be mutually exclusive, and have been observed at low incidence in a variety of tumor types. Entrectenib is being developed as an anticancer agent for the treatment of patients with tumors that harbor *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions.

The molecular formula for entrectinib is: $C_{31}H_{34}F_2N_6O_2$ and the molecular weight is 560.64 Daltons. The chemical name is N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzamide.

Entrectinib has the following chemical structure:

Figure 1: Organic Structure of Entrectinib



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Entrectinib is supplied as 100 mg and 200 mg capsules. The proposed dosage regimen for entrectinib is 600 mg orally daily for adults. The proposed dosage regimen for pediatric patients 12 years and older (adolescents) is body surface area (BSA)-based and is shown below:

- BSA greater than 1.50 m^2: 600 mg orally once daily
- BSA 1.11 to 1.50 m^2: 500 mg orally once daily
- BSA 0.91 to 1.10 m^2: 400 mg orally once daily.

Entrectinib is a new molecular entity and has not been previously marketed in the United States.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical, clinical pharmacology, nonclinical, and statistical review teams unanimously agree that the submitted evidence meets the statutory standards for approval under 21 CFR 314, Subpart H (accelerated approval) for the following indication:

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

- *have a neurotrophic receptor tyrosine 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 progressed following treatment or have no satisfactory alternative treatment.*

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

This approval recommendation is primarily based on pooled efficacy results from the first 54 adult patients with unresectable or metastatic solid tumors harboring an *NTRK* fusion enrolled across the following three-single arm trials:

- **Study ALKA-372-001** (GO40783), entitled, "A Phase 1, Dose Escalation Study of Entrectinib (RXDX-101) In Adult Patients with Advanced/ Metastatic Solid Tumors",
- **STARTRK-1**, entitled, "A Phase 1, Multicenter, Open-label Study of Oral Entrectinib (RXDX-101) in Adult Patients with Locally Advanced or Metastatic Cancer Confirmed to be Positive for *NTRK1, NTRK2, NTRK3*, *ROS1*, or *ALK* Molecular Alterations"
- **STARTRK-2**, entitled "An Open-Label, Multicenter, Global Phase II Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements".

The safety of entrectinib is supported by data from 338 adult patients, which includes the 54 patients supporting efficacy, treated with entrectinib for solid tumors with *NTRK* fusions or for other indications in the above trials and 30 pediatric patients with *NTRK* fusion-solid tumors treated with entrectinib in an additional trial, **STARTRK-NG**, entitled "A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, with or without *TRK, ROS1,* or *ALK* Fusions".

The effectiveness of entrectinib in adolescent patients 12 years of age and older was established based on extrapolation of data in adult patients with solid tumors harboring an *NTRK* gene fusion and pharmacokinetic (PK) data in adolescents enrolled in STARTRK-NG indicating that pharmacokinetic profiles in adult receiving a fixed 600 mg dose and in adolescent patients with BSA based dosage regimen were comparable. The review team determined that extrapolation of effectiveness to adolescent patients was appropriate given the totality of nonclinical and clinical evidence indicating that *NTRK* is the primary oncogenic driver across tissue histologies harboring *NTRK* fusions and the consistency of the treatment effect across multiple tumor histologies in adults. The safety of entrectinib in adolescent patients 12 years of age and older was established based on extrapolation of data in adults and data from the 30 pediatric patients enrolled in STARTRK-NG.

For pediatric patients less than 12 years, the clinical pharmacology review team determined that there was insufficient data available to determine the dose of entrectinib that can achieve comparable exposure to adults at the recommended dose of 600 mg daily. The safety and effectiveness of entrectinib in pediatric patients less than 12 years of age with solid tumors who have an *NTRK* gene fusion has not been established.

Entrectinib demonstrated a large and clinically meaningful overall response rate in patients with *NTRK* fusion-positive unresectable or metastatic solid tumors who had experienced disease progression following systemic therapy for their disease, if available, or who would have required surgery causing significant morbidity for locally advanced disease. These responses were also durable. In the first 54 patients with *NTRK* fusion-positive solid tumors enrolled in Study ALKA, Study STARTRK-1, and Study STARTRK-2, the estimated overall response rate (ORR) was 57% (95% confidence interval: 43%, 71%). At the time of data cutoff (May 31, 2018), the median duration of response (DOR) was not reached; among the 31 responding patients, 55% had a DOR of at least 6 months and 39% had a duration of response of at least 12 months. Based on an additional 5 months of follow-up from the time of primary analysis of ORR (updated data cutoff date: October 31, 2018), among the 31 responding patients, 68% had a DOR of at least 6 months and 45% had a duration of response of at least 12 months. Due to the small sample size, there is a degree of uncertainty regarding the magnitude of the treatment effect of entrectinib in any single histologic subtype of solid tumors with an activating *NTRK* fusion. Although the magnitude of the treatment effect is large and the effect appears durable, the estimated treatment effects are limited by the small number of patients

and limited follow-up that does not fully characterize durability of the observed responses; therefore, the review team determined that additional data are needed to further characterize the clinical benefit of entrectinib for the proposed indication. As a condition of approval, Genentech must conduct a postmarketing requirement (PMR) to conduct studies enrolling an adequate number of patients to verify and confirm the clinical benefit of entrectinib, particularly in histologic tumor types such as colon cancer and brain cancer for which the ORR is not well characterized. See Section 13 of this review for additional details regarding the PMR and post marketing commitments (PMC).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

It is estimated that approximately 1.7 million patients will be diagnosed with cancer and that over 600,000 people will die of cancer in the United States in 2018 [American Cancer Society Cancer Facts and Figures 2018]. Solid tumors with an activating neurotrophic receptor tyrosine kinase (*NTRK*) rearrangement are a heterogenous group of cancers. Although there is insufficient information to fully characterize the incidence of patients with solid tumors harboring an activating *NTRK* fusion, the annual incidence of *NTRK* fusion-driven tumors is estimated to be 1500-5000 cases in the United States (U.S.) [Kheder 2018]. Although either pathognomonic or common in some very rare cancers such as mammary analogue secretory carcinoma (MASC), secretory breast carcinoma (SBC), or infantile fibrosarcoma (IFS), the incidence of *NTRK* fusions is below 1% for most common cancers such as lung, prostate, and colon cancer. There are limited data regarding outcomes of patients with solid tumors with an *NTRK* fusions. Nevertheless, at least for the more common tumors that harbor *NTRK* fusions, compelling evidence does not exist that the presence of an *NTRK* fusion confers a favorable prognosis in the unresectable (b) (4) metastatic setting.

There is only one drug, larotrectinib, approved specifically for the treatment of patients with solid tumors harboring an *NTRK* fusion; when metastatic or unresectable, solid tumors are rarely curable and generally convey a poor prognosis. Although there are approved treatments for many common adult cancers that rarely have an *NTRK* fusion, such as lung, prostate, and colon cancer, this indication is limited to such patients who have progressed on approved treatments for adult solid tumors. Additionally, there are no approved treatments for mammary analogue secretory carcinoma, SBC, and IFS, which frequently harbor *NTRK* fusions. Moreover, 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).

The efficacy of entrectinib in adolescent and adult patients with *NTRK* fusion-positive solid tumors was demonstrated by the pooled results from the first 54 adult patients with unresectable or metastatic solid tumors with an *NTRK* gene fusion enrolled in one of three multicenter, open-label, single-arm clinical trials (Study ALKA-372-001 [GO40783], STARTRK-1, and STARTRK-2). All patients were required to have cancer that progressed following effective systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. Ninety-six percent of patients had metastatic disease and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic anti-neoplastic therapy. Of these, 63% (n = 34) received prior systemic therapy for metastatic disease, with a median of one prior systemic regimen and 17% (n = 9) received 3 or more prior systemic regimens. The most common cancers were sarcoma (24%), non-small cell lung cancer (19%), and salivary gland cancer (13%). A total

of 52 (96%) patients had an *NTRK* gene fusion detected by NGS and 2 (4%) had an *NTRK* gene fusion detected by other nucleic acid-based tests. Eighty-three percent of patients had central laboratory confirmation of *NTRK* gene fusion using an analytically validated NGS test.

Among these 54 patients, the overall response rate (ORR) was 57% (95% confidence interval: 43%, 71%), including 7% of patients with a complete response (CR) and 50% of patients with a partial response (PR) to entrectinib. Responses were durable. Among the 31 responding patients, 68% had a duration of response (DOR) of at least 6 months and 45% had a DOR of at least 12 months. At the time of the analysis, the median DOR had not been reached. The effectiveness of entrectinib in adolescent patients 12 years of age and older was established based on extrapolation of data in adult patients with solid tumors harboring an *NTRK* gene fusion and pharmacokinetic (PK) data in adolescents enrolled in STARTRK-NG indicating that pharmacokinetic profiles in adult and adolescent patients with BSA based dosage regimen were comparable. The review team determined that extrapolation of effectiveness to adolescent patients was appropriate given the totality of nonclinical and clinical evidence indicating that *NTRK* is the primary oncogenic driver across tissue histologies harboring *NTRK* fusions and the consistency of the treatment effect across multiple tumor histologies in adults.

Safety data supporting these applications reflected exposure to entrectinib in 355 patients, in which 48% of patients were exposed for greater than 6 months and 24% patients were exposed for greater than 12 months. The safety of entrectinib was evaluated in a pooled group of pediatric and adult patients enrolled in one of four multicenter, single-arm, open-label clinical trials: ALKA (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267), and STARTRK-NG (NCT02650401). All patients had an unresectable or metastatic solid tumor and no satisfactory alternative treatment options or disease progression following treatment. The population characteristics were: median age 55 years (range: 4 to 86 years); 5% (n = 17) were 18 years or younger; 55% were female; and 66% were White, 23% were Asian, and 5% were Black; 3% were Hispanic/Latino. The most common tumors (≥ 5%) were lung (56%), sarcoma (8%), and colon (5%). *ROS1* gene fusions were present in 42% and *NTRK* gene fusions were present in 20%. Most adults (75%) received entrectinib 600 mg orally daily. The dose ranged from 100 mg daily to 2600 mg daily in adults and 250 mg/m^2 to 750 mg/m^2 in pediatric patients.

Although assessment of a causal relationship between entrectinib and adverse events (AEs) was somewhat limited in the context of the single arm design of trials providing safety data, AEs observed in patients treated with entrectinib were consistent with the mechanism of action (multiple kinase inhibition) and toxicities observed in preclinical studies with entrectinib. The most common adverse reactions (≥ 20%) in order of decreasing frequency were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders. The most common laboratory abnormalities ((≥ 20%) worsening from baseline were increased creatinine, anemia, hyperuricemia, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), hypernatremia, hypocalcemia, hypophosphatemia, neutropenia, increased lipase, hypoalbuminemia, increased amylase, hyperkalemia, and increased alkaline phosphatase.

The primary serious risks of entrectinib are congestive heart failure (CHF), central nervous system (CNS) adverse reactions, skeletal fractures, hyperuricemia, hepatotoxicity, QT prolongation, and vision disorders. These adverse reactions largely appear manageable and reversible with dose modification or discontinuation of entrectinib and are adequately addressed in product labeling. Genentech has committed to post-marketing requirement (PMRs) for the conduct of additional studies to further characterize the risks of congestive heart failure and skeletal fractures with entrectinib and identify ways to mitigate these risks (See Section 13).

A broad spectrum of CNS adverse reactions can occur in patients receiving entrectinib, including impairment in cognitive function or mood, dizziness, and sleep disturbances. These CNS effects appear to be a class effect of TRK inhibitors and were observed in preclinical models.

Among the 355 patients (338 adult and 17 pediatric patients) who received entrectinib across clinical trials, congestive heart failure (CHF) occurred in 3.4% of patients, including Grade 3 (2.3%). In clinical trials, baseline cardiac function and routine cardiac monitoring other than electrocardiograms (ECGs) were not conducted and eligibility criteria excluded patients with symptomatic CHF, myocardial infarction, unstable angina, and coronary artery bypass graft within 3 months of study entry. Genentech is required to conduct a study as a postmarketing requirement to further assess the contribution of entrectenib to cardiac risk and characterize cardiac adverse reactions and risk mitigation strategies.

Entrectinib also increases the risk of skeletal fractures. In an expanded safety population (n=368) of 338 adult patients and 30 pediatric patients who received entrectinib across clinical trials, 5% of adult patients and 23% of pediatric patients experienced fractures. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients, all fractures occurred in patients with minimal or no trauma. Genentech was required to conduct a study as a postmarketing requirement to further assess the risk of fractures with entrectinib and identify ways to mitigate this risk.

Among 355 patients who received entrectinib across clinical trials, 32 patients (9%) experienced symptomatic hyperuricemia. Grade 4 hyperuricemia occurred in 1.7% of patients. Increased AST of any grade occurred in 42% of patients and increased ALT of any grade occurred in 36%. Grade 3 to 4 increased AST or ALT occurred in 2.5% and 2.8% of patients, respectively; the incidence may be underestimated as 4.5% of patients had no post-treatment liver function tests.

Among the 355 patients who received entrectinib across the clinical trials, 2.8% of patients with at least one post-baseline ECG assessment experienced QTc interval prolongation of >60 ms after starting entrectinib and 1.7% had a QTc interval >500 ms. In the QT substudy of STARTRK-2, of 113 patients receiving entrectinib 600 mg daily, there was no large increase in QTc change (i.e., 20 ms) from baseline. Based on QT-IRT review, the data did not support an exposure-response analysis because the exposure range was narrow and the PK/ECG sampling

schedule could not be used to evaluate possible PK/PD hysteresis. There is unclear significance of sporadic outliers in an uncontrolled study when the limited QT assessment does not support a large drug-effect. Due to the nature of single arm data, however, prolongation of QT could not be excluded; therefore, the package insert will include language in Warnings and Precautions that patients should be monitored who already have or who are at significant risk of developing QTc interval prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation.

Vision disorders can occur in patients receiving entrectinib. In preclinical studies in rats, microscopic findings of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium were and are considered entrectinib-related. There are no specific findings that suggested vision disturbances had a neurological etiology and vision disorders have been seen in other drugs that affect the ALK pathway, including crizotinib. The spectrum of visual impairment reported were blurred vision, photophobia, diplopia, visual impairment, photopsia, vitreous floaters, vitreous detachment, vitreous adhesions, blindness, corneal erosion, and retinal hemorrhage. The majority of vision disturbances were of low-grade severity and patients were able to continue entrectinib.

An additional risk related to the approval of this application involves the possibility that entrectinib could be ineffective for a specific tumor type despite the presence of an *NTRK* fusion due to de novo resistance mutations or the presence of other oncogenic mutations; however, based on the strong biologic rationale, preclinical data, and magnitude and consistency of response observed across multiple tumor types harboring a variety of *NTRK* fusion partners, this risk is expected to be low. This risk is acceptable because entrectinib is approved for the treatment of patients who have no satisfactory alternative treatment options or whose cancer has progressed following treatment; therefore, patients will not be forgoing effective therapies when treated with entrectinib. As a PMR, Genentech will conduct a study to obtain additional data to verify and confirm the clinical benefit of entrectinib through more precise estimation of ORR and response duration in a variety of tumor types (such as *NTRK*-fusion colorectal cancer, pediatric population, and CNS tumors) that are not well represented in the efficacy population supporting this application.

The safety and effectiveness of entrectinib in pediatric patients less than 12 years of age has not been established. As described above, the effectiveness of entrectinib in pediatric patients 12 years of age and older was established based on extrapolation of data in adult patients with solid tumors harboring an *NTRK* gene fusion and pharmacokinetic data in adolescents enrolled in STARTRK-NG. Entrectinib doses based on body surface area in pediatric patients 12 years and older resulted in comparable systemic exposure compared to that in adults who received an entrectinib dose of 600 mg. The safety of entrectinib in pediatric patients 12 years of age and older was established based on extrapolation of data in adults and data from the 30 pediatric patients who received entrectinib for the treatment of *NTRK*-fusion solid tumors in Study STRK-NG. Of these 30 patients, 7% were <2 years (n = 2), 77% were 2 to <12 years (n = 23), 17% were 12 to <18 years (n = 5); 57% had metastatic disease (n=17) and 44% had locally advanced disease (n=13); and all patients had received prior treatment for their cancer, including surgery,

radiotherapy, or systemic therapy. The most common cancers were neuroblastoma (47%), primary CNS tumors (30%), and sarcoma (10%). The median duration of exposure for all pediatric patients was 4.2 months (range: 0.2 to 22.7 months). Due to the small number of pediatric and adult patients, the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients compared to adult patients were neutropenia (27% vs 2%), bone fractures (23% vs 5%), thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma-glutamyl transferase (7% vs 0%), device-related infection (7% vs 0.3%), and increased weight (20% vs 7%). Three pediatric patients discontinued entrectinib due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis). In order to better characterize the safety of entrectinib in pediatric patients 12 years of age and older, some of whom may receive entrectinib for months to years, Genentech is required to conduct a study to assess whether entrectinib has adverse long-term effects on pediatric growth and development.

Overall, the toxicity profile of entrectinib is considered acceptable when balancing the anti-tumor effects (i.e., durable responses) across different cancer types in patients with limited or no effective treatment options. Physicians and patients will need to individually assess the risk-benefit profile of entrectinib to determine if treatment is appropriate for each patient. Consistent with other drugs intended for the treatment of patients with advanced cancer, risk will be managed through labeling. A Risk Evaluation and Mitigation Strategy (REMS) is not needed to ensure that the benefits of entrectinib outweigh its risks.

FDA generally considers ORR of a sufficient magnitude and duration to be a surrogate endpoint reasonably likely to predict clinical benefit in patients with refractory solid tumors. Although standard treatment regimens exist for most patients with unresectable locally advanced or metastatic solid tumors, such treatment generally is not curative and additional treatment is needed. In settings where no treatment is available or where available treatment would result in significant morbidity, based upon the response rate and durability of responses observed with entrectinib, an argument can clearly be made that treatment with entrectinib provides an advantage over available therapy for patients with *NTRK*-fusion solid tumors. Based upon the demonstrated durability of responses, such an argument could also be made in settings where the clinical effects of available therapy are modest. A review of the data in the NDA submitted by Genentech indicated that patients had received appropriate therapy prior to enrolling into entrectinib clinical trials; thus, the effects on ORR were demonstrated in the clinical setting for which the drug will be indicated.

The review team acknowledges that ORR and DOR may not fully capture the clinical benefit of entrectinib. In addition to partial shrinkage of tumors, some patients have experienced complete radiographic disappearance of their cancers. These patients, as long as tumor is

undetectable, would no longer be expected to be symptomatic (or become symptomatic) due to tumors affecting nerves or other vital organs. This would be important in patients that receive entrectenib instead of severely morbid surgeries such as limb amputation.

The risk-benefit assessment for entrectinib is favorable for the treatment of adult and adolescent patients with unresectable locally advanced or metastatic solid tumors with an activating *NTRK* rearrangement who have no satisfactory alternative treatment options or whose cancer has progressed following treatment. This patient population, with serious, life-threatening, and rare cancers, has a high unmet medical need. In this population, treatment with entrectinib resulted in a clinically meaningful ORR; moreover, responses are durable for 12 months or longer in 45% of responding patients. The major safety risks of entrectinib are toxicities that oncologists typically manage and are acceptable for a population with a serious and life-threatening condition in the context of the observed efficacy.

The tissue agnostic approach to drug approval is a new paradigm; prior to this approval, two drugs received accelerated approval for a tissue agnostic indication, pembrolizumab and larotrectinib. Pembrolizumab received accelerated approval for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (MMRD) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or for MSI-H colorectal cancer that has progressed following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. Larotrectinib received accelerated approval for the treatment of adult and pediatric patients with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment. This review had similar challenges to those encountered during the review of pembrolizumab and larotrectinib in that there were limited numbers of patients comprising the efficacy population (N=55 in larotrectinib and N=54 for entrectinib) who were sequentially enrolled on multiple single arm trials; however, unlike pembrolizumab, the safety population supporting the NDAs for larotrectinib and entrectenib is relatively small (N=176 and N=355, respectively) due to the rarity of *NTRK*-fusion solid tumors and because both larotrectinib and entrectinib are new molecular entities (NME) with no prior approved indications for which safety data are available.

The tissue agnostic pathway draws from the strength of scientific evidence that a biomarker identifies a population with common characteristics (e.g., serves as primary oncogenic driver when present) regardless of tumor histology and location, the strength of evidence that drug has the same pharmacologic effects on the biomarker across tumor types in nonclinical and clinical studies, and the ability to reliably identify the biomarker across tumor types, where the biomarker-defined population is a subset of a specific tumor type. For entrectinib, there was a strong scientific rationale that the inhibition of TRK would cause shrinkage of tumors with *NTRK* fusions. There was also strong non-clinical support of the antitumor activity of entrectinib across multiple cells lines and *NTRK*-fusion partners, and clinically, durable tumor shrinkage occurred in a consistent fashion in patients with a variety of tumors harboring a diverse array of *NTRK* fusions. In light of these factors, the FDA review teams concluded that pooling of results from patients with *NTRK* fusion-solid tumors was warranted and supported a

tissue agnostic indication.

Although the ORR for entrectinib is clearly high among certain tumor types such as *NTRK* fusion-positive sarcoma and salivary gland cancers, the treatment effects of entrectinib in some of the less well represented tumor types for which *NTRK* fusions are rare (such as pediatric and CNS cancers) are less well characterized. However, in the context of the acceptable safety profile observed in a limited number of patients (355 patients), this degree of uncertainty is acceptable in patients with *NTRK* fusion-positive solid tumors that are metastatic or who would otherwise undergo a morbid or life-threatening surgical procedure and who have no remaining satisfactory treatment options.

Accelerated approval offers the ability to make safe and effective new drugs available to the public earlier and is granted if the drug provides a meaningful advantage over available therapy and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit *or* on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e. an intermediate clinical endpoint). A recently published review by the FDA illustrated that in certain circumstances, particularly in rare cancer subsets when the drug has demonstrated safety and efficacy in other settings, ORR and DOR have been used for regular approval (Blumenthal, 2017). The applications highlighted in this review were supported by a clinically meaningful ORR with durable responses (including CRs) in rare subpopulations of patients with a specific histologic type of cancer. Although ORR, an endpoint that is "other than survival or irreversible morbidity", *may* support regular approval depending on the effect size and duration, FDA determined that additional data are needed to verify and describe the clinical benefit of entrectinib given the numerous histologic subtypes of cancer included in this indication and the relatively small efficacy database supporting this application. Granting accelerated approval allows for residual uncertainty to be addressed regarding the biomarker-defined indication, regardless of histology. Given the totality of data (scientific and clinical) submitted, the review teams determined that such an approach is appropriate rather than requiring a large number of additional patients to be enrolled in the pre-approval setting. Data submitted post-approval will allow for increased confidence in efficacy of entrectinib across multiple tumor types, some of which may not have yet been studied, and more precise characterization of the magnitude and durability of the observed responses.

As a condition of the accelerated approval, Genentech must provide additional data under a postmarketing requirement to verify and further describe the clinical benefit of entrectinib. Randomized trials would be challenging to conduct in the tissue-agnostic setting due to the extreme rarity of *NTRK*-fusion cancers. Furthermore, given the large number of primary tumor types that have different natural histories, it may not be scientifically appropriate to "lump" these tumor types together into a single randomized trial. Due to limited numbers of patients with *NTRK*-fusion-positive solid tumors, lack of equipoise in settings without available therapies, and expectations for patient cross-over (if a randomized clinical trial were conducted) it does not appear feasible or appropriate to conduct a randomized trial of entrectinib to demonstrate that entrectinib improves the overall survival (OS) in patients with *NTRK* fusion-positive solid tumors.

On May 12, 2017, entrectinib received breakthrough therapy designation for the treatment of unresectable or metastatic solid tumors with *NTRK*-fusion proteins in adult patients who require systemic therapy and who have either progressed following prior treatment or who have no acceptable alternative treatments. Breakthrough therapy designation conferred to entrectinib resulted in increased and enhanced interactions with an experienced multidisciplinary review team including upper level management, in addition to priority review of this application.

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. • There is 1 approved drug (larotrectinib) under accelerated approval for treatment of patients with solid tumors with an *NTRK* fusion. • When metastatic or unresectable, solid tumors are rarely curable and generally convey a poor prognosis. According to the American Cancer Society, the estimated 5-year survival rates for metastatic breast, colon, lung, and melanoma are 22%, 12%, 1%, and 15-20%, respectively. The likelihood of achieving a response to second-line or greater therapy is less than 50%; in the case of colon and NSCLC, much less than 50%. There is inadequate information to characterize the effects of *NTRK* gene fusions on prognosis, either favorable or unfavorable.	*NTRK* fusion-positive solid tumors that are refractory to available therapy or that have no satisfactory treatment options are life-threatening. The majority of such patients are expected to die in less than 5 years.
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. • There are limited treatment options for the tumors with the highest incidence that were enrolled on the 3 pivotal studies (sarcomas). • There is one FDA-approved treatment (accelerated approval) for rare cancers that commonly harbor *NTRK* fusions, larotrectinib. • The patient population studied had a variety of metastatic or	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. There is an unmet medical need for patients with metastatic or unresectable *NTRK*-fusion solid tumors that have no satisfactory treatment options or progressed following

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	unresectable *NTRK*-fusion solid tumors, encompassing 12 different types of cancers that either progressed following standard therapy or did not have satisfactory treatment.	treatment.
Benefit	• The efficacy of entrectinib in pediatric and adult patients with *NTRK*-fusion solid tumors was demonstrated by pooled data from the first 54 adult patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in one of three multicenter, open-label, single-arm clinical trials ALKA (EudraCT 2012-000148-88), STARTRK-1 (NCT02097810), STARTRK-2 (NCT02568267). All patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery with significant morbidity for locally advanced disease. • The ORR following treatment with entrectinib was 57% (95% confidence interval: 43%, 71%), including 7.4% of patients with a complete response (CR) and 50% of patients with a partial response (PR) to entrectenib. • Responses were observed across a variety of tumor types and appeared consistent across *NTRK*-fusion partners. • Median DOR was not estimable at the time of the analysis. • Among the 31 responding patients, 68% had a duration of response (DOR) of at least 6 months and 45% had a duration of at least 12 months. • The primary uncertainty is related to the consistency of treatment effect across tumor histologies, given the small size of the efficacy database. The review team determined that a histology-agnostic indication is justified based upon strong scientific evidence that *NTRK* fusions are primary oncogenic drivers in solid tumors and that	The magnitude and duration of responses observed in patients with *NTRK* fusion-positive solid tumors who have progressed following standard treatment or who had no available treatment options was large and clinically meaningful. For unresectable or metastatic solid tumors that are refractory to available therapy or for which there is no satisfactory therapy, ORR may be considered a surrogate endpoint reasonably likely to predict clinical benefit when the treatment effect is large and the responses are durable. The submitted evidence meets the statutory evidentiary standard for accelerated approval. As a condition of approval under 21 CFR 314 Subpart H, Genentech is required to conduct additional studies to verify and confirm the clinical benefit of entrectinib in patients with *NTRK*-fusion solid tumors. Per the Guidance for Industry: *In Vitro Companion Diagnostic Devices*, FDA may decide to approve a drug even if a companion diagnostic device is not yet approved when the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	inhibition of TRK would cause shrinkage of tumors with *NTRK* fusions, strong non-clinical support of the antitumor activity of entrectinib across multiple cells lines and *NTRK*-fusion partners, and the clinical evidence demonstrating durable tumor shrinkage in a consistent fashion in patients with a variety of tumors harboring a diverse array of *NTRK* fusions. In light of these factors, the FDA review teams concluded that pooling of results from patients with *NTRK* fusion-solid tumors was warranted and supported a tissue agnostic indication. However, in the context of the acceptable safety profile observed, this degree of uncertainty is acceptable in patients with *NTRK* fusion-positive solid tumors that are metastatic or who would otherwise undergo a morbid or life-threatening surgical procedure and who have no remaining satisfactory treatment options. • The clinical pharmacology review team determined that there was insufficient data available to determine the dose of entrectinib for pediatric patients less than 12 years of age that can achieve comparable exposure to adults at the recommended dose of 600 mg daily. The safety and effectiveness of entrectinib in pediatric patients less than 12 years of age with solid tumors who have an *NTRK* gene fusion has not been established. • Another uncertainty is lack of an approved companion diagnostic test to select patients with *NTRK* fusion solid tumors. In the pooled analysis of 54 patients with *NTRK*-fusion solid tumors, A total of 52 (96%) patients had an *NTRK* gene fusion detected by next-generation sequencing (NGS) and 2 (4%) had an *NTRK* gene fusion detected by other nucleic acid-based tests. Eighty-three percent of patients had central laboratory confirmation of *NTRK* gene fusion using an analytically validated NGS test.	drug is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the drug are so pronounced as to outweigh the risks from the lack of an approved device. Genentech has agreed to a postmarketing commitment to develop and seek approval of a companion diagnostic test to select patients with *NTRK*-fusion solid tumors for whom entrectinib is safe and effective.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety population included 355 patients, including 49% of patients exposed for greater than 6 months and 24% patients exposed for greater than 1 year. • Congestive heart failure (CHF), central nervous system (CNS) toxicity, skeletal fractures, hepatotoxicity, hyperuricemia, QT prolongation, and vision disorders are the primary safety risks identified for entrectinib. Hyperuricemia and transaminase elevations, although generally mild, can also occur. Uric acid should be monitored in patients receiving entrectinib. • The most common adverse reactions (≥ 20%) in order of decreasing frequency were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, pain, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders. • Serious adverse reactions including fatal events occurred in 39% of patients. The most frequent serious adverse reactions (≥2%) were pneumonia, dyspnea, pleural effusion, sepsis, pulmonary embolism respiratory failure, and pyrexia. • Grade 3 or 4 adverse reactions occurred in 60% of patients; the most common were lung infection, increased weight, dyspnea, fatigue/asthenia, cognitive disorders, syncope, pulmonary embolism, hypoxia, pleural effusion, hypotension, diarrhea, and urinary tract infection. • Due to the small number of pediatric patients in the entrectinib safety database, single arm nature of the trials supporting approval, and limited duration of patient follow-up, the effects of entrectinib (if any) on long-term growth and development of pediatric patients 12 years of age and older are not known.	The observed safety profile of entrectinib is acceptable when assessed in the context of the treatment of a life-threatening disease. The majority of adverse reactions to entrectinib were manageable with dosage modifications. The risks of severe and serious adverse reactions of CHF, neurotoxicity, skeletal fractures, hepatotoxicity, hyperuricemia, QT prolongation, and vision disorders are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Under 505(o), Genentech has a postmarketing requirement to conduct a study to further assess the risks of CHF and skeletal fractures of entrectinib. Under 505(o), Genentech has a postmarketing requirement to conduct a study of entrectinib in adolescent patients to assess the effects of entrectinib on growth and development. Additionally, Genentech has agreed to a

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Entrectinib is not expected to be effective in patients with solid tumors that do not harbor an *NTRK*-fusion, although additional studies may explore whether other alterations in *NTRK* may confer susceptibility to treatment with entrectinib. Most patients (96%) were enrolled on the entrectinib trials based upon documentation of an *NTRK* fusion by NGS testing test, and the Center for Devices and Radiological Health (CDRH) has been actively participating in discussions regarding development of a companion diagnostic test for detection of *NTRK*-fusions in patients with solid tumors.	postmarketing commitment to conduct studies needed to analytically and clinically validate an in vitro diagnostic device for use in selection of patients with *NTRK*-solid tumors for whom entrectinib is safe and effective and has expressed a commitment to seek a premarket approval application (PMA) for this device.

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	8.1.3, 8.1.5, 19.5
		☐	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.		

Cross-Disciplinary Team Leader
Martha Donoghue, MD

2 Therapeutic Context

FDA received the New Drug Application (NDA) 212726 from Genentech on December 18, 2018 requesting approval of entrectinib (ROZLYTREK) for the treatment of adult and pediatric patients with (b) (4) metastatic solid tumors harboring an *NTRK* gene fusion. The application was primarily supported by data obtained in three single-arm clinical trials.

Approval of NDA 212726 will mark the third approval for a drug that is indicated for use in patients independent of histological cancer type and based instead on identification of a oncogenic driver mutation within that patient's tumor (i.e., a "tissue agnostic" indication). The only previous drugs to be approved in this "tissue agnostic" setting are pembrolizumab, which is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options; and larotrectinib, which is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine 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 no satisfactory alternative treatments or that have progressed following treatment. Entrectinib is the second drug to be approved for the treatment of patients with solid tumors with an activating *NTRK* rearrangement.

Following approvals of larotrectinib and entrectinib, it is anticipated that testing for an *NTRK* rearrangement is likely to occur routinely in patients with solid tumors that are refractory to standard treatments (and potentially at diagnosis).

2.1. Analysis of Condition

Solid tumors harboring *NTRK* gene fusions are a heterogenous group of tumors; the incidence of solid tumors with *NTRK* fusions is not well characterized. Although there is insufficient information to fully characterize the incidence of patients with solid tumors harboring an activating *NTRK* fusion, the annual incidence of *NTRK* fusion-driven tumors is estimated to be 1500-5000 cases in the United States (U.S.) [Kheder and Hong 2018].

NTRK fusions are rare events in common adult cancers, e.g. frequency of <1% in NSCLC and 1-2% in CRC, and more frequently observed in some rare cancers, e.g. 90-100% in mammary analogue secretory carcinoma (MASC), a rare form of salivary gland cancer (representing < 1% of all cancer malignancies), and secretory breast cancer (SBC), for which *NTRK* fusion expression (*ETV6-NTRK3*) is a pathognomonic hallmark for both diseases (Vaishnavi et al. 2013; Chen and Chi 2018; Kheder and Hong 2018). *NTRK* fusions have also been described in several pediatric

tumors including infantile fibrosarcoma (IFS) or the related congenital mesoblastic nephroma (for which the *ETV6-NTRK3* fusion is also a characteristic feature), and with high frequency (~40%) in high grade glioma in patients <3 years of age (Wu et al. 2014). Although frequently present in certain rare cancers, the incidence of *NTRK* fusions is below 1% for most common cancer types such as lung, prostate, and colon cancer (see Table 1).

Table 1: Incidence of *NTRK* Fusions in Different Tumor Types – Foundation Medicine Data

Disease		Sample size	*NTRK* fusions
Sarcoma	NOS	2667	0.56%
Lung	adenocarcinoma	7616	0.09%
	squamous	1271	0%
	NOS	1740	0.11%
Salivary	Salivary gland carcinoma (NOS)	523	1.72%
Thyroid	Thyroid Cancer (NOS)	545	0.92%
CNS	glioblastoma	1968	0.05%
Biliary	(liver) Cholangiocarcinoma	968	0.10%
Colorectal	Colorectal adenocarcinoma	5034	0.12%
Other	Breast Cancer (NOS)	7053	0.07%
	melanoma	472	0%
	bile duct adenocarcinoma	167	0.6%
	Gastro-esophageal junction adenocarcinoma	983	0.10%
	Gastrointestinal Stromal Tumor	78	1.28%
	Unknown primary adenocarcinoma	1971	0.10%
	Unknown primary NOS	401	0.25%
	Uterine carcinoma	1019	0.10%

Source: modified from NDA submission, original data from Foundation Medicine
NOS=not otherwise specified

The types of *NTRK* fusions also vary among tumor types, as described in Table 2.

Table 2: Reported *NTRK* Fusions in Solid Tumors

Gene fusion	Cancer type	Authors (year)
LMNA-NTRK1	Colorectal	Sartore-Bianchi *et al.* (2016)
	Soft tissue sarcoma	Doebele *et al.* (2015)
	Spitzoid melanomas	Wiesner *et al.* (2014)
	AYA sarcoma	Morosini *et al.* (2015)
	Congenital infantile fibrosarcoma	Wong *et al.* (2015)
TPM3-NTRK1	Colorectal	Lee *et al.* (2015), Créancier *et al.* (2015), Ardini *et al.* (2014)

Gene fusion	Cancer type	Authors (year)
	Papillary thyroid carcinomas	Bongarzone *et al.* (1989), Butti *et al.* (1995)
	Glioblastoma	Wu *et al.* (2014)
SQSTM1-NTRK1	NSCLC	Farago *et al.* (2015)
NTRK1-SQSTM1	NSCLC	Siena *et al.* (2015)
NFASC-NTRK1	Glioblastoma multiforme	Frattini *et al.* (2013), Kim *et al.* (2014)
BCAN-NTRK1	Glioblastoma multiforme	Kim *et al.* (2014), Frattini *et al.* (2013)
PPL-NTRK1	Thyroid carcinoma	Farago *et al.* (2015)
RFWD2-NTRK1	Large cell neuroendocrine tumor (lung)	Fernandez-Cuesta *et al.* (2014)
CD74-NTRK1	Lung adenocarcinomas	Vaishnavi *et al.* (2013)
MPRIP-NTRK1	Lung adenocarcinomas	Vaishnavi *et al.* (2013)
RABGAP1L-NTRK1	ICC	Ross *et al.* (2014)
TFG-NTRK1	Thyroid carcinomas	Greco *et al.* (1995)
TP53-NTRK1	Spitzoid melanomas	Wiesner *et al.* (2014)
Unknown-*NTRK1*	Appendiceal adenocarcinoma	Braghiroli *et al.* (2016)
AFAP1-NTRK2	Low-grade glioma	Stransky *et al.* (2014)
AGBL4-NTRK2	Glioblastoma	Wu *et al.* (2014)
NACC2-NTRK2	Pilocytic astrocytomas	Jones *et al.* (2013)
PAN3-NTRK2	Head and neck squamous cell carcinoma	Wu *et al.* (2014)
QKI-NTRK2	Pilocytic astrocytomas	Jones *et al.* (2013)
TRIM24-NTRK2	Lung adenocarcinoma	Wu *et al.* (2014)
VCL-NTRK2	Glioblastoma	Wu *et al.* (2014)
ETV6-NTRK3	Glioblastoma	Zhang *et al.* (2013)
	Glioblastoma	Wu *et al.* (2014)
	MASC	Tognon *et al.* (2002), Ito *et al.* (2015), Del Castillo *et al.* (2015)
	Ductal carcinoma	Makretsov *et al.* (2004), Arce *et al.* (2005), Lagree *et al.* (2011)
		Pinto *et al.* (2014)
	Fibrosarcoma	Morerio *et al.* (2004), Punnett *et al.*
	Congenital mesoblastic nephroma	Watanabe *et al.* (2002)

Gene fusion	Cancer type	Authors (year)
	Radiation-associated thyroid cancer	Leeman-Neill *et al.* (2014)
	AML	Kralik *et al.* (2011), Eguchi *et al.* (1999),
	GIST	Brenca *et al.* (2015)
	MASC of salivary gland	Urano *et al.* (2015), Skàlovà *et al.* (2015)
	Papillary thyroid cancer	Leeman-Neill *et al.* (2014), Seungbok Lee *et al.* (2014)
	Colorectal	Hechtman *et al.* (2015)
BTBD1-NTRK3	Glioblastoma	Wu *et al.* (2014)

Source: Amatu et al., 2016.
Key: AFAP1, actin filament-associated protein 1; AGBL4, ATP/GTP-binding protein-like 4; AML, acute myeloid leukemia; AYA, adolescents and young adults; BCAN, brevican; BTBD1, BTB (POZ) domain containing 1; CD74, CD74 molecule; ETV6, ETS variant 6; GIST, gastrointestinal stromal tumor; ICC, intrahepatic cholangiocarcinoma; LMNA, lamin A/C; MASC, mammary secretory breast carcinoma; MPRIP, myosin phosphatase Rho interacting protein; NACC2, NACC family member 2, BEN and BTB (POZ) domain containing; NFASC, neurofascin; NSCLC, non-small cell lung cancer; PAN3, PAN3 poly(A) specific ribonuclease subunit; PPL, periplakin; QKI, KH domain containing RNA binding; RABGAP1L, RAB GTPase activating protein 1-like; RFWD2, ring finger and WD repeat domain 2, E3 ubiquitin protein ligase; SQSTM1, sequestosome 1; TFG, TRK-fused gene; TP53, tumor protein p53; TPM3, tropomyosin 3; TRIM24, tripartite motif containing 24; VCL, vinculin.

The assessment of the efficacy of entrectinib for the treatment of patients with solid tumors with an *NTRK* fusion is complicated by the rarity of *NTRK* fusions in most solid tumors, the heterogeneity of tumor types harboring an *NTRK* fusion, and the diversity of *NTRK* gene fusion partners.

2.2. Analysis of Current Treatment Options

There is only one drug approved specifically for the treatment of patients with solid tumors with an *NTRK* fusion. FDA granted accelerated approval to larotrectinib in November 2018 for the treatment of adult and pediatric patients with solid tumors that:

• have a neurotrophic receptor tyrosine 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 no satisfactory alternative treatments or that have progressed following treatment.

Due to the heterogeneity of solid tumors that can harbor an *NTRK* fusion, the information below focuses on providing a summary of the treatment options for the more common tumors that can harbor *NTRK* fusions.

Clinical Reviewer Comment: The indication for entrectinib that is recommended for approval by FDA is restricted to adult and pediatric patients 12 years of age and older with solid tumors harboring an NTRK in-frame gene fusion, and not alternate molecular aberrations, as there is insufficient clinical and preclinical data to support that the effects of entrectinib will be similar in tumors harboring other NTRK gene aberrations as for tumors harboring in-frame gene fusions . The indication is also restricted to the treatment of patients with solid tumors that are metastatic or where surgical resection is likely to result in severe morbidity and that have no satisfactory alternative treatment options or have progressed following such treatment as this is the population studied and there the relative benefits as compared to available therapies, which may prolong survival, has not been evaluated.

Salivary Gland Cancer

Mammary analogue secretory carcinoma (MASC) is an unusual and rare malignant salivary gland tumor first described in 2010. *ETV6-NTRK3* fusion is detected in 100% of MASC cases (Bishop 2013). It shares histologic, immunohistochemical, and genetic features with secretory carcinoma of the breast. The clinical behavior of MASC ranges from slowly growing tumors that infrequently recur after surgical resection to aggressive tumors that cause widespread metastasis and death (Sethi 2014). The accepted initial treatment for low-grade malignant salivary gland tumors is radical surgical resection with post-operative radiation reserved for incomplete resection. Radiation may also be administered for unresectable disease or palliation of metastatic disease. There are no FDA-approved drugs for its treatment with the exception of larotrectinib.

Secretory Breast Cancer

This is a rare but distinct subtype of infiltrating ductal carcinoma that was originally described in children and adolescents but is now known to occur in adults. In 2002, Tognon *et al*. reported the *ETV6-NTRK3* gene fusion t(12;15)(p12;q26.1) as a pathognomonic genetic feature of this rare carcinoma. *ETV6-NTRK3* fusion is detected in 92% of SBC cases. The primary treatment option for secretory carcinoma is surgery (Aktepe 2016) as there are no FDA-approved drugs for its treatment with the exception of larotrectinib.

Sarcoma (Soft Tissue Sarcoma, Gastrointestinal Stromal Tumor, Infantile Fibrosarcoma)

Sarcomas represent a wide spectrum of uncommon tumors. In a study published by Drilon *et al*. (2018), which included 17 different *NTRK* fusion-positive tumor types detected by FISH or NGS, 21/55 (38%) patients were diagnosed with sarcoma including three patients with gastrointestinal tumor (GIST). Drilon *et al.* showed that sarcomas including soft tissue, IFS and GIST comprise the largest cohort of cancer patients to harbor *NTRK* fusions in their study. Overall, the estimated prevalence rate of *NTRK* fusions in sarcomas ranges from 1% in adult sarcomas to 92% in patients with congenital fibrosarcoma (Drilon 2018, Stransky 2014).

Treatment for soft tissue sarcomas (STS) depend on tumor histology and are a combination of neoadjuvant chemotherapy and surgery, and radiation. Stage 4 are rarely curable as they are metastatic. The chemotherapy drugs doxorubicin and ifosfamide are often the first choice —

either together or along with other drugs. If doxorubicin is used, it might be given along with FDA-approved olaratumab which is FDA-approved in combination for the treatment of adult patients with STS with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery (prescribing information for olaratumab). Gemcitabine and docetaxel may be given alternatively as treatment (American Cancer Society website accessed 1 Aug 2018).

GIST that are unresectable or metastatic require systemic therapy with imatinib which is FDA-approved for patients with Kit (CD117) positive unresectable and/or metastatic malignant GIST and adjuvant treatment of adult patients following resection of Kit (CD117) GIST (prescribing information for imatinib). Sunitinib malate is FDA-approved for the treatment of patients with GIST after disease progression or who are intolerant to imatinib mesylate (prescribing information for sunitinib). Regorafenib is FDA-approved for the treatment of patients with locally advanced, unresectable or metastatic GIST who have been previously treated with imatinib mesylate and sunitinib malate (prescribing information for regorafenib). Pazopanib is FDA-approved for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy (prescribing information for pazopanib).

Although IFS is a rare tumor, it is the most common soft tissue sarcoma in children less than 1 year of age. Local recurrence may occur after initial conservative surgery (17–43%), the latter being the mainstay of treatment, aiming for a total resection. However, IFS may present with locally advanced disease and surgery may be mutilating or cause functional damage (Orbach 2016). There are no FDA-approved systemic therapies for IFS with the exception of larotrectinib for surgically morbid cases, although IFS is typically treated with vincristine-actinomycin-D chemotherapy and has shown good responses in children older than 3 months (Orbach 2016).

Thyroid Carcinoma

In 1989, Bongarzone *et al*. (1989) described an oncogenic version of *NTRK1* in papillary thyroid cancer (PTC). According to Greco *et al.*, the estimated prevalence of *NTRK* fusions in patients with PTC does not exceed 12% and varies among study populations according to geographical distribution and methods of detection. *NTRK* fusion oncogenes were also detected in seven of 27 (26%) pediatric patients with PTC (Wajjwalku 1992). Patients having *NTRK*-rearranged PTC can present with extensive disease and may have a worse prognosis than those with *BRAF* mutations (Prasad 2016). While *ETV6* (ETS Variant 6)-*NTRK3* is a rare somatic gene fusion in sporadic thyroid cancers, it was found to be more common in radiation-related tumors (Leeman 2014).

Current treatment of papillary carcinoma consists of radioiodine treatment, a kinase inhibitor, or external beam radiation therapy (EBRT). Sorafenib is FDA-approved for treatment of locally recurrent or metastatic, progressive, differentiated thyroid carcinoma (DTC) that is refractory to radioactive iodine treatment. Lenvatinib is also FDA-approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC (prescribing information for lenvatinib). Trametinib is FDA-approved for the treatment of patients with

locally advanced or metastatic *BRAF V600E* mutation-positive anaplastic thyroid cancer (ATC) who have no satisfactory locoregional treatment options.

Colorectal Cancer

The first published report of a *NTRK* rearrangement in colorectal cancer (CRC) dates back to 1986 (Martin-Zanca *et al*., 1986) when a *TPM3-NTRK*1 translocation was detected in a tumor biopsy, and thereafter very little has been reported about these gene defects in CRC. According to Table 1, Foundation Medicine incidence of *NTRK*-rearrangement or mutation in patients with CRC is 0.12%. Ardini *et al*. (2013) characterized the *TPM3-NTRK*1 gene rearrangement as a recurring, although rare, event in CRC, and described nonclinical studies of entrectinib (RXDX-101) indicating that entrectinib suppressed TPM3-TRKA phosphorylation and downstream signaling in KM12 cells and showed antitumor activity in mice bearing KM12 tumors. In 2015, Créancier *et al*. reported the 0.5% prevalence of *NTRK* fusions in 408 CRC clinical samples, including a *TPM3-NTRK*1 (TRK-T2 fusion). Recently, in the molecular screening for the first-in-human study of entrectinib, abnormal expression of the TrkA protein was identified in tumor and liver metastases of a patient with CRC refractory to standard therapy, and molecular characterization documented a *LMNA-NTRK*1 rearrangement within chromosome 1 that had oncogenic potential (Créancier *et al*., 2015).

Outcomes data are available in unselected (for *NTRK* status) patients with metastatic CRC who received prior oxaliplatin, irinotecan, fluoropyrimidine, anti-VEGF antibody, and anti-EGFR antibody (if RAS wild-type). In a randomized clinical trial of patients receiving TAS-102, patients in the TAS-102 arm lived for a median of 7.1 months versus 5.3 months in patients who received placebo (HR 0.68; 95% CI, 0.58 to 0.81; $p < 0.001$) (Marcus 2017; Mayer 2015). Median estimated progression-free survival (PFS) was 2 months and the overall response rate (ORR) was 1.5% for patients in the TAS-102 arm. Efficacy results were similar in the randomized clinical trial supporting the approval of regorafenib. Median OS was 6.4 months in the regorafenib arm versus 5.0 months in the placebo arm. Median estimated PFS was 2.0 months in the regorafenib arm and the ORR was 1% (HR 0.77; 95% CI, 0.64, 0.94; $p = 0.0102$) (prescribing information for regorafenib, Grothey 2013).

Overall survival was assessed in a randomized non-inferiority clinical trial comparing the two anti-EGFR antibodies (cetuximab and panitumumab) in patients with KRAS exon 2 wild-type metastatic CRC who received prior irinotecan, oxaliplatin, and a fluoropyrimidine. Approximately 25% of the population received prior bevacizumab. Median estimated survival was 10.4 months for patients who received cetuximab versus 10 months in patients who received panitumumab. Response rates across both arms were approximately 20% (prescribing information for panitumumab); however, DOR in both arms was less than 6 months (3.8 months for panitumumab versus 5.4 months for cetuximab) (Price 2014).

In summary, available data suggest that patients with metastatic CRC who have received irinotecan, fluoropyrimidine, and oxaliplatin-based chemotherapy have a poor prognosis irrespective of *NTRK* status, and that response rates are low with TAS-102 and regorafenib

(standard available therapies). Although anti-EGFR antibodies (in patients who had not received prior anti-EGFR antibody therapy) resulted in higher response rates in patients with RAS wild-type tumors, durability of response was limited. Based on these data and the data supporting the use of entrectinib (generally in the third or greater-line settings) in patients with metastatic CRC (see section on efficacy below), it is appropriate to approve entrectinib in patients who have received prior irinotecan, fluoropyrimidine, and oxaliplatin-based chemotherapy, since such patients have limited alternatives (regorafenib, trifluridine/tipiracil, or single agent anti-EGFR antibodies) in which the response rates are less than 20%; of note, these drugs were approved based on improvements in survival or progression-free survival.

Lung

In 2013, the pivotal study with Vaishnavi *et al*. described two different gene fusions involving the *NTRK*1 gene that lead to constitutive TrkA TK domain activation. Platinum-based combination chemotherapy is the standard first-line treatment for subjects with Stage IV NSCLC without genetic tumor alterations. The patients with NSCLC harboring an *EGFR* mutation, rearrangement of the anaplastic lymphoma kinase (*ALK*) gene, or *ROS1* mutation undergo a different medical treatment paradigm involving tyrosine kinase inhibitors. Crizotinib is FDA-approved treatment for patients with metastatic NSCLC whose tumors are *ALK* or *ROS1*-positive as detected by an FDA-approved test (prescribing information for crizotinib) while alectinib and ceritinib are FDA-approved for the first-line treatment of patients with *ALK*-positive metastatic NSCLC as detected by an FDA-approved test (prescribing information for ceritinib). Additionally, several anti-PD-(L)1 monoclonal antibodies (nivolumab, pembrolizumab, and atezolizumab) are approved for treatment of metastatic NSCLC following prior treatment (nivolumab, pembrolizumab, atezolizumab), as single agents or in combination with platinum-based chemotherapy as first-line treatment (pembrolizumab), or as a single agent for first-line treatment of PD-L1 strongly positive NSCLC (pembrolizumab). Additionally, nivolumab and pembrolizumab are approved for treatment of small cell lung cancer following prior treatment.

Glioblastoma

The principles of therapy for primary CNS tumors are multimodality therapy as initiation treatment (temozolomide, radiation, and surgery) for glioblastoma multiforme; treatment varies according to tumor histology and location for other primary CNS tumors. In 2014, Wu *et al*. applied a whole genome, whole exome and/or transcriptome sequencing to 127 samples of pediatric high-grade glioma (HGG), identifying recurrent fusions involving the neurotrophin receptor genes *NTRK1*, *2*, or *3* in 40% of non-brainstem HGG (versus 3% in adults [Kheder and Hong 2018]).

Summary

In conclusion, expected response rates to later lines of treatment in a refractory setting for metastatic and locally advanced unresectable solid tumors are typically <30% and median duration of response (mDOR) is generally less than <10 months across available approved agents for various solid tumor types (Table 3). Patients who have exhausted these options or

who have no standard or approved options available receive best supportive care or are entered into early phase clinical trials where the expected response rates are ≤10%.

Table 3: Efficacy of Approved Therapies for Patients with Solid Tumors with *NTRK* Fusions and have either Progressed Following Prior Therapies or have No Satisfactory Alternative Treatment

	Therapy	Line of treatment	ORR (%)	mDOR (months)	mPFS (months)	mOS (months)	Reference
Non Small-Cell Lung Cancer (EGFR or ALK negative)	Docetaxel	2L	6.8	6.0	2.8 (TTP)	7.9	Shepherd et al. 2000
	Pemetrexed	2L	9.1	4.6	2.9	8.3	Hanna et al. 2004
	Bevacizumab+Paclitaxel	2L or 3L	22.5	NA	5.4	9.9	Cortot et al. 2016
	Docetaxel+Ramucirumab	2L	22.9	NA	4.5	10.5	Garon et al. 2014
	Pembrolizumab[a]	≥2L	18.5	NR	4.0	12.7	Herbst et al. 2016
	Docetaxel+Nintedanib	2L	4.7	NA	3.4	12.6	Reck et al. 2014
	Nivolumab	≥2L	19.2	17.2	2.3	12.2	Borghaei et al. 2015
Colorectal Carcinoma	Cetuximab+Irinotecan[b]	2L	16.4	5.7	4.0	10.7	Sobrero et al. 2008
	Panitumumab+FOLFIRI[b]	2L	35.4	7.6	5.9	14.5	Peeters et al. 2010
	Bevacizumab+FOLFOX-4	2L	22.7	NA	7.3	12.9	Giantonio et al. 2007
	Aflibercept+FOLFIRI	≥2L	19.8	NA	6.9	13.5	Van Cutsem et al. 2012
	Ramucirumab+FOLFIRI	2L	13.4	NA	5.7	13.3	Tabernero et al. 2015
	Regorafenib	≥2L	1.0	NA	1.9	6.4	Grothey et al. 2013
	Trifluridine/Tipiracil	≥2L	1.6	NA	2.0	7.1	Mayer et al. 2015
Breast Cancer incl. Secretory Breast	Gemcitabine+Paclitaxel	≥2L	41.4	9.9	6.1 (TTP)	18.6	Albain et al. 2007
	Lapatinib+Capecitabine[c]	≥2L	22	9.9	5.5 (TTP)	17.0	Cameron et al. 2008; 2010
	Capecitabine+Docetaxel	≥2L	41.6	7.3	6.1 (TTP)	14.5	O'Shaugnessy et al. 2002
	Fulvestrant+Palbociclib	≥2L	24.6	9.3	9.5	NA	Cristofanilli et al. 2016
	Eribulin	≥2L	12.2	4.2	3.7	13.2	Cortes et al. 2011
Salivary Gland Cancer incl. MASC	Sunitinib	≥1L	0	NA	7.2 (TTP)	18.7	Chau et al. 2012
	Gefitinib	≥1L	0.0	NA	4.3/2.1	25.9/16.0	Jakob et al. 2015
	Platinum+Gemcitabine	≥1L	24.2	6.7	NA	13.8	Laurie et al. 2010
Soft Tissue Sarcoma	Eribulin[d]	≥2L	4.0	NA	2.6	13.5	Schöffski et al. 2016
	Sunitinib[e]	2L	6.8	NA	24.1	72.7	Demetri et al. 2006
	Regorafenib[f]	≥2L	4.5	NA	1.1-5.6	4.7-21.0	Mir et al. 2016
	Trabectedin	≥2L	9.9	6.5	4.2	12.4	Demetri et al. 2016
	Pazopanib[g]	≥2	4.0	9.7	4.6	12.6	van der Graf et al. 2012
	Dacarbazine+Gemcitabine	≥2L	12	10.2	4.2	16.8	García-del-Muro et al. 2011
	Olaratumab+Doxorubicin	≥1L[h]	18.2	8.3	6.6	26.5	Tap et al. 2016

Source: Copied from submission, Table 1, Clinical Overview Module 2.5
Key: NA, not available; NR, not reached.
[a] in patients with PD-L1 expression on at least 1% of tumor cells.
[b] for patients with RAS wt tumors.
[c] patients with HER2-positive advanced/metastatic BC.
[d] for patients with liposarcomas.
[e] patients with unresectable and/or metastatic gastrointestinal stromal tumors (GIST) after failure of imatinib.

[f] non-adipocytic STS (excluding liposarcomas).
[g] 59% of patients had at least one previous treatment.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Rozyltrek (entrectinib) is a new molecular entity (NME) that is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Significant regulatory activities relevant to the development program for entrectinib are summarized in the Table 4 below.

Table 4: Regulatory History

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Date	Regulatory History
February 3, 2014	Final written response was issued in response to a pre-IND meeting request (IND 120500) seeking feedback on the design of the first-in-human trial of entrectinib (STARTRK-1).
February 27, 2014	Ignyta, Inc. (Ignyta) submitted IND 120500 for the initiation of clinical studies with entrectinib in the US.
March 28, 2014	IND 120500 was deemed safe to proceed.
February 17, 2015	Meeting minutes were issued for a Type B meeting held on January 29, 2015 to discuss the overall design of two proposed studies: • STARTRK-2, proposed as a multicenter, single-arm study of entrectinib in any line in patients with crizotinib-naïve *ROS1* or TrkA/B/C rearranged advanced NSCLC • STARTRK-3, proposed as a randomized, multicenter study comparing entrectinib versus docetaxel as second-line treatment for patients with *ROS1* or TrkA/B/C rearranged advanced NSCLC
October 21, 2015	Meeting minutes were issued for a Type B EOP1 meeting, held on September 22, 2015, to discuss STARTRK-2, entitled "An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements," and to discuss Ignyta's overall clinical development plan.
November 10, 2016	Ignyta Trailblaze Pharos Assay, the proposed companion diagnostic assay for selection of patients for whom entrectinib is indicated, received Expedited Access Pathway designation.
March 2, 2017	Meeting minutes were issued for a Type C meeting, held on November 17, 2016, to discuss the proposed clinical pharmacology program intended to support the filing of the planned NDA for entrectinib.
May 12, 2017	Entrectinib was granted Breakthrough Therapy Designation (BTD) for the treatment of *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.
May 31, 2017	FDA issued a Revised Pediatric Written Request (original request was submitted December 22, 2016; amendment was submitted May 3, 2017) for Study RXDX-101-03 (STARTRK-NG), proposed as a multicenter, open-label dose escalation study in pediatric

Date	Regulatory History
	patients (birth to <22 years) with relapsed or refractory extracranial solid tumors, with expansion cohorts in patients with primary brain tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* molecular alterations, neuroblastoma, infantile (congenital) fibrosarcoma, and other non-neuroblastoma, extracranial solid tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions.
July 5, 2017	Entrectinib received orphan drug designation for treatment of *NTRK* fusion-positive solid tumors.
September 12, 2017	Meeting Minutes were issued for an initial comprehensive multidisciplinary BTD meeting, held on September 7, 2017, to discuss the development plan for entrectinib for the treatment of *NTRK* fusion-positive solid tumors.
June 12, 2018	Ignyta transferred sponsorship of IND 120500 and all rights and responsibilities related to the IND application to Genentech.
November 5, 2018	Meeting minutes were issued for a Type B pre-NDA meeting, held on October 17, 2018, to discuss the planned NDA submission for entrectinib for the proposed indication of the treatment of adult and pediatric patients with *NTRK* fusion-positive (b) (4) metastatic solid tumors whose cancer has progressed (b) (4) (b) (4).
November 26, 2018	Meeting minutes issued for a CMC only meeting, held on November 7, 2018, to discuss the data to be presented in the future NDAs, including that to support the selection of the solid form for launch of entrectinib, and to capture agreements regarding the contents of a complete application under the PDUFA VI Program for the two NDAs to be submitted for entrectinib. Meeting minutes issued for a CMC only meeting, held on November 7, 2018, to discuss the data to be presented in the future NDAs, including those to support the selection of the solid form for launch of entrectinib, and to capture agreements regarding the contents of a complete application under the PDUFA VI Program for the two NDAs (NDA 212725 & NDA 212726) to be submitted for entrectinib.
December 18, 2018	NDA 212726 was submitted and accelerated approval was requested (NDA 212725 for *ROS1*-positive NSCLC was submitted on the same day).
February 13, 2019	FDA issued a Priority Review Designation letter.
March 1, 2019	FDA issued a Filing Communication outlining the filing review issues identified.

Date	Regulatory History
March 13, 2019	Meeting minutes were issued for the Mid-cycle communication meeting, held March 18, 2019. Issues discussed included the financial disclosure information, the sufficiency of the pediatric data in demonstrating safety and effectiveness of entrectinib in pediatric patients ≥4 years and < 18 years of age, and postmarketing requirements (PMRs) and postmarketing commitments (PMCs).
May 13, 2019	The proposed proprietary name, ROZLYTREK, was conditionally accepted.
July 15, 2019	Meeting minutes were issued for the Late cycle meeting, held June 17, 2019. Key review issues discussed included substantive review issues related to limiting the proposed indication to adult and pediatric patients 12 years of age and older, and the new safety data submitted on two pediatric patients with femoral neck fractures. Issues related to ROZLYTREK labeling, and PMRs and PMCs were also discussed.

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

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigations (OSI) to perform an audit of 4 clinical trial sites (Site #19011: Dr. Alexander Drilon and Site #19022: Dr. Robert Doebele, Site #14001, Dr Byoung Chul Cho, and Site #013, Dr. Jeeyun Lee), and the contract research organization (CRO) that performed blinded central review of imaging (b) (4) to identify any issues that could affect the quality and interpretation of the data submitted with these applications regarding the clinical trials, ALKA, STARTRK-1/RXDX-101-01, STARTRK-2/RXDX-101-02, STARTRK-NG/RXDX-101-103. DOP2, in consultation with OSI, selected these clinical sites for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, patterns of efficacy reporting, and patterns of serious adverse event (SAE) reporting. Specifically, the sites were selected based on high enrollment and treatment efficacy and the fact that they had not been inspected by FDA recently.

The final compliance classification for these inspections is No Action Indicated (NAI). OSI concluded that the data submitted by Genentech to support NDA 212726 appear reliable based on information from the inspections.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) did not identify any product quality issues that would preclude approval of entrectinib capsules under NDA 212726 or NDA 212725.

Entrectinib is a small molecule new molecular entity with the molecular formula of $C_{31}H_{34}F_2N_6O_2$ and the molecular weight of 560.64 Daltons.

Entrectinib is an achiral, white to (b) (4) pale pink crystalline powder (b) (4). Entrectinib is a free base with the melting point between 198.2 to 200.7°C. Entrectinib is non-hygroscopic and shows an exponential increase in aqueous solubility in acidic media compared to neutral conditions, which is indicative of a potential food effect. However, the pivotal clinical formulation (F2A) and the proposed to-be-marketed commercial formulation (F06) include an (b) (4). The clinical study, RXDX- 101-15 established BA/BE between F2A and F06 formulations and the absence of food effect on in vivo exposure with F06 formulation, which is reviewed by clinical pharmacology review team.

Entrectinib is considered as a Biopharmaceutics Classification System (BCS) Class 2 compound with low solubility and low-moderate permeability. Entrectinib exhibits polymorphisms with Form A being selected for development and for use in the commercial drug product.

The proposed commercial drug product is an immediate-release hard Hypromellose (HPMC) capsule containing 100 mg and 200 mg of entrectinib for oral administration.

- Entrectinib 100 mg capsule is a size 2, 2-piece capsule with yellow opaque body and cap with ENT 100 imprinted in blue on the body and is packaged in (b) (4) HDPE bottle with 30 capsule counts.
- Entrectinib 200 mg capsule is a size 0, 2-piece capsule with orange opaque body and cap with ENT 200 imprinted in blue on the body and is packaged in (b) (4) HDPE bottle with 90 capsule counts.

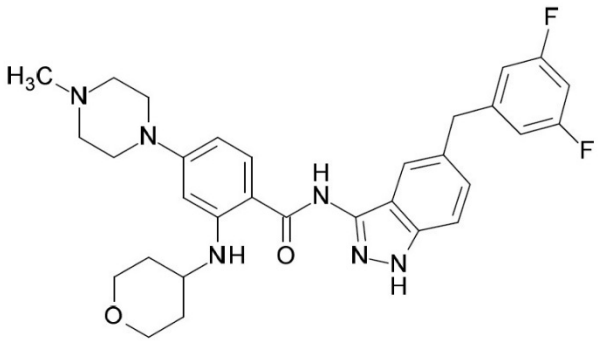
(b) (4)

The drug products are packaged in HDPE bottle with (b) (4) (b) (4) caps.

Drug Substance

The entrectinib drug substance (DS) has the following chemical name, structural formula, molecular formula, and molecular weight.

Figure 2: Entrectinib Structure and Chemical Name



Chemical Name: *N*-{5-[(3,5-difluorophenyl)methyl]-1*H*-indazol-3-yl}-4-(4- methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide
Mol. Formula: $C_{31}H_{34}F_2N_6O_2$ Mol. Wt.: 560.64 g/mol
The drug substance is manufactured (b) (4) (b) (4) (b) (4). The CMC review team determined that the proposed

starting materials are acceptable and that the control strategy (b) (4) appears to ensure the impurity profile of the drug substance.
The drug substance (DS) specification for entrectinib includes the following critical quality attributes (CQAs): appearance and color by visual inspection, identification by HPLC, IR, and XRPD (b) (4), impurities (organic impurities by HPLC and residual solvents by HS-GC), assay by HPLC, particle size by laser diffractometry, (b) (4) by ICP-MS per USP <232>, and residue on ignition per USP <281>.
Specified and unspecified impurities are controlled to the ICH Q3A qualification and identification thresholds, respectively. A total of seven compounds were identified as genotoxic or potentially genotoxic in accordance with the classification scheme outlined in ICH M7. All other compounds that underwent the assessment belong to Class 5 after being tested *in silico* negative using two orthogonal methods, or after Ames-negative testing following a positive *in silico* result in at least one of the two *in silico* methods. A thorough analysis of the clinical batches and of purging studies found only negligible amounts of the genotoxic impurities. Therefore, no specific controls are included in the drug substance specification for potential or known genotoxic impurities except for benzene.
(b) (4)

The NDA submission included batch analyses data for 28 DS batches including the development, clinical, toxicology, stability, and commercial batches. The CMC review team determined that the batch analyses data conformed to the proposed DS specification for commercial, primary stability, and late clinical batches. Twelve months of primary stability data were available for four DS batches. In addition, up to 24 months of supportive stability data were also provided. The container closure system used for these batches was representative of the proposed commercial packaging to support the proposed retest period of (b) (4) months while store at no more than (b) (4) in the proposed container closure system (b) (4) (b) (4). Forced degradation study showed that entrectinib is not sensitive to the combination of elevated temperature, thermal, light, and humidity conditions. It is however, unstable under acidic, basic, and oxidative conditions.
Twelve months stability data on four primary stability batches supports an initial retest period of (b) (4) months for entrectinib DS while (b) (4) in the proposed container closure system.

Drug Product [Entrectinib Capsules, 100 and 200 mg]
The proposed commercial drug product (DP) is an immediate-release hard Hypromellose (HPMC) capsule containing 100 mg and 200 mg of entrectinib for oral administration.

The two strengths are visually distinguishable by size, color, and script. The excipients are all compendial or composed of compendial components. Excipient of animal origin (lactose) is supported by BSE/TSE compliance statements. These excipients have all been used in approved drug products at levels greater than proposed in the current product.

There are no overages in the drug product.

The proposed commercial formulation is an immediate-release hard capsule for oral administration manufactured with standard excipients using conventional equipment and manufacturing process. The intended market formulation (F06) is designed to be equivalent to the clinical formulation (F2A) and enable a robust commercial-scale manufacturing process using compendial excipients. Bioequivalence between the market (F06) and pivotal (F2A) formulations was demonstrated.

The drug product commercial manufacturing process (b) (4) (b) (4). The composition of the 100 mg and 200 mg capsule (b) (4) (b) (4) use the same commercial manufacturing process. (b) (4) (b) (4) (b) (4). The proposed commercial batch size for the 200 mg and 100 mg doses is (b) (4) (b) (4) for both strengths. (b) (4) (b) (4)

Genentech provided 12 months primary stability data at 30oC/65%RH and 6 months primary stability data at 40oC/75%RH for three primary batches of each entrectinib capsules, 100 mg and 200 mg, manufactured at the intended commercial manufacturing site (Mayne Pharma) and packed at Mayne Pharma. Genentech also provided 6 months supportive site-specific stability data at 30oC/75%RH and 6 months stability data at 40oC/75%RH for three batches of each entrectinib capsules, 100 mg and 200 mg, manufactured at the intended commercial bulk manufacturing site (b) (4) and packed at the commercial packaging site (Roche Kaiseraugst).

All batches were tested for stability indicating parameters (description of capsule and capsule content, content per capsule of entrectinib, degradation products, (b) (4) dissolution, and microbial limits). All stability data show that there is no apparent change of quality attributes on long-term (30°C/65% RH or 30°C/75% RH) or accelerated stability (40°C/75% RH). On the basis of 12 months long-term stability data for the registration stability batches, a 24-month shelf life is granted when the product is stored below 30°C (86°F).

Both photo-stability and in-use stability to simulate the actual use of the product were also provided with no significant changes/trends noted. Thus, no stated in-use period is necessary in the labeling.

The Quality review team recommended that the drug product be granted a 24-month shelf life when stored below 30°C (86 °F)

Pursuant to 21 CFR 25.31(b), Genentech submitted a request for Categorical Exclusion from the requirement to prepare an environmental assessment for entrectinib. OPQ granted the

request for a waiver from an environmental analysis since this product is indicated for an orphan population and quantities entering the aquatic environment will be exceptionally low (below 1 part per billion). No extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action.

Facility Evaluation

The Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

(b) (4)

The Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable" for the following drug product manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile.

(b) (4)

- F. Hoffmann-La Roche Ltd. (FEI #: 3002807200) in Basel, Switzerland
- F. Hoffmann-La Roche Ltd. (FEI #: 3003973536) in Kaiseraugst, Switzerland

Biopharmaceutics Evaluation

Biopharmaceutics review evaluated 1) the proposed dissolution method, 2) the proposed dissolution acceptance criterion, 3) the need for bridging the different formulations and packaging site throughout the product development stage, and 4) the biowaiver request for the 100 mg F06 to-be-market drug product.

The dissolution profile data for various testing parameters and discriminating ability of the proposed dissolution method below was determined to be acceptable as a quality control tool for batch release and stability testing of the 100 mg and 200 mg entrectinib capsules.

The proposed acceptance criterion of "Q= (b) (4)% in 60 minutes" for batch release and on stability for the proposed drug product based on the bio-batch, clinical, and stability batches was also determined to be acceptable.

The comparative dissolution profiles using the proposed dissolution method and f2 similarity analysis with f2 value (50.51) > 50 indicates that three registration batches of the 100 mg and 200 mg F06 drug product manufactured (b) (4) and packaged at (b) (4) and Roche Kaiseraugst are similar and provide a bridge between the two packaging sites.

The biowaiver request for the 100 mg F06 drug product was granted based on 1) the compositional proportionality between the 100 mg and 200 mg strength drug product with respect to entrectinib, the active pharmaceutical ingredient (API) and excipients; 2) bioequivalence between the 200 mg F06 and F2A drug products in the bioequivalence (BE) study RXDX-101-15; 3) linear pharmacokinetics of the F06 drug product between the dose ranges of 100 mg - 600 mg under fasted condition based on the bioavailability study RXDX-101-12; and 4) similarity in the dissolution profile data for the 100 mg and 200 mg F06 drug product.

4.3. Clinical Microbiology

The application was reviewed by OPQ's Division of Microbial assessment. The reviewers did not identify any issues that would preclude approval of entrectinib capsules under NDA 212726 or NDA 212725. CMC microbiology reviewers determined that the microbiology controls for the entrectinib solid dosage form was adequate. Due to the controls on raw materials, dry manufacturing process, and manufacturing site inspection history, microbial limits testing was deemed unnecessary.

4.4. Devices and Companion Diagnostic Issues

Test for activating *NTRK* rearrangements

Several challenges remain for *NTRK* fusion testing in the post-approval setting. For example, the most popular commercially available DNA next-generation sequencing (NGS0 panels, such as FoundationOne CDx, may not detect certain *NTRK* gene fusions (Kheder *et al.* 2018). However, the addition of RNAseq to NGS testing has resulted in high sensitivity and specificity rates, 93% and 100% respectively, in detecting clinically actionable gene fusions. In addition, RNAseq requires no prior knowledge of fusion partners or intronic/exonic break points. For this reason, FDA requested and Genentech agreed to a post-marketing requirement to identify an analytically validated test for detection of *NTRK* in-frame gene fusions.

Kheder *et al.* (2018) stated that while FISH is considered the gold standard for detecting gene fusions, it can only detect a single target at a time. For instance, commonly used break-apart FISH probe scans detect gene fusions but not the fusion partner. In addition, designing multiple probes for detecting *NTRK* fusion partners is cost ineffective and time consuming, making it not amenable for high-throughput screening.

Hechtman *et al.* (2017) reported that a pan-TRK fusion immunohistochemistry (IHC) test had sensitivity and specificity rates of 95.2% and 100%, respectively. However, researchers at MD Anderson Cancer Center were not able to replicate these findings. A two-step diagnostic method incorporating rapid IHC screening that uses a cocktail of antibodies including anti-pan-Trk antibodies, followed by anchored multiplex PCR (AMP) showed that IHC screening had a 100% negative predictive value for excluding samples devoid of gene rearrangements.

According to IR-37 received May 10, 2019, out of the 54 efficacy evaluable patients, 56% (n=30) of genomic alterations in tumor samples were confirmed by RNA-based NGS, 35% (n=19) by DNA-based NGS, 3 tumor samples by DNA and RNA-based NGS, 1 tumor sample by PCR, and 1 tumor sample by Nanostring. The fusion was predicted to be in-frame for 46 patients. There was no information available to predict frameness for 8 patients. The concomitant oncodrivers were assessed for 25 patients, and not assessed for 29 patients. No tissue was available for retesting of any sample from either the *ROS1* or the *NTRK* cohort. For the 54 patients enrolled in entrectinib studies comprising the pooled efficacy population supporting this application requiring the documented presence of an *NTRK* fusion for determination of patient eligibility, most of the tests performed were NGS-based (96%).

For inclusion in the integrated *NTRK*-fusion positive efficacy analysis set, only patients harboring in-frame fusions of the *NTRK1*, *NTRK2* or *NTRK3* gene that were detected by a nucleic acid-based diagnostic method with a functional kinase domain were considered to have a positive gene fusion status. Patients with a second oncodriver (e.g. EGFR, ALK) were excluded from the efficacy evaluable population, but were eligible to receive treatment in the "non-evaluable" basket.

Molecular pathology reports including 43 local and 58 Pharos tests were provided in response to an informational request (IR-11) and were reviewed by the FDA genomics staff. Preliminarily, many of the provided molecular pathology reports (both local and Pharos) did not provide *NTRK* fusion breakpoints or indicated finding of an in-frame fusion, and secondary oncodrivers were not systematically assessed in all patients (such that if a patient was screened by a local comprehensive test, additional information on other oncodrivers may have been available).

There were 3 patients identified as having a second oncodriver or out-of-frame fusion (1 flagged with a second oncodriver (USUBJID RXDX-101 (b) (6), flag of Y for ONCOEXFL), 1 patient with both a second oncodriver and out-of-frame fusion (USUBJID RXDX-101 (b) (6), flags of Y for ONCOEXFL and FRAMEOUT), and 1 patient with an out of frame fusion (USUBJID RXDX-101 (b) (6), flag of Y for FRAMEOUT). These were the 3 patients excluded from the efficacy analysis set under the Failure to meet eligibility criteria (non-evaluable cohort) bin of "*NTRK* biomarker ineligibility."

Genentech did not submit (or identify a corporate partner to develop and submit) a premarket approval application (PMA) for an in vitro companion diagnostic device contemporaneously with these NDAs (212725 and 212726). Therefore, approved labeling will state that there is no approved companion diagnostic test for the identification of patients with *NTRK*-fusion solid tumors. DOP2 consulted the Center for Devices and Radiologic Health (CDRH) regarding use of local tests for determination of *NTRK* fusion status. Given the efficacy of entrectinib in patients with *NTRK* gene fusions in unresectable or metastatic solid tumor specimens and the availability of non-companion diagnostic testing for *NTRK* fusions in solid tumors, the clinical review team and CDRH agreed that it is in the best interest of U.S. patients to approve entrectinib before one or more companion diagnostic assays are ready for a PMA submission.

Clinical Reviewer Comment: *Genentech has agreed to a postmarketing commitment (PMC) to develop an analytically and clinically validated companion diagnostic test for selection of patients with NTRK fusion-positive solid tumors for whom entrectinib is safe and effective.*

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Entrectinib (RXDX-101) is a small molecule drug with an established pharmacological class of kinase inhibitor. In biochemical assays, entrectinib inhibited wild-type tropomyosin receptor kinases (TRK) A, B, and C, ROS proto-oncogene1 (ROS1), and anaplastic lymphoma kinase (ALK) proteins at inhibitory concentrations (IC_{50}) between 0.057 and 3.55 nM, with M5, the major human metabolite of entrectinib, having activity at similar inhibitory concentrations ranging from 0.007 to 6.97 nM. These concentrations are clinically achievable based on a maximum concentration (Cmax) of 3130 nM in patients treated at the once daily oral dose of 600 mg and >99% protein binding (~30 nM free entrectinib). In a second biochemical assay, entrectinib inhibited ALK, TRKA, and ROS1, as well as JAK2, ACK1, and JAK1 at IC_{50} values ranging from 0.019 to 0.164 µM.

TrkA, TrkB, and TrkC are encoded by the neurotrophic tyrosine receptor kinase [*NTRK*] genes *NTRK1, NTRK2,* and *NTRK3,* respectively. ROS1 is encoded by the gene *ROS1* and ALK is encoded by the gene *ALK*. *NTRK*, *ROS1*, and *ALK* gene fusions resulting from chromosomal rearrangements can generate novel fusion oncoproteins that act as dominant drivers of tumorigenesis. Activation of the endogenous proteins occurs upon binding of ligands to the extracellular domains of the receptors, leading to receptor dimerization, phosphorylation, and signaling via the Ras/MEK/ERK, PI3K/AKT, and PLC-γ pathways; fusion proteins from gene rearrangements often lead to constitutive activation of the resulting proteins in the absence of ligand binding. Genentech conducted additional studies investigating the activity entrectinib and M5 against TRKs, ROS1, and ALK. In cellular anti-proliferation assays, entrectinib and M5 had IC_{50} values of less than 1 µM against 14 cell lines: five with *NTRK* fusions, four with *ROS1* fusions, and five with *ALK* dysregulation. The IC_{50} values for entrectinib inhibition of proliferation in cells overexpressing *NTRK* or *ROS1* fusions ranged from 0.37 to 20.1 nM. Evaluation of the mechanism of action in cells with TRK, ROS1, or ALK fusion proteins indicated that both entrectinib and M5 led to inhibition of downstream signaling pathways and induced cellular apoptosis.

Entrectinib showed in vivo antitumor activity in *NTRK*, *ROS1*, and *ALK* fusion-driven xenograft tumor models, leading to tumor growth inhibition (TGI) and tumor regressions in multiple tumor types expressing these fusions, including non-small cell lung carcinoma (NSCLC). Entrectinib was also able to inhibit tumor growth of *NTRK* and *ALK* fusion lines in intracranial implantation models, suggesting that therapeutic concentrations of entrectinib can reach the brain, and consistent with the finding that both entrectinib and M5 had significant distribution to the brain in rats (up to 60% of the plasma concentration following a single IV infusion) and dogs (approximately equal to the plasma concentrations in the one-month toxicology study).

Genentech evaluated the safety of entrectinib in toxicology studies of up to 13 weeks' duration in rats and dogs. In both species, in the one-month studies at doses that resulted in exposures ≥ human exposures at the 600 mg dose (~48 µM*hr), there was evidence of central nervous system (CNS) toxicity characterized by abnormal gait and lack of coordination, decreased activity, tremors, depression, decreased grip strength and impaired righting reflex. Based on the roles of the TRK proteins in multiple aspects of neurologic function, CNS effects are consistent with the expected pharmacological activity of entrectinib and occur clinically as well. In addition, in a secondary pharmacology screening assay, entrectinib had potential activity against other receptors that could contribute to CNS effects. As these preliminary assessments were conducted at concentrations that are significantly higher than those that are clinically relevant, FDA requested a PMR for conduct of follow-up assays to determine the potential for contribution of other targets to the toxicity of entrectinib. There was also evidence of anemia in both species accompanied by increased spleen weight and reticulocytes and, in the rat, extramedullary hematopoiesis. Anemia occurs clinically as well.

In the rat, the skin was a major target organ, with early deaths in the 13-week study attributable to skin lesions (sores/ulcerative dermatitis) at doses ≥15 mg/kg/day (approximately 0.3 times the human exposure by AUC at the 600 mg dose). Trk-deficient mice exhibit defective nociception (Smeyne et al., 1994), suggesting that there is a potential pharmacologically-mediated decrease in sensitivity to bodily damage that may contribute to the poor skin condition in rats. Increased neutrophils, likely associated with skin infections, also occurred. In addition, there was evidence of very mild phototoxicity with entrectinib in both in vitro and in vivo assays. Rash is a common finding clinically. In the in vivo phototoxicity assay, Genentech reported entrectinib-related findings of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium at 200 mg/kg, consistent with corneal opacity that occurred in 1-month studies in rats at exposures similar to the clinical dose. Ocular disturbances are a common clinical finding with entrectinib. Finally, consistent with literature reporting hyperphagia and obesity in mice that express reduced amounts of TrkB (Xu et al, 2003) and in a human with a missense mutation in *NTRK2*, the gene encoding TrkB (Yeo et al., 2004), in the 13-week study, entrectinib-treated male rats demonstrated increased food consumption.

In the 13-week dog study, there were no treatment-related deaths. The gastrointestinal tract was a target organ with clinical signs included discolored/liquid/mucoid feces and weight loss accompanied by dosing holidays and a need for canned food supplementation at the high dose level of 30 mg/kg (~0.16 times the human exposure at the 600 mg dose), as well as hypophosphatemia. Diarrhea, nausea, and hypophosphatemia occur frequently in entrectinib-treated patients. In the same study, multiple animals at dose levels ≥7.5mg/kg/day (~ 0.04 times the human exposure at the 600 mg dose) experienced footpad injuries and related skin complications (sores, scabs, swollen/discolored areas). In addition, animals at the 30 mg/kg dose level exhibited a trend towards QTc prolongation. QTc prolongation occurred more clearly in the 4-week repeat-dose study and single-dose study in dogs treated with 120 mg/kg entrectinib (3.2 times the human exposure by AUC at the 600 mg dose). These findings were

consistent with in vitro effects of entrectinib on hERG inhibition (IC_{50} of 0.6 µM) and clinical reports of QTc prolongation.

Although not typically recommended for drugs intended for the treatment of children with advanced cancer, Genentech also performed a study to evaluate the effect of entrectinib administration in juvenile rats. Animals received entrectinib at doses of 4, 8, or 16 mg/kg/day (approximately 0.06, 0.14, and 0.18 times the human exposure by AUC at the 600 mg dose at the end of the dosing period) between postnatal days 7-97, corresponding to the neonatal through young adult stages. Three preterm deaths associated with CNS toxicity occurred at the high dose. Two deaths (1 high dose, 1 low dose) were associated with kidney toxicity and one death (high dose) was accompanied by skin toxicity. Entrectinib caused dose-dependent delays in development including decreases in the rate of weight gain in all male dose groups and the high-dose females, growth rate (as measured by femur length), and delays in sexual maturation (statistically significant for all dose groups in both sexes). In juvenile animals, CNS-related toxicity was clear and included clinical signs of abnormal gait, tremors, decreased activity, convulsions, hunched posture, repetitive behavior, partly closed eyes, and piloerection. In addition, in high-dose animals there were decreases in forelimb and hindlimb grip strength as well as deficits in spatial learning and memory. The impairment in memory is consistent with known effects of TrkA signaling deficiencies in humans associated with the rare recessive disorder, congenital insensitivity to pain and anhidrosis (Indo et al., 1996). Other clinical signs included dehydration (seen in humans), skin scabs, and thin/lost fur. Consistent with studies in adult rats, dogs, and humans, entrectinib resulted in decreases in red blood cells, hemoglobin, and hematocrit, accompanied by increased spleen size and extramedullary hematopoiesis.

Genentech did not conduct carcinogenicity or fertility studies with entrectinib and, consistent with ICH S9, these studies were not warranted for the development of a drug intended for the treatment of patients with advanced cancer. Genentech did include a histopathological assessment of reproductive organs in all general toxicology studies and, with the exception of decreased prostate weight, there were no clear signs of effects on fertility. Entrectinib was aneugenic, but not mutagenic in in vitro genotoxicity studies.

To address the potential reproductive effects of entrectinib, Genentech conducted an embryo-fetal development study in rats. Administration of entrectinib to pregnant rats during the period of organogenesis (Gestation Days 6-17) did not result in maternal mortality or evidence of embryolethality; however, entrectinib did cause dose-dependent reductions in gravid uterine and fetal weight. The fetal weight decrements were statistically significant at doses ≥ 12.5 mg/kg (~0.2 times the human exposure at the 600 mg dose), the lowest tested dose. Fetal malformations occurred primarily at the high dose level of 200 mg/kg (~2.7 times the human exposure at the 600 mg dose) and included body closure defects (omphalocele and gastroschisis), micromelia, adactyly, limb hyperextension, and filamentous tail. Reduced skeletal ossification occurred frequently at doses ≥50 mg/kg (~ 0.9 times the human exposure at the 600 mg dose).

Beyond the animal findings in the embryo-fetal development study, there are additional concerns about the use of entrectinib during pregnancy due to the established role of Trk proteins in neuronal development (Tucker et al., 2001; Smeyne et al., 1994). Published reports of congenital somatic mutations in TRK proteins or their ligands suggest a relationship between deficient Trk signaling and development of schizophrenia, mood disorders, obesity, and peripheral sensory and motor disorders (Krantz 2015; Otnaess et al., 2009; Knable 1999; Lewis et al., 2005; Indo et al., 1996; Yeo et al., 2004). While embryo-fetal development studies can detect malformations in brain structure, they are not designed to assess motor development or psychiatric function and though a pre- and postnatal development study may be capable of evaluating some of these endpoints, they are not typically required for a drug intended to treat patients with advanced cancer. The clear CNS findings at low clinical exposure multiples in the juvenile animal study do, however, suggest an increased risk for entrectinib-mediated neurological effects during development. Given the published literature on the importance of Trk signaling in neural development, including human syndromes, the limitations of the embryo-fetal development studies to assess the toxicities of particular concern following disruption of this pathway, and the available animal data, there is a potential for significant neurocognitive effects in children exposed to entrectinib during prenatal development. The combination of the clear teratogenic findings in animals and the potential for neurological risks suggested by the mechanism of action and literature reports warrants a warning in the label for embryo-fetal risk. In addition, consistent with current recommendations for genotoxic compounds with embryo-fetal risk, the label also includes recommendations for contraception of 3 (b) (4) months for males (b) (4). Based on the half-life of entrectinib the label also includes a recommendation not to breastfeed for one week after the last dose of ROZLYTREK.

There are no outstanding issues from a nonclinical perspective that would prevent approval of entrectinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is *ROS1*-positive, and for the treatment of adult and adolescent patients with (b) (4) (b) (4) metastatic solid tumors that are neurotrophic tyrosine receptor kinase (*NTRK*) fusion-positive who have either progressed (b) (4) (b) (4).

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

Genentech evaluated the selectivity of entrectinib (RXDX-01-0177, RXDX-101, NMS-01191372) using a HotSpot Kinase profiling assay (Study #1087232). Briefly, Genentech screened for entrectinib activity against a panel of 7 kinases using serial dilutions of entrectinib and ^{33}P-ATP

(0.01 µCi/µL) and calculated IC_{50}s based on the amount of radioactive substrate on ion exchange filters. Entrectinib inhibited TRK A, B and C, ROS1, and ALK at concentrations that were clinically relevant based on a Cmax at the 600 mg clinical dose of 3130 nM and considering the >99% level of entrectinib protein binding (~31 nM free entrectinib). Using a similar assay, Genentech showed that M5, the major human metabolite of entrectinib had similar inhibitory activity against TRK targets, ROS1, and ALK compared to entrectinib (Study #1087249, Table 5).

Table 5: Entrectinib and M5 IC_{50} values for TRKs, ROS1, and ALK

Target	RXDX-101* IC_{50} (nM)	RXDX-101[a] IC_{50} (nM)	M5[a] IC_{50} (nM)
TRKA	1.66	3.55	6.97
TRKB	0.0567	0.008	0.05
TRKC	0.107	0.007	0.007
ROS1	0.181	0.05	0.25
ALK	1.58	0.996	1.94
JAK2	-	5.38	14.15

*Study report 1087232. [a]Study report 1087249, data represents mean from two separate experiments.

In a second kinase screening selectivity assay (Study #1087233), Genentech assessed entrectinib selectivity against 51 kinases. Entrectinib inhibited ALK, TRKA, ROS1, JAK2, ACK1, and JAK1 at IC_{50} values ranging from 0.019 to 0.164 µM (Table 6). Other kinases with an IC_{50} values less than 1 µM included AUR2, FAK, BRK, JAK3, IGFR1, FLT3, IR, and RET.

Table 6: Entrectinib IC_{50} values against selective kinases

Target	IC_{50} (µM)	Target	IC_{50} (µM)	Target	IC_{50} (µM)	Target	IC_{50} (µM)	Target	IC_{50} (µM)
TRKA	0.002	AUR2	0.220	FLT3	0.299	LCK	1.519	VEGFR2	4.058
ROS1	0.007	FAK	0.227	IR	0.366	KIT	1.725	PKCβ	4.061
ALK	0.019	BRK	0.241	RET	0.540	MELK	2.926	EphA2	4.964
JAK2	0.038	JAK3	0.277	FGFR1	1.033	AUR1	2.986	Syk	5.021
ACK1	0.068	IGFR1	0.294	VEGFR3	1.244	C-ABL	3.647	CDK2/CYCA	5.773
JAK1	0.164	-	-	-	-	-	-	-	-

Additional screening using a SelectScreen™ profiling service against 293 kinases (Study # 1089804) demonstrated that 100 nM of entrectinib inhibited 6 kinases greater than 95%, including ALK, ROS1, TXK, TRKA, TRKB, and TRKC, and 2 kinases greater than 80% (CSF1R and JAK2), 4 kinases greater than 60% (ITK, LTK, MuSK, and TYK2).

In Studies #1087234 and 1090429, Genentech evaluated the anti-proliferative activity of entrectinib and the M5 metabolite in panels of up to 308 cell lines (269 adult and 39 pediatric). Briefly, investigators seeded cells into 384 well plates with serial dilutions of entrectinib or M5 for 72 hours then determined cell proliferation using the CellTiterGlo assay by measuring ATP concentration (#1087234) or the Vi-CELL analyzer (#1090429) and calculated IC_{50} values. The panels consisted of tumor cell lines derived from leukemia/lymphoma, lung, colorectal, breast, kidney adenocarcinoma, melanoma, multiple myeloma, ovarian, glioblastoma, pancreatic

adenocarcinoma, prostatic carcinoma, cervical adenocarcinoma, astrocytoma, osteosarcoma, neuroblastoma, bladder carcinoma, and gliosarcoma tumors as well as non-tumoral cell lines. In the first assay, entrectinib had the highest anti-proliferative activity against cell lines known to bear constitutively active forms of ALK such as anaplastic large cell lymphoma (ALCL) lines Karpas-299 (IC_{50} = 0.031 µM), SR-786 (IC_{50} = 0.081 µM), SU-DH-1 (IC_{50} = 0.020 µM), and SUP-M2 (IC_{50} = 0.041 µM). Entrectinib also inhibited the growth of the NSCLC line NCI-H2228, which bears the *EML4- ALK* gene rearrangement, with an IC_{50} of 0.068 µM, and of KM12, a colorectal cancer cell line with the *TPM3-TrkA* gene rearrangement, with an IC_{50} of 0.017 µM. In the second study, both entrectinib and M5 had IC_{50} values of < 1 µM in 15 cell lines, including five cell lines with *NTRK* fusions, four with *ROS1* fusions, and five with *ALK* dysregulation (Table 7).

Table 7: Anti-proliferative activity of entrectinib and M5 against cell lines harboring specific *NTRK*, *ROS1*, and *ALK* fusion

Fusion	Cell line	Cancer type	Specific fusion	Entrectinib IC_{50} (nM)	M5 IC_{50} (nM)
NTRK	IMS-M2	AML	ETV6-NTRK3	12	15
	M0-91	AML	ETV6-NTRK3	17	9
	CUTO-3	NSCLC	MPRIP-NTRK1	94	122
	KM12	CRC	TPM3-NTRK1	77	113
	G111	Glioma	EML4-TRK3	276	157
ROS1	CUTO-27	NSCLC	CD74-ROS1	201	135
	CUTO-28	NSCLC	TPM3-ROS1	215	244
	HCC1493	Breast carcinoma	CD74-ROS1	230	199
	HCC-78	NSCLC	CD74-ROS1	524	621
ALK	SU-DHL-1	T-cell ALCL	NPM-ALK	188	147
	DEL	T-cell ALCL	NPM-ALK	204	294
	NB-1	Neuroblastoma	ALK amplification	240	138
	KARPAS-299	T-cell ALCL	NPM-ALK	257	197
	NCI-H2228	NSCLC	EML4-ALK	669	798
Other	MV-4-11	BBML	FLT3-ITD	431	243

ALCL=anaplastic large-cell lymphoma; AML=acute myeloid leukemia; CRC=colorectal cancer; NSCLC=non-small cell lung cancer; BBML=biphenotypic B myelomonocytic leukemia

Genentech further assessed the in vitro anti-proliferative activity of entrectinib against cells bearing *NTRK* fusion genes by transducing mouse Pro B Ba/F3 cells with *NTRK* fusion cDNAs using a lentiviral system (Study #1087236). Investigators incubated *NTRK* fusion expressing Ba/F3 cells with serial dilutions of entrectinib and measured proliferation using the CellTiterGlo assay. Mouse Ba/F3 cells normally require IL3 for proliferation; however, cells with *NTRK* fusions proliferate independent of IL3. Entrectinib inhibited *NTRK* fusion-dependent growth with IC_{50} values ranging from 0.37 to 5.39 nM (Table 8). Ba/F3 cells without *NTRK* fusions served as controls and did not proliferate without IL3 present; the entrectinib IC_{50} for control cells incubated in IL3 was greater than 1000 nM.

Table 8: Anti-proliferative activity of entrectinib against *NTRK* fusion expressing Ba/F3 cells

NTRK fusion	IL3 independent Proliferation	IC_{50} (nM)	NTRK fusion	IL3 independent Proliferation	IC_{50} (nM)
Ba/F3 control	No	>1000	PLEKHA6-NTRK1	Yes	1.05
TPM3-NTRK1	Yes	2.52	VCL-NTRK2	Yes	5.39
LMNA-NTRK1	Yes	1.28	AFAP1-NTRK2	Yes	2.85
ETV6-NTRK1	Yes	2.50	TRIP13-NTRK2	Yes	0.70
BCAN-NTRK1	Yes	0.51	ETV6-NTRK2	Yes	4.12
SQSTM1-NTRK1	Yes	0.85	ETV6(e5)-NTRK3(e15)	Yes	4.47
SCYL3-NTRK1	Yes	1.42	ETV6(4)-NTRK3(e14)	Yes	0.37

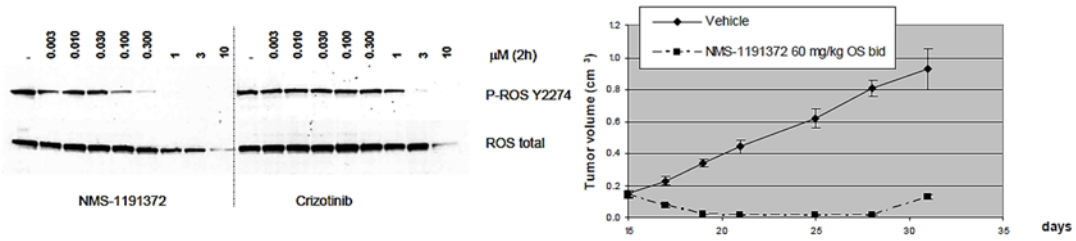
In Study #1087687, investigators evaluated the anti-proliferative activity of entrectinib and other available ROS1 inhibitors against the NSCLC line CUTO-28, which harbors a *TPM3-ROS1* fusion. Entrectinib inhibited the proliferation of CUTO-28 cells with IC_{50} values that were similar to several other inhibitors known to target ROS1 including crizotinib, ceritinib, and lorlatinib (Table 9).

Table 9: Comparison of anti-proliferative activity of entrectinib to other available ROS1 inhibitors in a *TPM3-ROS1* fusion expressing NSCLC line

Compound	IC_{50} (nM)	Compound	IC_{50} (nM)	Compound	IC_{50} (nM)
Entrectinib	20.1	Cabozantinib	34.8	Ensartinib	>1000
Ceritinib	176.9	Altiratinib	113.2	TAE684	18
Crizotinib	36.6	Brigatinib	81.5	Dovitinib	>1000
Lorlatinib	1.1	TPX-0005	10.5	Belizatinib	98.1

In the Ba/F3 ROS1-dependent TEL-ROS1 cell line, entrectinib inhibited in vitro cellular proliferation with an IC_{50} of 5 nM. Western blot analysis showed that a 2-hour incubation with entrectinib decreased phosphorylated ROS, with complete inhibition observed at 1 µM, compared to 10 µM for crizotinib. Adult SCID mice bearing subcutaneous Ba/F3 TEL-ROS1 tumors (left flank) treated with 60 mg/kg entrectinib starting on Day 15 for 10 consecutive days showed tumor growth inhibition (TGI) of 98% (Figure 3).

Figure 3: Entrectinib decreased phosphorylated ROS in Ba/F3 TEL-ROS1 cells (left) and showed anti-tumor activity in mice bearing Ba/F3 TEL-ROS1 tumors (right)



(Figure excerpted from Study #1087258)

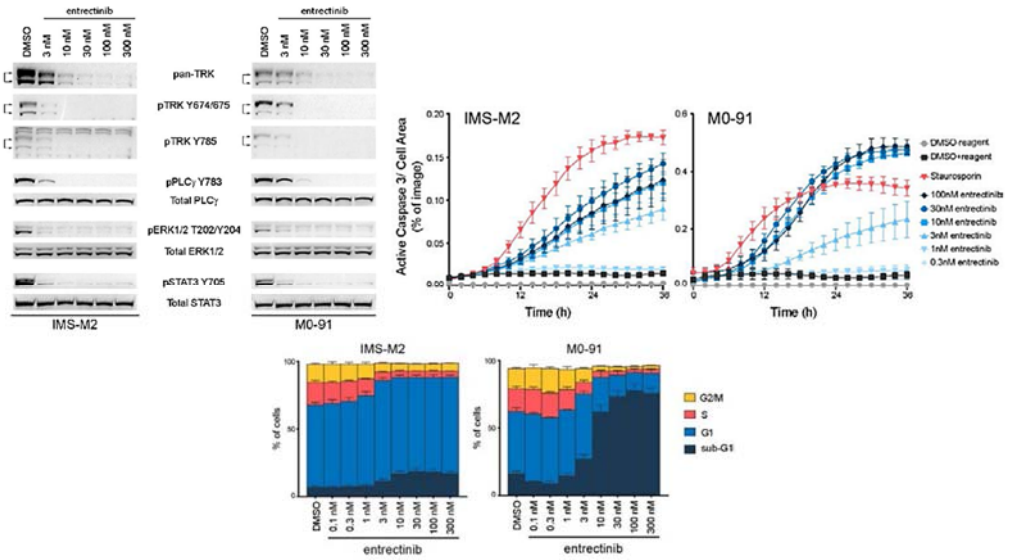
In a CellTiterGlo assay, entrectinib had anti-proliferative activity against two acute myeloid leukemia (AML) cell lines harboring *ETV6-TRK3* fusions (IMS-M2 and M0-91) at 6 to 190-fold lower concentrations compared to larotrectinib, crizotinib, and TSR-011 (Table 10). In addition, entrectinib inhibited phosphorylation of the ETV6-TRK3 fusion protein and known downstream TRKC targets, induced apoptotic cell death as measure by Caspase 3 activity, and induced cell cycle arrest in the G1 phase in a dose dependent manner (Figure 4).

Table 10: Entrectinib had greater anti-proliferative activity compared to crizotinib, larotrectinib, and TSR-011 against AML cells bearing *ETV6-TRK3* fusions

IC_{50} (nM)	Entrectinib	Crizotinib	Larotrectinib	TSR-011
IMS-M2	0.47	60.9	3.06	27.7
M0-91	0.65	121.9	4.1	51.7
Kasumi-1	>1000	>1000	>1000	>1000

IMS-M2 and M0-91 carry the ETV6-NTRK3 fusion.
Kasumi-1 AML cells carry the RUNX1-RUNK1T1 translocation.

Figure 4: Entrectinib inhibits phosphorylation of TRKC and its downstream targets (upper left) and led to dose-dependent increases in caspase 3 (upper right) and cell cycle arrest in G1 (bottom) in two AML cell lines bearing the *ETV6-TRK3* fusion

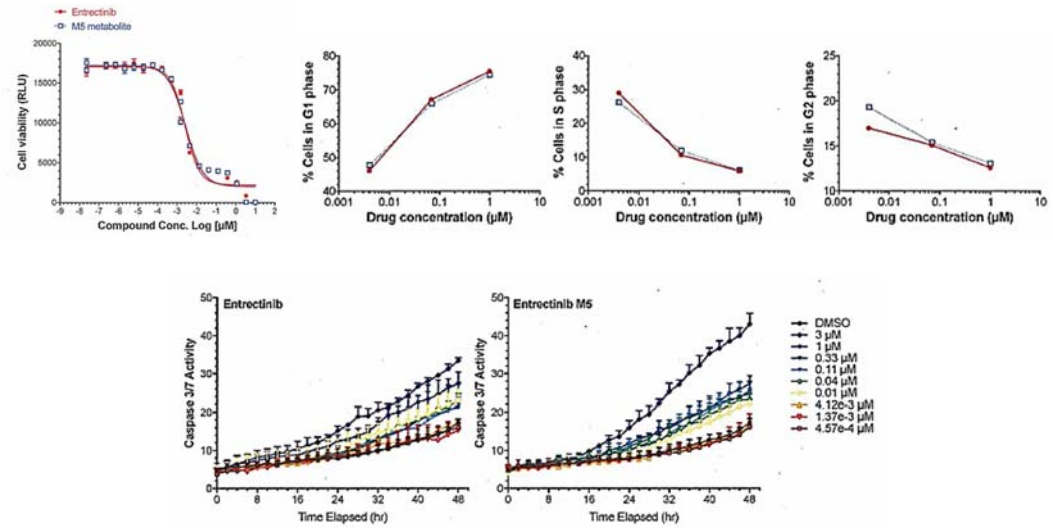


(Figure excerpted from Study #1087247)

Study #1089907 investigated the anti-proliferative, cell cycle, and apoptotic activity of entrectinib and its major metabolite M5 against the human colorectal carcinoma cell line KM12, which contains the *TPM3-NTRK1* fusion. Investigators treated KM12 cells with serial dilutions of entrectinib or M5 then assessed cell cycle and caspase 3/7 activity. The EC_{50} values for induction of cell death for entrectinib and M5 were 2.76 and 2.63 nM, respectively. Both compounds increased the percentage of cells in the G1 phase of the cell cycle with a

compensatory decrease in the number in the S and G2 phases, consistent with inhibition of the cell cycle. Additionally, both entrectinib and M5 increased the percentage of cells positive for caspase 3/7 activity, indicating that both enhanced apoptosis in the KM12 cell line. Entrectinib also reduced phosphorylation of TRKA and its downstream targets PLCγ, AKT, and MAPK in a second study (Study #1087242)

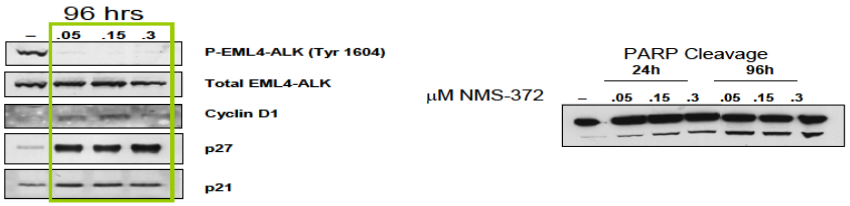
Figure 5: Entrectinib showed anti-proliferative activity, led to cell cycle arrest in G1, and increased caspase 3/7 activity in a dose-dependent manner in CRC cells bearing the TPM3-NTRK1 fusion



(Figure excerpted from Study #1089907)

Entrectinib inhibited proliferation of NCI-H2228 (EML4-ALK fusion) cells in vitro after 72 hours of incubation with an IC_{50} of 68 nM in Study #1087265. A 96-hour treatment inhibited ALK phosphorylation with concomitant induction of markers of G1 block such as cyclin D1, p27, and p21. Following 24 and 96 hours of treatment, there was a time-dependent accumulation in the GI phase of the cell cycle (data not shown) and cleavage of PARP as a marker of apoptosis (Figure 6).

Figure 6: Entrectinib inhibited ALK phosphorylation and induced markers of G1 block (right) and led to PARP cleavage (left) in NSCLC cells with the *EML4-ALK* fusion



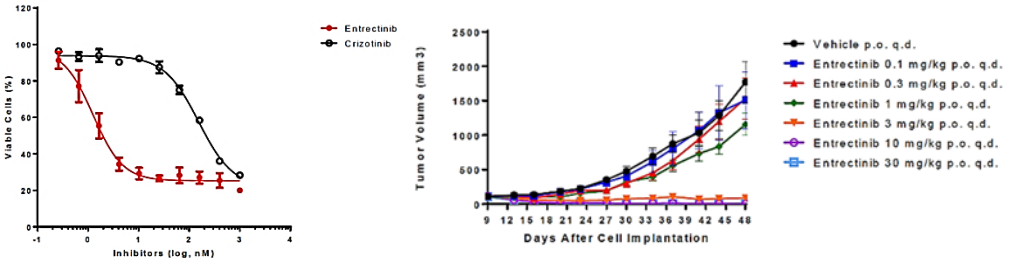
(Figure excerpted from Study #1087265)

B. In Vivo Studies

NTRK fusions

In Study #1087237 Genentech evaluated the in vitro and in vivo anti-proliferative and anti-tumor activity of entrectinib in the NSCLC line CUTO-3 which contains the *MPRIP-NTRK1* fusion gene. Using the CellTiterGlo assay to measure in vitro cellular proliferation, Genentech compared entrectinib and crizotinib and showed that entrectinib inhibited proliferation of CUTO-3 cells at concentrations 100 times lower than crizotinib, with IC_{50}s of 1.6 and 153.5 nM, respectively (Figure 7; left panel). In vivo, CUTO-3 cells were implanted subcutaneously in the right flank of adult athymic nu/nu female mice, and treated with vehicle or 0.1, 0.3, 1, 3, 10, or 30 mg/kg of entrectinib orally once daily after tumors reached approximately 130 mm^3. Entrectinib showed dose-dependent tumor growth inhibition (TGI), with 3 mg/kg having a 100% TGI and 10 and 30 mg/kg reducing tumor volume below measurable limits resulting in TGI for both of greater than 100% (Figure 7; right panel).

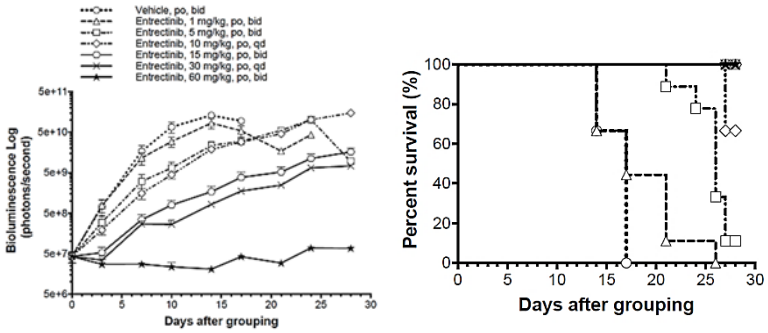
Figure 7: Entrectinib had greater anti-proliferative activity against NSCLC cells bearing the MPRIP-NTRK1 fusion compared to crizotinib (left) and showed dose-dependent anti-tumor activity in a xenograft mouse model (right)



(Figure excerpted from Study #1087237)

Entrectinib showed dose-dependent anti-tumor activity in an intracranial mouse model using a luciferase labeled colorectal carcinoma cell line, KM12-luc, that contains the *TPM3-NTRK1* fusion, suggesting blood brain barrier penetration by entrectinib. In Study #1090134, investigators injected adult female Balb/c mice with 3 x 10^4 KM12-luc cells into the right lobe of the brain and allowed tumors to grow for 5 days before measuring baseline bioluminescence and beginning dosing on Day 6 with entrectinib at dose levels of 0, 1, 5, 15, or 60 mg/kg twice daily (BID) for 28 days or 10 and 30 mg/kg three times daily (TID) for 28 days. Treatment with entrectinib did not affect body weight. Entrectinib decreased the bioluminescence with 60 mg/kg having the greatest effect, decreasing the amount of tumor bioluminescence and increasing survival up to 30 days compared to 7-12 for vehicle treated mice (Figure 8).

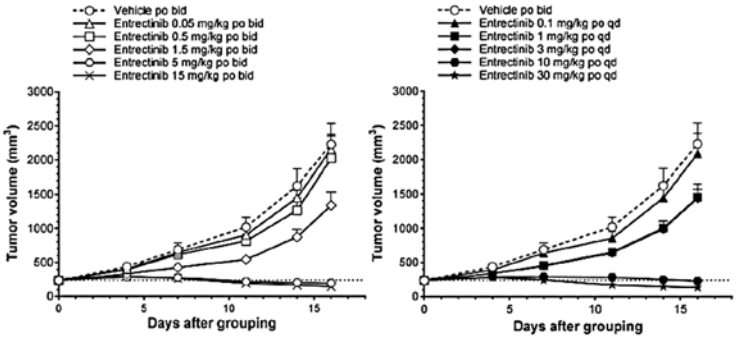
Figure 8: Entrectinib had anti-tumor activity and increased survival in a mouse intracranial tumor model using CRC cells with a *TPM3-NTRK1* fusion



(Figure excerpted from Study #1090134)

In Studies 1090136 and 1087241, adult female and male Balb/c nude mice were subcutaneously injected with 5 x 10^6 KM12-luc labeled or unlabeled cells into the right or left flank. Females received entrectinib orally starting on Day 15 at doses of 0, 0.05, 0.5, 1.5, 5, or 15 mg/kg BID or 0.1, 1, 3, 10, or 30 once daily (QD) for 15 days. BID doses of ≥5 mg/kg and QD doses of ≥10 mg/kg led to tumor regression (Figure 9). Males received entrectinib at doses of 0, 15, 30, or 60 mg/kg BID starting on Day 8 for 10 consecutive days and showed TGI ranging from 87-94% compared to vehicle controls (data not shown).

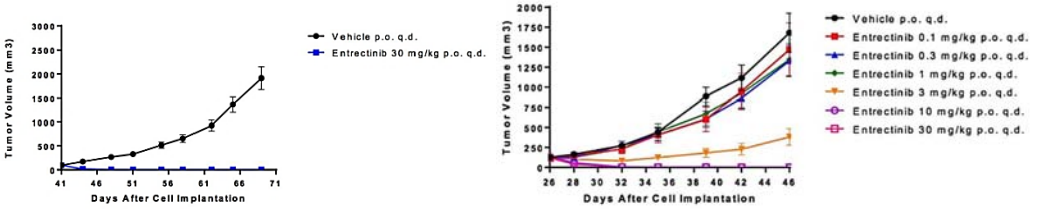
Figure 9: Entrectinib had anti-tumor activity against subcutaneous CRC tumors bearing the TPM3-NTRK1 fusion



(Figure excerpted from Study #1090136)

In Study #1087257, mice bearing patient derived xenograft (PDX) sarcoma, G002, harboring the *TPM3-NTRK1* fusion, treated with 30 mg/kg entrectinib orally once daily for 28 days had TGI of greater than 100% for all days measured. In a dose range activity study (#1087246) G002 bearing mice treated with entrectinib orally once daily at doses ranging from 0.1 and 30 mg/kg indicated that doses greater than 1 mg/kg resulted in significant tumor inhibition and regression, with doses starting at 3 mg/kg having a TGI of 84% or greater (Figure 10).

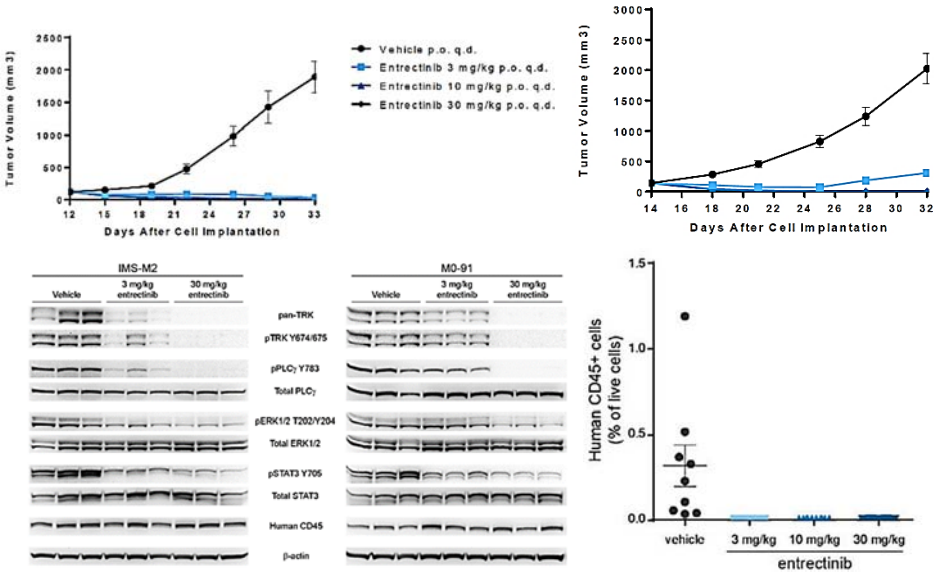
Figure 10: Entrectinib had dose-dependent anti-tumor activity against a PDX sarcoma bearing the TPM3-NTRK1 fusion



(Figures excerpted from Studies #1087257 and 1087246)

In Studies #1087247 and #1087243, Genentech evaluated the antitumor activity of entrectinib against 2 acute myeloid leukemia (AML) cell lines (IMS-M2 and M0-91) driven by the *ETV6-NTRK3* fusion gene. Investigators subcutaneously injected $1x10^6$ tumor cells into the right flank of adult female CB.17 SCID mice and allowed tumor volume to reach 120-140 mm^3 before initiation of entrectinib at daily oral doses of 0, 3, 10, or 30 mg/kg for a total of 21 days. Entrectinib decreased tumor growth by 100% in IMS-M2 and M0-91 tumors at the 10 and 30 mg/kg dose levels. A single dose of 3 or 30 mg/kg resulted in dose-dependent decreases in phosphorylated TRKC in harvested tumors, plus decreased phosphorylation of downstream targets PLCγ, ERK1/2, and STAT3. Evaluation of the effect of entrectinib on leukemic cells in sites such as bone marrow, where leukemic cells spontaneously migrate, showed that entrectinib eliminated bone marrow resident tumor cells as measure by flow cytometry separation of human CD45+ cells (Figure 11).

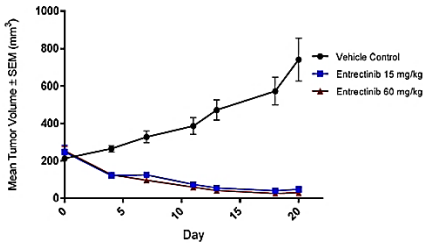
Figure 11: Entrectinib had anti-tumor activity (top), decreased phosphorylated TRKC (bottom left), and decreased leukemic cells in bone marrow in an ETV6-NTRK3 fusion bearing AML xenografts (bottom right)



(Figures excerpted from Studies #1087247 and 1087243)

In Study #1087238 assessing a patient derived xenograft (PDX) model of human head and neck cancer, CTG-0798 harboring the *ETV6-NTRK3* fusion, mice treated with entrectinib at 15 and 60 mg/kg PO, BID for 21 days had significant tumor regressions of 146 and 149% TGI at the 15 and 60 mg/kg doses, respectively (Figure 12).

Figure 12: Entrectinib showed anti-tumor activity against a PDX HNSCC harboring the ETV6-NTRK3 fusion



(Figure excerpted from Study #1087238)

ALK fusions

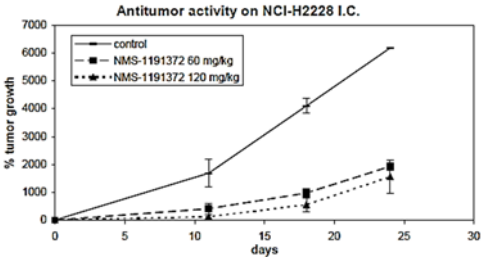
In Studies #1087263 and #1087265, Genentech evaluated the antitumor activity and mechanism of action of entrectinib using subcutaneously and intracranially implanted NCI-H2228 (NSCLC line containing the *EML4-ALK* fusion) tumors. Briefly, adult male Balb Nu/Nu mice were subcutaneously injected with 1 x 10^7 cells into the left flank and treated with entrectinib orally at 15, 30, or 60 mg/kg BID or 30, 60, or 90 mg/kg QD for 10 days starting on Day 14. For intracranial tumors, mice were injected with 2 x 10^6 cells intracranially and treated with entrectinib at 60 and 120 mg/kg BID for 10 days starting on Day 18. Entrectinib led to tumor growth inhibition ranging from 87-99% at all dose levels and schedules (Table 11) in the subcutaneous tumor model. The 30 and 60 mg/kg BID doses led to 2/7 and 3/7 mice being tumor free; the QD doses did not include any tumor free mice at the end of the study. In the intracranial tumor model, both doses of entrectinib led to significant inhibition of tumor growth compared to vehicle controls (Figure 13). Entrectinib at any dose or schedule had little to no effect on body weight (<3% change in BW compared to controls).

Table 11: Anti-tumor activity of different doses and schedules of entrectinib in a subcutaneous NSCLC xenograft bearing the EML4-ALK fusion

Treatment	TGI%	Treatment	TGI%
15 mg/kg BID	87 (Day 34)	30 mg/kg PO	96 (Day 24-27)
30 mg/kg BID	98 (Day 43)	60 mg/kg PO	98 (Day 27-53)
60 mg/kg BID	98 (Day 31-52)	90 mg/kg PO	98 (Day 27-53)
60 mg/kg BID[a]	99 (Day 43-71)	-	-

BID - twice daily oral dosing. PO - once daily oral dosing. Treatment started on Day 14 post inoculation and continued for 10 consecutive days. TGI% is compared to vehicle controls from individual experiments.
[a]TGI confirmed in separate experiment.

Figure 13: Entrectinib had anti-tumor activity in the intracranial model of NSLCL bearing the *EML4-ALK* fusion



(Figure excerpted from Study #1087263)

Similar results were obtained in a subcutaneous xenograft study (Study 1907262) using Karpas-299 human Anaplastic Large Cell Lymphoma (ALCL) cells containing the *ALK* gene fusion *NPM-ALK*. The oral BID dose of 60 mg/kg given for 5 consecutive days or 20 consecutive days led to 4/7 and 3/7 animals with no observable tumors by the end of the experiment. Entrectinib had no effect on body weight. In single dose multi-dose level experiment, investigators harvested Karpas-299 tumors from mice at several time points then analyzed tumors for phosphorylation of ALK and STAT3 by Western blot. The 60 mg/kg dose inhibited NPM-ALK and STAT3 phosphorylation starting 3 hours post dose and maintained for 18 hours with 50% inhibition still evident after 24 hours for both (Figure 14). Similar data were obtained in Study #1087264 utilizing in vitro incubation of NPM-ALK fusion protein containing cell lines SR-786, SUP-M2, and SU-DHL-1, with entrectinib (data not shown).

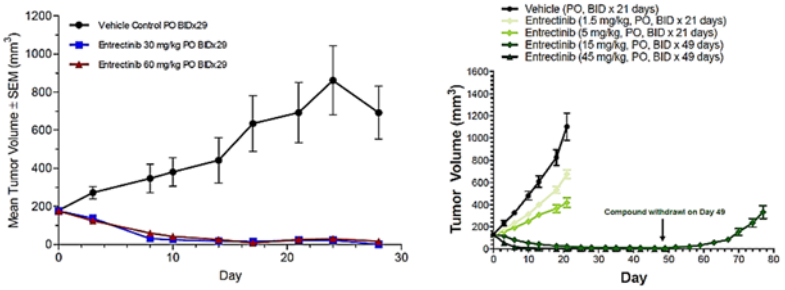
Figure 14: Entrectinib decreased phosphorylated AK and STAT3 in ALCL xenograft tumors containing the NPM-ALK fusion

(Figure excerpted from Study #1087262)

ROS1 fusions

In Study #1087260, entrectinib given at 30 or 60 mg/kg orally BID for 29 days to CTG-0848 (NSCLC PDX model bearing *CD75-ROS1* fusion) tumor bearing mice resulted in tumor regression of 134 and 131%, respectively. In a separate study of another *ROS1* fusion model (Study 1087259), entrectinib at doses of 0, 1.5, 5, 15 and 45 mg/kg orally BID for 21 or 49 resulted in dose-dependent inhibition of tumor growth in mice bearing LU-01-0414 NSCLC PDX (*SCD4-ROS1* fusion), with 15 and 45 mg/kg having a TGI of 111 and 113%, respectively.

Figure 15: Entrectinib had anti-tumor activity in a PDX NSCLC model bearing the CD75-ROS1 fusion



(Figures excerpted from Studies #1087260 and 1087259)

Secondary Pharmacology

Genentech screened off-target activity of entrectinib and its active metabolite M5 against a panel of 89 targets (receptors, ion channels, and transporters) in Studies 1089509, 1089510, 1089511, and 1089512. These studies indicated that at the concentration of 10 µM, either entrectinib or M5 activity had greater than 50% inhibition or activation for multiple targets.

Receptors: Adrenergic receptors α1A, 2A, 2C; cannabinoid receptor CB2; dopamine receptors D1, D2s, D3, D5; opioid receptors δ (DOP), κ (KOP), µ (MOP), glucocorticoid receptor GR; sigma 2 receptor; orexin receptor OX1; histamine receptors H1, H2; muscarinic receptors M1, 4, 5; peroxisome proliferator-activated receptor PPARγ, serotonin receptors 5-HT1B, 2A, 2B, 5a, 6, 7; somatostatin receptor sst4, COX2 receptor: *Channels:* L-type Ca^{2+} channels (dihydropyridine, verapamil, diltiazem, phenylalkylamine, and benzothiazepine sites); hERG potassium channel; sodium channel (site 2): *Transporters:* norepinephrine, serotonin, dopamine, and choline transporters. Less than 1% of entrectinib or M5 is protein bound, leaving free-compound C_{max} values at steady state of approximately 0.031 and 0.013 µM, respectively, 323x and 769x lower, respectively, compared to the 10 µM used in these assays. This study was, therefore, inadequate on its own to determine whether entrectinib is likely to affect any of these potential targets at clinically achievable concentrations.

Safety Pharmacology

In non-GLP Study #1087271, HEK293 cells stably expressing human hERG potassium channel were incubated with entrectinib (0.05, 0.5, 1.5, 15 µM) or 0.12% DMSO (negative control) followed by measurement of potassium current using the patch-clamp technique. No positive control was used in the study. The negative control behaved as expected. Entrectinib dose-dependently inhibited the hERG potassium current with an IC_{50} value of 0.6 µM, suggesting some potential for interference of cardiac repolarization and risk of QT prolongation in humans taking entrectinib. In Study #1087275, the M5 metabolite demonstrated an IC_{50} value of greater than 10 µM for inhibition of hERG potassium channel current. The positive control Cisapride (0.05 µM) inhibited hERG potassium channel current by 64%, as expected.

In GLP-compliant Study #1087273, radiotelemetry-instrumented male (n=2) and female (n=2) beagle dogs received single oral doses of entrectinib at 60 and 120 mg/kg with a 1-week washout between doses to assess the effects of entrectinib on cardiovascular parameters. Arterial pressure, ECG, and body temperature were recorded from one hour before to 24 hours post dose, and cardiovascular data (systolic, diastolic, and mean arterial pressure, heart rate, ECG intervals, body temperature) were obtained from 60 minutes before treatment to 7 hours post treatment. A prolongation in QTc occurred at the dose of 120 mg/kg from 15-105 minutes (7-14 msec) and again from 270-360 (10 msec) post dose. Oral administration of entrectinib to male and female beagle dogs at doses of 60 and 120 mg/kg did not have any effect on other cardiovascular measurement intervals or body temperature.

In GLP-compliant study #1087274, Genentech assessed entrectinib for the potential to induce respiratory toxicity by administering a single oral dose at 0, 50, 100, or 200 mg/kg to female Sprague-Dawley rats followed by measurement of respiratory parameters (tidal volume, minute volume, respiratory rate, peak inspiratory flow, peak expiratory flow, inspiration time, expiration time, relaxation time, Penh (an index of bronchoconstriction)) from 30 minutes before to 4 hours after treatment. The study included only female rats due to higher systemic exposure in females compared to males. Oral administration of entrectinib at doses up to 200 mg/kg did not have any physiologically relevant effects on respiratory parameters.

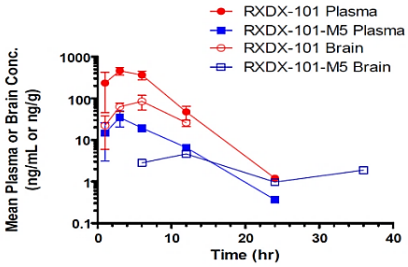
5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Protein Binding</td></tr>
<tr><td>Study#1087282: Determination of plasma protein binding. Cross species comparison</td><td>No significant differences in protein binding of RXDX-101 occurred between any species tested.
<table>
<tr><th>Species</th><th>Mean % binding 5 µM</th><th>Mean % binding 50 µM</th></tr>
<tr><td>Mouse</td><td>97.4</td><td>98.4</td></tr>
<tr><td>Rat</td><td>99.4</td><td>99.3</td></tr>
<tr><td>Dog</td><td>98.8</td><td>100</td></tr>
<tr><td>Monkey</td><td>98.4</td><td>99.2</td></tr>
<tr><td>Human</td><td>99.5</td><td>99.4</td></tr>
</table></td></tr>
<tr><td>Study #1087285: Evaluation of the plasma protein binding of RXDX-101*M5 in mouse, rat, dog, monkey, and human plasma by equilibrium dialysis</td><td>No significant differences in protein binding of metabolite M5 occurred across any species tested, with similar fractions of protein binding occurring at all M5 concentrations tested (0.5, 2.5, 10 µM).
<table>
<tr><th>Species</th><th>Mean % binding</th></tr>
<tr><td>Mouse</td><td>99.7-99.8</td></tr>
<tr><td>Rat</td><td>99.8-100</td></tr>
<tr><td>Dog</td><td>99.7-99.8</td></tr>
<tr><td>Monkey</td><td>99.6-99.7</td></tr>
<tr><td>Human</td><td>99.9-100</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td></td></tr>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Study #1087277:
Evaluation of the pharmacokinetics following single IV and oral administration and evaluation of brain levels following single IV administration to male Sprague Dawley rats
and
Study# 1087278:
Evaluation of bioavailability of NMS-1191372 following single IV and oral administration to beagle dog</td><td>A single-dose PK study in the rat using an intravenous (IV) dose of 10 mg/kg and oral doses of 10 and 30 mg/kg showed a dose-dependent bioavailability for oral administration. Brain concentration in rats treated intravenously was 5% of the plasma concentration.
<table>
<tr><th rowspan="2">Administration Route
Parameter</th><th>IV</th><th colspan="2">Oral</th></tr>
<tr><th>10 mg/kg</th><th>10 mg/kg</th><th>30 mg/kg</th></tr>
<tr><td>Cmax (µM)</td><td>11</td><td>0.461</td><td>1.433</td></tr>
<tr><td>AUC (µM*hr)</td><td>15.1</td><td>3.95</td><td>19.2</td></tr>
<tr><td>F% (AUC)</td><td>-</td><td>33</td><td>48</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>3.8</td><td>-</td><td>3.9</td></tr>
</table>
<table>
<tr><th>Parameter</th><th>IV 10 mg/kg</th></tr>
<tr><td>Brain concentration (µM)</td><td>0.591</td></tr>
<tr><td>Plasma concentration (µM)</td><td>11.17</td></tr>
<tr><td>Blood to plasma ratio</td><td>0.053</td></tr>
</table>
A single-dose PK study in the dog using an IV dose of 10 mg/kg and oral doses of 10 and 60 mg/kg showed a dose-dependent bioavailability for oral administration.
<table>
<tr><th rowspan="2">Administration Route
Parameter</th><th>IV</th><th colspan="2">Oral</th></tr>
<tr><th>10 mg/kg</th><th>10 mg/kg</th><th>60 mg/kg</th></tr>
<tr><td>Cmax (µM)</td><td>8.55</td><td>0.595</td><td>2.7</td></tr>
<tr><td>AUC (µM*hr)</td><td>17.1</td><td>5.35</td><td>48.5</td></tr>
<tr><td>F% (AUC)</td><td>-</td><td>31.2</td><td>48</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>11.9</td><td>15.2</td><td>8.99</td></tr>
</table></td></tr>
<tr><td>Study #1087302:
Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to rats
<i>and</i>
Study #1087301:
Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to dogs</td><td>RXDX-101 accounted for 29-40% (oral 20 mg/kg) or 45-53% (IV 2 mg/kg) of the total circulating plasma radioactivity in rats and 13.8% (oral) and 7.48% (IV) in dogs.

M5 accounted for 0.6-0.9% (oral or IV) of the total circulating plasma radioactivity in rats and 27% (oral) and 4.5% (IV) in dogs.

Oral bioavailability was 38% in the rat and 74% in the dog.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Study #1090366: Entrectinib (RO7102122) and M5 (RO7278378) concentrations in plasma, CSF, and brain after single intravenous bolus dose followed by IV infusion in rats</td><td>Rats received a single intravenous (IV) dose of 6 mg/kg entrectinib followed by a 6-hour continuous infusion of 1.2 mg/kg entrectinib.
<table>
<tr><th rowspan="2">Parameter Mean</th><th>Entrectinib</th><th>M5</th></tr>
<tr><th>6 hrs pSOI</th><th>6 hrs pSOI</th></tr>
<tr><td>Plasma (nM)</td><td>1400</td><td>84.8</td></tr>
<tr><td>Brain (nM)</td><td>843</td><td>37.3</td></tr>
<tr><td>CSF (nM)</td><td>0.813</td><td><0.178</td></tr>
<tr><td>Brain/Plasma</td><td>0.598</td><td>0.435</td></tr>
<tr><td>CSF/Free plasma</td><td>0.227</td><td>0.180</td></tr>
<tr><td>M5/Parent plasma</td><td>0.0604</td><td>-</td></tr>
<tr><td>M5/Parent brain</td><td>0.0446</td><td>-</td></tr>
</table>
pSOI – post start of infusion</td></tr>
<tr><td>Study #1087283: Plasma and brain pharmacokinetics of RXDX-101 and RXDX-101-M5 in SD rats following single oral dose of RXDX101</td><td>Mean plasma and brain concentrations of RXDX-101 and its metabolite M5 following a single oral dose of 20 mg/kg RXDX-101


(Figure excerpted from Study #1087283)</td></tr>
<tr><td>Study# 1087284: Quantitative whole-body autoradiography of male rats after oral administration of [14C] RXDX-101</td><td>Quantitative whole-body radiography to determine tissue distribution in the male Long Evans and Sprague Dawley rats following administration of a single 20 mg/kg oral dose of [^{14}C] RXDX-101 (111 µCi/kg) evaluated for up to 168 hours was comparable between the two species, with the exception of distribution to ocular melanin in the pigmented Long Evans rats.

The highest mean Cmax values were observed in lungs, pituitary gland, liver, uveal tract, adrenal glands, bile, and urine. Tissues with the lowest mean Cmax values observed were bone, testes, abdominal fat, epididymis, and seminal vesicles.

[^{14}C]RXDX-101 distribution did not occur in the central nervous system.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td></td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td>Study # 1087479: Metabolic profiles of entrectinib in mouse, rat, dog, monkey, and human liver microsomes</td><td>Following a 60-minute incubation of [^{14}C] entrectinib in mouse, rat, dog, monkey, and human liver microsomes, approximately 33 to 79% entrectinib remained.

No metabolite was human specific, with M5 and M7 present in microsomes from all species.

<table>
<tr><th>Species</th><th>M1</th><th>M2</th><th>M3[a]</th><th>M5</th><th>M7</th><th>M13[a]</th><th>Others[b]</th><th>Entrectinib</th><th>Total</th></tr>
<tr><td>Mouse</td><td>ND</td><td>ND</td><td>ND</td><td>14.1</td><td>6.53</td><td>ND</td><td>ND</td><td>79.3</td><td>100</td></tr>
<tr><td>Rat</td><td>ND</td><td>ND</td><td>ND</td><td>17.8</td><td>8.96</td><td>ND</td><td>2.30</td><td>70.9</td><td>100</td></tr>
<tr><td>Dog</td><td>ND</td><td>ND</td><td>ND</td><td>29.9</td><td>36.5</td><td>ND</td><td>ND</td><td>33.6</td><td>100</td></tr>
<tr><td>Monkey</td><td>5.05</td><td>ND</td><td>5.40</td><td>40.4</td><td>3.77</td><td>10.6</td><td>2.20</td><td>32.6</td><td>100</td></tr>
<tr><td>Human</td><td>7.48</td><td>8.05</td><td>1.97</td><td>28.4</td><td>1.69</td><td>5.74</td><td>0.108</td><td>46.5</td><td>100</td></tr>
</table>
[a] Overlapped in the radioactive chromatogram, relative percentage was based on the mass response from selective ion monitoring; [b] Others refer to unassigned minor radioactive peaks

One metabolite, M5, was a major human metabolite (i.e. comprised ≥10% of parental AUC), and was detected in mice, rats, dogs, and monkeys with M5-to-parent AUC ratios of 0.05 (rat) and 2 (dog) in repeat-dose toxicology studies in adult animals with quantitative toxicological coverage obtained in the dog. The M5-to-parent AUC ratio in juvenile rats was similar to that observed in adult rats. There were no other major human metabolites.</td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Study #1087302: Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to rats
<i>and</i>
Study #1087301: Pharmacokinetics, metabolism, and excretion of [^{14}C]RXDX-101 after oral and intravenous administration to dogs</td><td>RXDX-101 elimination occurred primarily through fecal excretion (rat 97-101%; dog 78-84%) after IV (dog 1 mg/kg; rat 2 mg/kg) or oral (dog 10 mg/kg; rat 20 mg/kg) administration.

Elimination was completed by 48 hours in rats regardless of route of administration, and 48 hours (oral) and 72hours (IV) in dogs.

<table>
<tr><th>Route of administration</th><th colspan="2">Oral</th><th colspan="2">IV</th></tr>
<tr><th>Route of excretion</th><th>Feces</th><th>Urine</th><th>Feces</th><th>Urine</th></tr>
<tr><td>Rat</td><td>97.6%</td><td>0.77%</td><td>100.8%</td><td>1.5%</td></tr>
<tr><td>Dog</td><td>84.6%</td><td>0.4%</td><td>78%</td><td>0.6%</td></tr>
</table></td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

Study title / Study number: RXDX-101: 13-Week Toxicity and Toxicokinetic Study in Rats with an 8-Week Recovery Phase / 1087349

Key Study Findings

- Preterm deaths were attributable to sores/ulcerative dermatitis in mid-dose and high-dose males and females.
- Key target organs were the skin, bone marrow, and spleen.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Group 1: 0 mg/kg/day
Group 2: 7.5 mg/kg/day
Group 3: 15 mg/kg/day
Group 4: 30 mg/kg/day
(once daily for 13 weeks)

Route of administration: Oral gavage

Formulation/Vehicle: 0.5 % (w/v) methylcellulose in reverse osmosis-purified water

Species/Strain: Rat / Sprague-Dawley

Number/Sex/Group: Main: Groups 1-4: 10/sex
Recovery: Groups 1, 3, and 4 only: 5/sex

Age: 6-7 weeks at initiation of dosing

Satellite groups/unique design: Toxicokinetic: Group 1: 3/sex; Groups 2-4: 9/sex

Deviation from study protocol affecting interpretation of results: None that affected interpretation of results

Observations and Results: Changes from Control

Parameters	**Major Findings**
Mortality	3 HD males, 1 HD female, and 1 MD female were sacrificed in moribund condition due to skin toxicity (sores/ulcerative dermatitis) generally after Day 70; cause of death undetermined for 1 MD male.
Toxicity Mitigation (Dosing Suspensions, Veterinary Treatments)	HD and MD animals frequently required dosing holidays of between 1 and 3 weeks because of significant skin lesions and, in some cases, resulting infections (treated with antibiotics).
Clinical Signs	Skin abnormalities occurred and persisted to a reduced degree in the recovery period.

Skin-Related Clinical Signs (13-Week Study; Rats)

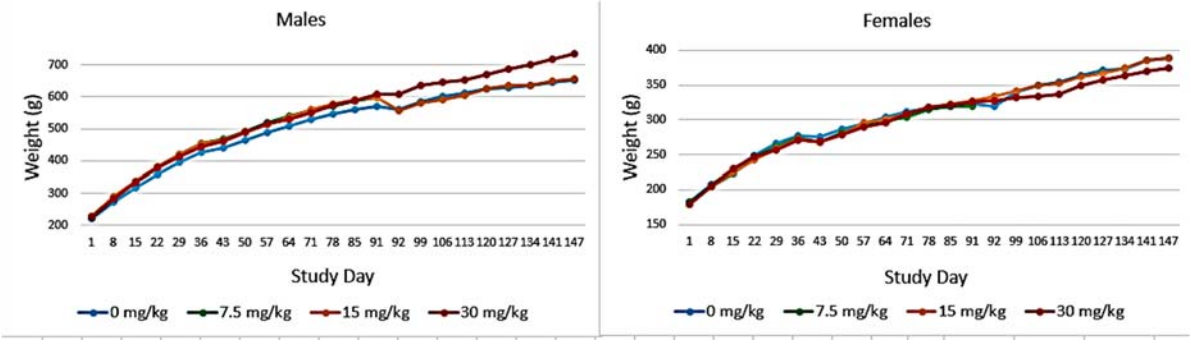
	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Sore; scab; discolored/broken skin	6	0	35, 1R	67, 5R	0	7	28, 1R	38, 1R

Alopecia/thinning/discolored haircoat	8, 5R	3	18	17, 5R	3, 6R	8	20, 4R	10, 2R

R: Recovery groups (0, 15, and 30 mg/kg only)

Body Weights and Feed Consumption	• Main group males had modest increases in body weight gain compared to controls that correlated with increased food consumption. • No clear changes in female weight.

Mean Body Weights (13-Week Study; Rats)



Note: Day 92 is the start of the recovery period (0, 15, and 30 mg/kg; 5 animals/sex/group)

Ophthalmoscopy	Unremarkable
Hematology and Coagulation	In males and females, changes consistent with anemia occurred; these correlated with increased spleen weight and extramedullary hematopoiesis. In males and females, dose-dependent increases in white blood cells and neutrophils, and an increase in serum globulin, likely correlated with inflammation associated with skin lesions.
Hematology	

Hematology and Coagulation: % Change from Concurrent Control (13-Week Study; Rats)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
RBC	End of dosing	-0.7%	-6.3%	-8.6%	-1.4%	-6.8%	-13.2%
	End of recov.		0.7%	-10.2%		-0.8%	-0.1%
RETIC	End of dosing	16.7%	44.1%	56.1%	17.8%	36.1%	119.9%
	End of recov.		16.9%	25.0%		4.3%	22.0%
PLT	End of dosing	7.1%	15.6%	27.6%	-0.1%	0.6%	15.7%
	End of recov.		0.7%	6.9%		5.4%	15.3%
WBC	End of dosing	2.7%	11.8%	38.7%	5.6%	10.5%	34.0%
	End of recov.		3.6%	29.6%		-15.2%	26.5%
NEUT	End of dosing	29.2%	72.0%	127.4%	14.3%	59.3%	168.1%
	End of recov.		11.8%	37.3%		-0.8%	19.4%
FIB	End of dosing	1.5%	4.4%	2.9%	-4.5%	-5.1%	3.5%
	End of recov.		7.0%	1.5%		-7.3%	-5.6%

End of dosing: Day 92; end of 13-week dosing period
End of recov: Day 57 of the recovery period; end of the 8-week recovery period, which only included the 0, 15, and 30 mg/kg groups

Clinical Chemistry	

Clinical Chemistry: % Change from Concurrent Control (13-Week Study; Rats)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
GLOB	Day 42	8.7%	8.7%	8.7%	9.5%	19.0%	14.3%
	End of dosing	3.6%	3.6%	3.6%	7.7%	7.7%	11.5%
	End of recov.		8.0%	4.0%		0%	0%
CHOL	End of dosing	-7.7%	-11.0%	-14.3%	-5.3%	-9.7%	-19.5%
	End of recov.		1.1%	13.7%		3.3%	-17.1%
TRIG	End of dosing	34.9%	7.0%	34.9%	-8.7%	10.9%	15.2%
	End of recov.		-0.9%	36.8%		66.7%	62.2%
PHOS	Day 42	8.0%	11.4%	8.0%	4.1%	5.4%	10.8%
	End of dosing	-1.3%	5.3%	4.0%	-3.0%	-1.5%	4.5%
	End of recov.		5.0%	6.7%		7.0%	16.3%

End of dosing: Day 92; end of 13-week dosing period
End of recov: Day 57 of the recovery period; end of the 8-week recovery period, which only included the 0, 15, and 30 mg/kg groups

Urinalysis	A dose-related increase of urine occult blood in MD and HD males and females occurred during the dosing period; it was reversible.
Gross Pathology	Skin findings upon macroscopic examination were consistent with skin-related clinical signs.

Gross Pathology Findings (13-Week Study; Rats)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Scabs	0	6	7	2	4	5
Sores	0	1	1	0	2	3

Note: There were no findings in the male or female control group, nor any treatment-related findings in any of the recovery groups.

Organ Weights	In males and females, dose-dependent increases in spleen weight were accompanied by increased extramedullary hematopoiesis, which partially resolved during the recovery period.

Organ Weights (13-Week Study; Rats)

mg/kg/day	**0**	**7.5**	**15**	**30**
Spleen (Males)				
Absolute weight	0.990 g (1.102 g)	11% (NA)	36% (16%)	47% (37%)
Spleen (Females)				
Absolute weight	0.570 g (0.671 g)	6% (NA)	9% (2%)	39% (-2%)

Note: Values in parentheses are from the recovery period.
Note: Values for the dosed groups are expressed as percent change relative to controls
NA: Recovery groups included only 0, 15, and 30 mg/kg

Histopathology (Adequate Battery: Yes)	Refer to Table 12 for selected histopathology findings. The main histological target organs were the skin and spleen, correlating with skin lesions and clinical pathology findings of suppressed RBC indices, respectively. Minimal mononuclear cell infiltration was also present in several tissue types.
Toxicokinetics	• Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose in males and females on Days 1, 42, and 91. • Entrectinib exposures were slightly higher in females than males, while M5 exposures were generally lower in females than males.

- Entrectinib accumulation ratios in all treatment groups on Day 42 and 91 ranged from 1.24 to 1.91.
- M5 accumulation ratios in the MD and HD treatment groups on Day 42 and 91 ranged from 1.61 to 7.97 (M5 was below the limit of quantitation for the LD groups on Day 1.)

Toxicokinetic Parameters for Entrectinib (13-Week Study; Rats)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	4	4	4	4	4	8
Cmax (µM)	0.382	0.589	1.40	0.344	0.756	1.77
AUC(0-24) (µM*hr)	3.13	6.87	15.5	4.11	8.22	22.0
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	8	8	8	8	4
Cmax (µM)	0.458	0.879	1.41	0.474	1.05	1.67
AUC(0-24) (µM*hr)	4.70	11.4	20.0	6.74	14.0	27.3
AUC(0-24) AR	1.50	1.66	1.29	1.64	1.70	1.24
Day 91						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.631	0.851	1.45	0.629	1.13	2.57
AUC(0-24) (µM*hr)	5.98	10.5	19.4	6.71	15.4	29.6
AUC(0-24) AR	1.91	1.53	1.25	1.63	1.87	1.35
Dose exposure multiple*	0.13X	0.27X	0.51X			

AR: Accumulation ratio; NA: Not applicable
* Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses [F2A formulation] in Study STARTRK-1); sexes averaged; Day 91

Toxicokinetic Parameters for M5 Metabolite (13-Week Study; Rats)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	NA	8	4	NA	4	8
Cmax (µM)	0	0.0255	0.0802	0	0.0088	0.0567
AUC(0-24) (µM*hr)	0	0.177	0.892	0	0.576	0.627
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	4	4	NA	4	4
Cmax (µM)	0.0285	0.0689	0.155	0	0.0368	0.0914
AUC(0-24) (µM*hr)	0.215	0.905	2.43	0	0.321	1.01
AUC(0-24) AR	NA	5.11	2.72	NA	5.57	1.61
Day 91						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.0521	0.0965	0.193	0.0062	0.0465	0.112
AUC(0-24) (µM*hr)	0.349	0.950	2.54	0.0218	0.459	1.10
AUC(0-24) AR	NA	5.37	2.85	NA	7.97	1.75

AR: Accumulation ratio; NA: Not applicable

LD: low dose; MD: mid dose; HD: high dose.
- or + : indicates reduction or increase in parameters compared to control.

Table 12: Selected Histopathology Findings (13-Week Study; Rats)

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Animals examined (dosing/recovery)	10/5	10/0	10/4	9/4	10/5	10/0	9/4	10/4
MARROW, FEMUR								
Hypercellular; minimal			2	4			1	2
Inflammation, chronic; minimal			1					
MARROW, STERNUM								
Hypercellular; minimal			3	5			1	2
MUSCLE, BICEPS FEMORIS								
Infiltrate, mononuclear cell; minimal				2				1
SKIN/SUBCUTIS								
Acanthosis								
--minimal			4	3		1	4	3
--slight			2	3				2
Crust, serocellular; present			6	6		2	4	6
Erosion/ulcer								
--minimal			1				1	1
--slight							2	1
--moderate			1	4			1	4
Granuloma; minimal				2			1	1
Hemorrhage								
--minimal			2	2			1	2
--slight				1				1
Infiltrate, mononuclear cell; minimal	1		2		1, 1R	1		
Inflammation, mixed cell								
--minimal			2	4		1	2	1
--slight			2	1			2	3
--moderate				1				2
SPLEEN								
Hematopoiesis, extramedullary, increased; minimal	3	2	6	7, 1R			2	6

R: Recovery cohort; "9/9" for that tissue type, only 9 specimens were examined instead of 10; finding was present in 9 of 9 specimens.
Note: Histopathology was only performed on control and high-dose groups, with the exception of macroscopic skin lesions, spleen, sternum bone marrow, and femur bone marrow that were also examined for the low-dose and mid-dose groups.
Note: Table does not include data from a few unscheduled sacrifices/deaths.

Study title / Study number: RXDX-101: 13-Week Toxicity and Toxicokinetic Study in Dogs with an 8-Week Recovery Phase / 1087343

Key Study Findings

- Key target organs were the skin and gastrointestinal tract.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 7.5, 15, 30 mg/kg/day Daily for 13 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 % (w/v) methylcellulose in reverse osmosis-purified water
Species/Strain:	Dog / Beagle
Number/Sex/Group:	Main: 4/sex/group Recovery: 2/sex/group, 0 and 30 mg/kg only
Age:	7- 9 months
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	None that affected interpretation

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	There were no unscheduled test article-related deaths.
Toxicity Mitigation (Dosing Suspensions, Veterinary Treatments)	Dose suspensions (in 2 HD animals; for 3 and 6 days) mitigated gastrointestinal toxicity, canned food mitigated weight loss, and skin issues necessitated soft padding and lanolin, nonsteroidal anti-inflammatory drugs and/or antibiotics.
Clinical Signs	Footpad skin sores and other skin toxicity occurred most frequently in high-dose males and females. Animals may have lacked adequate pain feedback to avoid damaging their feet. Gastrointestinal toxicity occurred at all dose levels but only required dose suspension at the HD level. Skin issues are described in the table below. Clinical signs generally reversed during the recovery period.

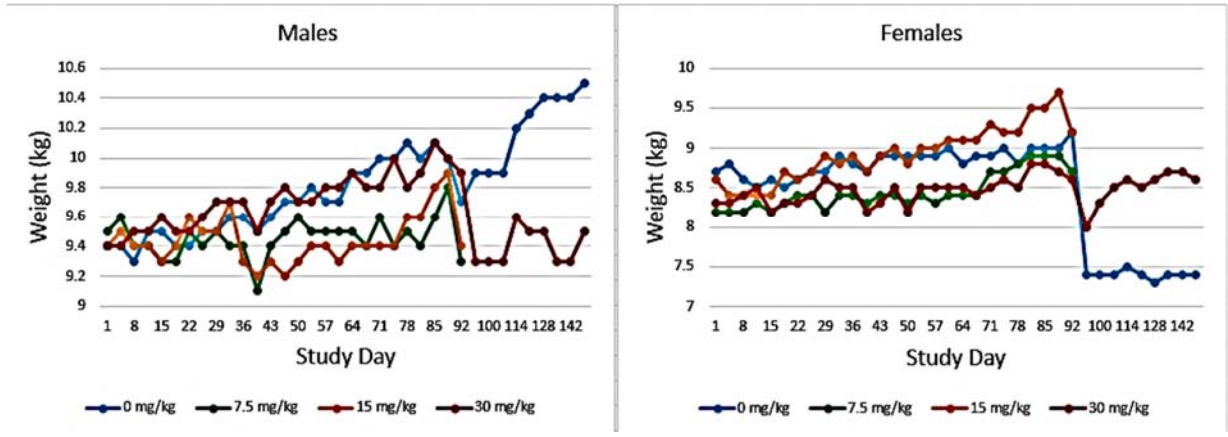
Skin-Related Clinical Signs (13-Week Study; Dogs)

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Dry skin; scaly skin; scabs	0	8	4	19, 2R	1	2	8	13, 1R
Sores; broken skin	0	3	0	14, 2R	0	0	2	8
Discolored skin	1	4	1	4	0	0	2	6
Swollen digits/limited use of leg/foot	0	1	0	4, 1R	0	0	2	4

R: Recovery groups (0 and 30 mg/kg only)

Body Weights and Feed Consumption	Overall, there was no clear dose-dependent effect on body weight or feed consumption during the dosing period, except for decreased feed consumption noted in several animals in (see Toxicity Mitigation section); an effect on weight loss was blunted by the humane use of canned food supplementation. During the recovery period, differences appeared to be based on recovery group (2/sex/group) mean weights at the start of that period, which did not closely reflect the respective means at the end of the dosing periods.

Mean Body Weights (13-Week Study; Dogs)



Note: Day 93 is the start of the recovery period (0 and 30 mg/kg; 2 animals/sex/group)

Ophthalmoscopy	Unremarkable
Electrocardiography	• In HD males during the dosing period, the QTc interval was higher than the control group on Days 40 and 90, predose and 2 hours post-dose; the change was statistically significant for Day 90 predose. • No notable changes in females.

QTc and QT Intervals in Males (13-Week Study; Dogs)

	Males			
mg/kg/day	**0**	**7.5**	**15**	**30**
QTc Interval (msec)				
Prior to start of dosing period	243	240	237	244
Day 40, predose	227	232	235	245
Day 40, 2 hours postdose	229	227	232	243
Day 90, predose	230	233	234	256*
Day 90, 2 hours postdose	236	232	243	252
Day 55 of the recovery period	239	NA	NA	239

* $p \leq 0.05$; NA: Only 0 and 30 mg/kg groups in the recovery period.

Hematology and Coagulation	• Decreased RBC parameters occurred in males and females; these were partially reversible during the recovery period. • Increases in WBCs and neutrophils, likely associated with skin/footpad toxicities; these were partially reversible during the recovery period. A reversible increase in fibrinogen also occurred.

Hematology and Coagulation: % Change from Concurrent Control (13-Week Study; Dogs)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
RBC	End of dosing	-0.2%	-2.3%	-11.4%	-0.3%	-6.7%	-6.4%
	End of recov.			-1.0%			0%
RETIC	End of dosing	49.1%	20.3%	7.6%	-23.6%	-22.3%	-0.3%
	End of recov.			-0.7%			-33.7%
WBC	End of dosing	37.0%	31.8%	74.5%	4.3%	65.9%	27.4%
	End of recov.			-7.9%			-29.8%
NEUT	End of dosing	60.3%	63.4%	120.6%	19.7%	106.3%	43.3%
	End of recov.			-7.7%			-34.4%
MONO	End of dosing	40.0%	33.3%	96.7%	36.8%	142.1%	115.8%
	End of recov.			-35.6%			-23.2%
FIB	End of dosing	37.1%	29.0%	79.2%	3.9%	54.7%	79.7%
	End of recov.			7.4%			-23.0%

End of dosing: Day 90; end of 13-week dosing period
End of recov: Day 55 of the recovery period; end of the 8-week recovery period, which only included the 0 and 30 mg/kg groups

Clinical Chemistry	Partially reversible increases in globulin were likely associated with an inflammatory response to footpad/skin issues.

Clinical Chemistry: % Change from Concurrent Control (13-Week Study; Dogs)

		Males			Females		
	mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Parameter	Time point						
Albumin	End of dosing	-3.1%	-9.4%	-15.6%	-6.1%	-15.2%	-15.2%
	End of recov.			0%			0%
Calcium	End of dosing	-0.9%	-2.8%	-4.6%	-1.8%	-2.7%	-4.5%
	End of recov.			-4.5%			0%
Glucose	End of dosing	-7.5%	-6.5%	-6.5%	-1.0%	-10.4%	-7.3%
	End of recov.			3.2%			-2.9%
Phosphorus	End of dosing	2.0%	0.0%	-12.2%	-6.1%	0.0%	-18.4%
	End of recov.			-6.7%			-7.3%
Globulin	End of dosing	34.8%	21.7%	52.2%	19.0%	57.1%	47.6%
	End of recov.			9.5%			16.7%
Total Prot.	End of dosing	10.7%	1.8%	10.7%	3.7%	13.0%	9.3%
	End of recov.			5.6%			5.8%

End of dosing: Day 90; end of 13-week dosing period
End of recov: Day 55 of the recovery period; end of the 8-week recovery period, which only included the 0 and 30 mg/kg groups

Urinalysis	Unremarkable
Gross Pathology	After dosing period: Foot sores/scabs in 1 HD M and 2 HD F After recovery period: unremarkable
Organ Weights	Dose-dependent and non-reversible decreases in prostate weight occurred. Mild and reversible increases in liver weight at the MD and HD level in both sexes, and in spleen weight at the HD in both sexes, occurred.

Organ Weights (13-Week Study; Dogs)

mg/kg/day	0	7.5	15	30
Liver (Males)				
Absolute weight	284 g (296 g*)	11% (NA)	10% (NA)	17% (4%)
Liver (Females)				
Absolute weight	281 g (228 g)	-3% (NA)	10% (NA)	8% (13%)
Spleen (Males)				
Absolute weight	38.9 g (37.0 g)	-7% (NA)	-8% (NA)	44% (-10%)
Spleen (Females)				
Absolute weight	40.1 g (23.2 g)	-8% (NA)	20% (NA)	25% (-12%)
Prostate				
Absolute weight	7.3 g (9.5 g)	-8% (NA)	-19% (NA)	-35% (-33%)

* Values in parentheses are from the recovery period.
Note: Values for the dosed groups are expressed as percent change relative to controls
NA: Recovery groups included only 0 and 30 mg/kg

Histopathology (Adequate Battery: Yes)	Refer to Table 13 for selected histopathology findings. • The main histological target organ was the footpad. • Occasional findings in the kidney, liver, thymus, and rectum.
Toxicokinetics	Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose in males and females on Days 1, 42, and 91. No large differences in entrectinib or M5 exposure was noted in males versus females. Entrectinib accumulation ratios in all treatment groups on Day 42 and 91 ranged from 1.68 to 5.35. M5 accumulation ratios in all treatment groups on Day 42 and 91 ranged from 1.55 to 3.54.

Toxicokinetic Parameters for M5 Metabolite (13-Week Study; Dogs)

	Male			Female		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	4	3	4	4	4	4
Cmax (µM)	0.203	0.262	0.403	0.158	0.261	0.451
AUC(0-24) (µM*hr)	2.00	2.53	4.73	1.52	3.12	5.77
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.382	0.400	0.663	0.241	0.473	0.663
AUC(0-24) (µM*hr)	4.34	5.85	8.99	2.93	6.71	9.40
AUC(0-24) AR	2.85	2.49	1.92	1.80	3.11	2.00
Day 91						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.239	0.350	0.699	0.204	0.488	0.605
AUC(0-24) (µM*hr)	2.66	4.46	9.06	2.44	6.45	8.06
AUC(0-24) AR	1.92	2.13	1.95	1.55	3.54	1.59

AR: Accumulation ratio; NA: Not applicable

Toxicokinetic Parameters for Entrectinib (13-Week Study; Dogs)

	Males			Females		
mg/kg/day	**7.5**	**15**	**30**	**7.5**	**15**	**30**
Day 1						
Tmax (hr)	2	1.5	2	2	1.5	2
Cmax (µM)	0.195	0.274	0.528	0.136	0.229	0.564
AUC(0-24) (µM*hr)	1.06	1.52	3.31	0.773	1.92	4.17
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Day 42						
Tmax (hr)	4	2	2	3	2	2
Cmax (µM)	0.311	0.325	0.830	0.187	0.481	0.775
AUC(0-24) (µM*hr)	2.16	2.66	7.09	1.49	3.89	6.81
AUC(0-24) AR	3.73	1.79	2.01	1.97	3.15	1.93
Day 91						
Tmax (hr)	3	2	2	2	2	2
Cmax (µM)	0.276	0.496	0.912	0.226	0.978	0.839
AUC(0-24) (µM*hr)	1.93	3.39	8.04	1.81	5.04	7.09
AUC(0-24) AR	4.37	2.88	2.51	2.39	5.35	1.68
Dose exposure multiple*	0.04X	0.09X	0.16X			

AR: Accumulation ratio; NA: Not applicable
* Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses [F2A formulation] in Study STARTRK-1); sexes averaged; Day 91

LD: low dose; MD: mid dose; HD: high dose.
- or +: indicates reduction or increase in parameters compared to control.

Table 13: Selected Histopathology Findings (13-Week Study; Dogs)

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Animals examined (dosing/recovery)	4/2	4/0	3/0	4/2	4/2	4/0	4/0	4/2
ADRENAL, CORTEX								
Vacuolation; slight							1	1
FOOT/FOOTPAD								
Acanthosis; slight								2
Erosion/ulcer, skin								
--slight								1
--marked								1
Inflammation, acute; marked								1
Inflammation, mixed cell								
--slight								1
--moderate				1				
KIDNEY								
Dilatation, tubule(s); minimal		1						1
Infiltrate, mononuclear cell								
--minimal				1				1
--slight								
Regeneration, tubule cell								
--minimal			1	2	1			1
--slight								1

	Males				Females			
mg/kg/day	**0**	**7.5**	**15**	**30**	**0**	**7.5**	**15**	**30**
Animals examined (dosing/recovery)	4/2	4/0	3/0	4/2	4/2	4/0	4/0	4/2
LIVER								
Infiltrate, mixed cell								
--minimal	1			2			1	1
--slight								1
PANCREAS								
Apoptosis, increased, acinar cell; min.	1		1				1	
RECTUM								
Erosion/ulcer, squamous epithelium, anus; minimal							2	1
Hemorrhage; minimal							1	
Infiltrate, neutrophils; minimal			1	1			2	2
URINARY BLADDER								
Mineralization; minimal			1			1		

R: recovery
Number per group: control and HD: 6/sex (4 to sacrifice at end of dosing; 2 to sacrifice at end of recovery)
LD and MD: 4/sex, 4 to sacrifice at end of dosing (none for recovery)
1 MD male was prematurely sacrificed due to behavior issues and is not included in the table.

General toxicology; additional studies

In a 4-week GLP-compliant toxicology study in Sprague Dawley rats (Study # 1087346), animals received entrectinib at doses of 50, 100, and 200 mg/kg/day via oral gavage. For the 200 mg/kg dose, the average exposure for males and females by AUC_{0-24} was 3.2 times the human exposure by AUC at the 600 mg dose. Findings were generally similar to those observed in the 13-week rat study; however, additional findings in the 4-week study included deaths of 3 high-dose females associated with CNS toxicity (lack of motor coordination), decreased female weights at the mid- and high-dose levels (no effect in males), corneal opacity at the high dose, and deficits in the modified Irwin's test (not performed in the 13-week study) predominantly at the high dose of 200 mg/kg, including abnormal gait and decreases in startle response, visual placing grip strength, and righting reflex.

In a 4-week GLP-compliant toxicology study in Beagle dogs (Study #1087335), animals received entrectinib at doses of 30, 60, and 120 mg/kg/day via oral gavage. For the 120 mg/kg dose, the average exposure for males and females by AUC_{0-24} was 3.2 times the human exposure by AUC at the 600 mg dose. Findings were generally similar to those observed in the 13-week dog study. Additional findings in the 4-week study included deaths of 4 females at the high dose associated with CNS toxicity (lack of coordination, abnormal gait, tremors, hypoactivity, and lateral recumbency) and gastrointestinal toxicity, additional CNS-associated clinical signs (stereotypy and depression), impaired weight gain (decreased weight gain compared to controls without weight loss), and QTc prolongation (observed in 2 of 4 males and in 4 of 4 females [mean increases of 29 and 80 msec, respectively] at 120 mg/kg; more pronounced than in the 13-week study).

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: NMS-1191372 (RO7102122; entrectinib): Bacterial Reverse Mutation Assay / 1087350

Key Study Findings:

- Entrectinib was not mutagenic in four *Salmonella typhimurium* strains or in one *Escherichia coli* strain, in the presence or absence of S9 activation
- Standard positive controls confirmed the sensitivity and validity of the assay.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA 1535, TA1537, and *Escherichia coli* strain WP2 uvrA; entrectinib tested up to 312.5 µg/plate; +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (Micronucleus and FISH) / 1087352

Key Study Findings:

- Entrectinib resulted in a statistically significant increase in micronuclei after a 24-hour incubation in the absence of S9 (Table 14); FISH analysis demonstrated that an aneugenic mechanism resulted in the micronuclei (data not shown).
- The performance of the positive controls confirmed the sensitivity and validity of the study.

Table 14: In Vitro Micronucleus Findings

	4 hours (no S9)		4 hours with S9		24 hours (no S9)	
Treatment	**% Cytotox.**	**Mean % MN**	**% Cytotox.**	**Mean % MN**	**% Cytotox.**	**Mean % MN**
Vehicle						
DMSO		0.4		0.3		0.5
Positive controls						
Mitomycin C	43-65	3.7**	NT	NT	NT	
Cyclophosphamide	NT	NT	43-72	1.3**	NT	
Vinblastine	NT	NT	NT	NT	32-64	1.3**
Entrectinib (µg/mL)						
3	4	NT	5	NT	6	**0.8**
7.5	12	**0.4**	13	**0.4**	22	**0.6**
15	30	**0.5**	32	**0.7**	53	**1.6****
20	49	NT	50	**0.6**	86	NT

25	52	**0.8**	51	NT	100	NT
30	81	NT	55	NT	100	NT
35	93	NT	57	NT		NT
40	98	NT	61	NT		NT
45	98	NT	74	NT		NT

4-hour doses:
24-hour doses:
Cytotox: Cytotoxicity, relative to DMSO vehicle control; MN: Micronuclei; NT: Not tested
** p ≤ 0.01, relative to the DMSO control.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes; entrectinib up to 45 µg/mL; +/- S9
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: In Vivo Micronucleus and Comet Assay in Rats / 1087353

Key Study Findings:

- Entrectinib did not induce DNA damage in rat hepatocytes (as detected by a comet assay) or a significant increase in rat micronucleated bone marrow polychromatic erythrocytes.
- The performance of the positive controls confirmed the sensitivity and validity of the study.

GLP compliance: Yes
Test system: Rats, given entrectinib 0, 250, 1000, or 2000 mg/kg by oral gavage on Days 1, 2, and 3; (positive control: 200 mg/kg/day ethyl methanesulfonate [EMS] on Days 2 and 3; comet assay; bone marrow micronucleus assay
Study is valid: Yes

Other Genetic Toxicity Studies

None

5.5.3. Carcinogenicity

No studies were submitted or needed for the proposed indication.

5.5.4. Reproductive and Developmental Toxicology

While embryo-fetal development studies can detect anatomic malformations in brain structure, they are not designed to assess functional changes that might presage functional alterations in movement, nociception, behavior, or neuropsychiatric function. Numerous published reports describe the relationship between human congenital somatic mutations in the Trk signaling

pathway and development of neuropsychiatric conditions such as schizophrenia and mood disorders (Krantz 2015; Otnaess et al., 2009; Knable 1999; Lewis et al., 2005). Others have demonstrated the role of Trk mutations in development of hyperphagic obesity, and peripheral sensory and motor disorders in humans (Indo et al., 1996; Yeo et al., 2004). Studies involving mice deficient in individual Trk receptors further support the crucial role of Trk signaling in development. Mice deficient in TrkA have sensory and sympathetic neuropathies but normal motor function; these animals typically die within 1 month of birth (Smeyne, 1994). Mice deficient in TrkB lack populations of motor neurons, dorsal root neurons, and trigeminal ganglia neurons and die shortly after birth (Klein, 1993). TrkC deficient mice appear normal at birth but develop abnormal posture and growth defects and generally die within a few weeks of birth (Klein, 1994). These studies demonstrate the critical role of Trk proteins in neural development.

Consistent with FDA guidance on the development of drugs to treat patients with advanced cancer, Genentech did not conduct a pre- and postnatal development study, though such a study may have had greater capacity to detect relevant changes in functional endpoints, such as motor and nociceptive deficits.

Fertility and Early Embryonic Development; Prenatal and Postnatal Development

No studies were submitted or needed for the proposed indication.

Embryo-Fetal Development

Study title / number: RXDX-101: An Oral (Gavage) Study of the Effects on Embryo/Fetal Development in Rats / 1087361

Key Study Findings

- Entrectinib caused maternal toxicity at the HD (discharge from orifices) but did not cause maternal mortality or embryolethality.
- The incidence of the following malformations in the HD group (200 mg/kg; 2.7 times the human exposure by AUC at the 600 mg dose) exceeded the maximum historical control incidence: micromelia, omphalocele, gastroschisis, and adactyly, limb hyperextension, and filamentous tail.
- Skeletal malformations and variations occurred frequently in the HD group, and lower fetal weights and reduced skeletal ossification occurred at doses ≥12.5 and 50 mg/kg (approximately 0.2 and 0.9 times the human exposure by AUC at the 600 mg dose), respectively).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

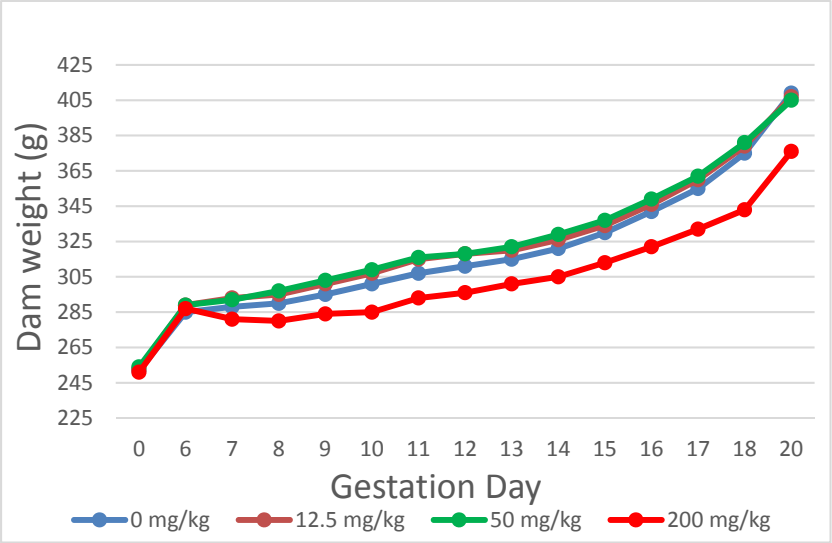
Methods

Dose and frequency of dosing:	0, 12.5, 50, or 200 mg/kg; daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose in deionized water
Species/Strain:	Sprague Dawley [Crl:CD(SD)] rats
Number/Sex/Group:	25 females per group
Satellite groups:	Toxicokinetic groups (control: 4 rats; LD, MD, HD: 8 rats each)
Study design:	Time-mated rats were treated once daily via oral gavage from Gestation Days (GD) 6 to 17 Laparohysterectomies were performed on GD 20 TK was collected from 4 animals per group on GD 6 and 17 (1, 2, 4, 8, 12, and 24 hours post dose)
Deviation from study protocol affecting interpretation of results:	None that affected study interpretation

Observations and Results

Parameters	Major findings
Mortality	No test article-related mortality
Clinical Signs	HD: Red material around nose (~4 hours post-dose, GD 13-20) HD: Red material around urogenital area; yellow material around urogenital area/rump; red vaginal discharge (~4 hours post-dose, GD 15-18)
Body Weights and Feed Consumption	Body weight gain and feed consumption were significantly decreased in HD dams.

Dam Weight (EFD Study; Rats)



Gravid Uterine Weights	Significant decreased mean gravid uterine weight in the HD group, attributed to lower fetal weights, was observed.
Necropsy Findings: Maternal, Gross	LD: Skin scabbing (1); Skin mass (1) MD: Nongravid (1); Skin scabbing (4) HD: Enlarged placenta (2); Red fluid in amniotic sac (1)
Necropsy Findings: Cesarean Section Data	No embryolethality was observed, but entrectinib caused intrauterine growth retardation in both sexes, statistically significant starting at the low dose.

Cesarean Section Data (EFD Study; Rats)

mg/kg/day	**0**	**12.5**	**50**	**200**
Pregnancy index (%)	100%	100%	96%	100%
# Females w/ viable fetuses for GD20 exam	25	25	24	25
Number pregnant	25	25	24	25
Number not pregnant	0	0	1	0
Gravid uterine weight (g)	87.5	↓0.1%	↓0.1%	↓23.8%**
Mean corpora lutea	17.4	17.2	17.5	16.8
Mean implantation sites	15.9	16.0	16.0	15.0
Mean % pre-implantation loss	7.7	6.3	7.6	8.5
Mean % post-implantation loss	6.5	3.8	4.3	4.2
Mean litter size***	14.8	15.4	15.4	14.4
Mean early resorptions	1.0	0.6	0.7	0.6
Mean late resorptions	1.0	0	1.0	0
Fetal weight change relative to controls				
Male (g)	3.9	↓5.1%*	↓10.3%**	↓35.9%**
Female (g)	3.7	↓5.4%*	↓10.8%**	↓35.1%**

* Significantly different from control group (p<0.05)
** Significantly different from control group (p<0.01)
*** Note: All fetuses were viable

Necropsy Findings: Offspring	As shown in Table 15+++, the incidence of the following malformations in the HD group (200 mg/kg; 2.7 times the human exposure by AUC at the 600 mg dose) exceeded the maximum historical control incidence: micromelia, omphalocele, gastroschisis, and adactyly, limb hyperextension, and filamentous tail. Skeletal malformations and variations occurred frequently in the HD group and reduced skeletal ossification occurred at doses ≥ 50 mg/kg (approximately 0.9 times the human exposure by AUC at the 600 mg dose).
Toxicokinetics	Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose on GD 6 and 17. Entrectinib accumulation ratios in the 3 treatment groups on GD 17 ranged from 1.23 to 1.63. M5 accumulation ratios in the 3 treatment groups on GD 17 ranged from 1.72 to 7.05.

Toxicokinetic Parameters in Dams for Entrectinib and M5 (EFD Study; Rats)

	Entrectinib			**M5 Metabolite**		
mg/kg/day	**12.5**	**50**	**200**	**12.5**	**50**	**200**
Gestational Day 6						
Tmax (hr)	8	8	12	4	8	12
Cmax (µM)	0.518	2.43	5.12	0.005	0.079	0.184
AUC(0-24) (µM*hr)	6.24	33.8	89.5	0.016	0.851	2.96
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Gestational Day 17						
Tmax (hr)	8	2	12	4	4	4

Cmax (µM)	0.820	2.65	6.09	0.017	0.096	0.440
AUC(0-24) (µM*hr)	10.2	41.5	127	0.110	1.46	8.52
AUC(0-24) AR	1.63	1.23	1.42	7.05	1.72	2.88
Dose exposure multiple*	0.2X	0.9X	2.7X			

AR: Accumulation ratio; EFD: Embryo-fetal development; NA: Not applicable
* Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses [F2A formulation] in Study STARTRK-1)

LD: low dose; MD: mid dose; HD: high dose; GD: Gestation Day

Table 15: Fetal Malformations and Variations (EFD Study; Rats)

mg/kg/day	0	12.5	50	200
Number of Fetuses/Litters Evaluated	371/25	385/25	370/24	360/25
Gross malformations: # of fetuses affected, (% of fetuses); number of litters affected				
Micromelia				6 (1.7); 3
Omphalocele				2 (0.6); 2
Gastroschisis				2 (0.6); 2
Filamentous tail				1 (0.3); 1
Limb hyperextension				1 (0.3); 1
Adactyly				1 (0.3); 1
Localized fetal edema				1 (0.3); 1
Vertebral agenesis			1 (0.3); 1	
Hydrocephaly with or without dome head		1 (0.3); 1		
Gross variations: # of fetuses affected, (% of fetuses), # of litters affected				
Skin area(s) white				2 (0.6); 2
Visceral malformations: # of fetuses affected, (% of fetuses); # of litters affected				
Transposition of the great vessels				2 (0.6); 2
Situs inversus	2 (0.5); 2			
Trachea – cartilaginous rings absent				1 (0.3); 1
Retroesophageal aortic arch				1 (0.3); 1
Right-sided aortic arch				1 (0.3); 1
Lungs – lobular dysgenesis	1 (0.3); 1			
Visceral variations: # of fetuses affected (% of fetuses); # of litters affected				
Major blood vessel variation (HD:)		1 (0.3), 1	1 (0.3); 1	5 (1.4); 5
Renal papilla(e) not developed and/or distended ureter	6 (1.6); 5	2 (0.5); 2	2 (0.5); 2	3 (0.8); 3
Hemorrhagic ring around the iris		1 (0.3); 1	1 (0.3); 1	
Liver – accessory lobule(s)	2 (0.5); 1	2 (0.5); 1	1 (0.3); 1	
Thyroid gland(s) - small	1, 0.3, 1			
Skeletal malformations: # of fetuses affected (% of fetuses); # of litters affected				
Bent limb bone(s) (				50 (13.9**); 15
Only 12 pairs of ribs present				5 (1.4); 5
Vertebral anomaly and/or rib anomaly				4 (1.1); 4
Vertebral centra anomaly				3 (0.8); 3
Rib anomaly				3 (0.8); 3
Sternoschisis			1 (0.3); 1	1 (0.3); 1
Skeletal variations: # of fetuses affected (% of fetuses)				
Reduced ossification of the vertebral arches	4 (1.1)	2 (0.5)	31 (8.4)	320 (88.9)**
Bent rib(s)	1 (0.3)	3 (0.8)	32 (8.6)	280 (77.8)**
Unossified sternebra(e) #5 and/or 6	15 (4.0)	13 (3.4)	31 (8.4)	154 (42.8)**

mg/kg/day	0	12.5	50	200
Number of Fetuses/Litters Evaluated	371/25	385/25	370/24	360/25
Bent scapula(e)				147 (40.8)**
Reduced ossification of the skull	1 (0.3)	4 (1.0)	25 (6.8)	127 (35.3)**
Reduced ossification of the 13th rib(s)	2 (0.5)		5 (1.4)	119 (33.1)**
Reduced ossification of the rib(s)			9 (2.4)	77 (21.4)**
Sternebra(e) malaligned (slight or moderate)	1 (0.3)	5 (1.3)	6 (1.6)	19 (5.3)*
Unossified sternebra(e) #1, 2, 3, and/or 4			2 (0.5)	12 (3.3)
Unossified hyoid	3 (0.8)	7 (1.8)	3 (0.8)	12 (3.3)
Unossified pubis				5 (1.4)
Unossified ischium				1 (0.3)
Unco-ossified vertebral centra			1 (0.3)	1 (0.3)
25 presacral vertebrae			1 (0.3)	4 (1.1)
7th cervical rib(s)	6 (1.6)	4 (1.0)	4 (1.1)	8 (2.2)
Ossified cervical centrum #1	66 (17.8)	78 (20.3)	38 (10.3)	5 (1.4)
14th rudimentary rib(s)	25 (6.7)	34 (8.8)	10 (2.7)	1 (0.3)
27 presacral vertebrae		2 (0.5)	1 (0.3)	
14th full rib(s)		2 (1.5)		

* Significantly different from the control group at 0.05
** Significantly different from the control group at 0.01

+++In the summary tables, Genentech included a % by litter summary for malformations and variations, however, upon closer examination the calculations in these tables appears to represent the percentage of malformations in the total number of fetuses rather than a % litter calculation. Reproductive toxicology experts within the FDA confirm that the litter is the more appropriate read out for malformations and total numbers of litters with findings are therefore included in Table 15.

Juvenile Animal Data

Study title / number: RXDX-101: Oral (Gavage) 13-Week Toxicity Study in Juvenile Sprague-Dawley Rats with a 4-Week Recovery Period / 1087245

Key Study Findings

- Preterm deaths were associated with CNS toxicity (3 deaths), kidney toxicity (2), or skin toxicity (1).
- Key target organs were CNS, bone marrow, kidney, and skin
- Entrectinib caused decreased weight gain, femur length, delayed sexual maturation.
- CNS-related clinical signs included abnormal gait, tremors, decreased activity, convulsions, hunched posture, repetitive behavior, eyes partly closed, and piloerection; HD animals displayed deficits in spatial learning and memory (Morris water maze).

Conducting laboratory and location: (b) (4)

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 4, 8, or 16 mg/kg, daily, Days 7 through 97
Route of administration: Oral gavage
Formulation/Vehicle: 0.5% (w/v) methylcellulose in reverse osmosis-purified deionized water
Species/Strain: Rats / Sprague-Dawley
Number/Sex/Group: Subset 1: Main Study: 10M/10F/group
Subset 2: Neurohistopathology:5M/5F/group
Subset 3: Recovery: 20M/20F/group (of which 5M/5F for recovery neurohistopathology)

Satellite groups/unique design: Subset 4: Toxicokinetics: 24M/24F/group, except 6M/6F in control group
Deviation from study protocol affecting interpretation of results: None that affected study interpretation

Observations and Results

Parameters	**Major findings**
Mortality	Three preterm deaths associated with central nervous system (CNS) toxicity occurred at the HD. Two deaths (1 HD, 1 LD) were associated with kidney toxicity) and one death (HD) was accompanied by skin toxicity; deaths occurred after at least 2 weeks of dosing.
Clinical Signs	CNS-related clinical signs included abnormal gait, tremors, decreased activity, convulsions, hunched posture, repetitive behavior, eyes partly closed, and piloerection. Other clinical signs included dehydration (also seen in humans), skin scabs, and thin/lost fur.

Clinical Signs, Main Study Cohort, Dosing Period (Juvenile Study: Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Eyes, partly closed	10	10	10	10	10	10
Piloerection	10	10	10	10	10	8
Dehydration, suspected	4	2	5	2	3	6
Abnormal gait			5			5
Activity decreased					2	7
Tremors			3			
Hunched posture	1		2	1		
Convulsions, non-sustained			1			
Skin, scab						2
Breathing, labored						1
Prostration			1			
Low carriage						1
Skin, pale						1
Fur loss			1			

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Fur staining, yellow						1
Fur staining, orange				1		

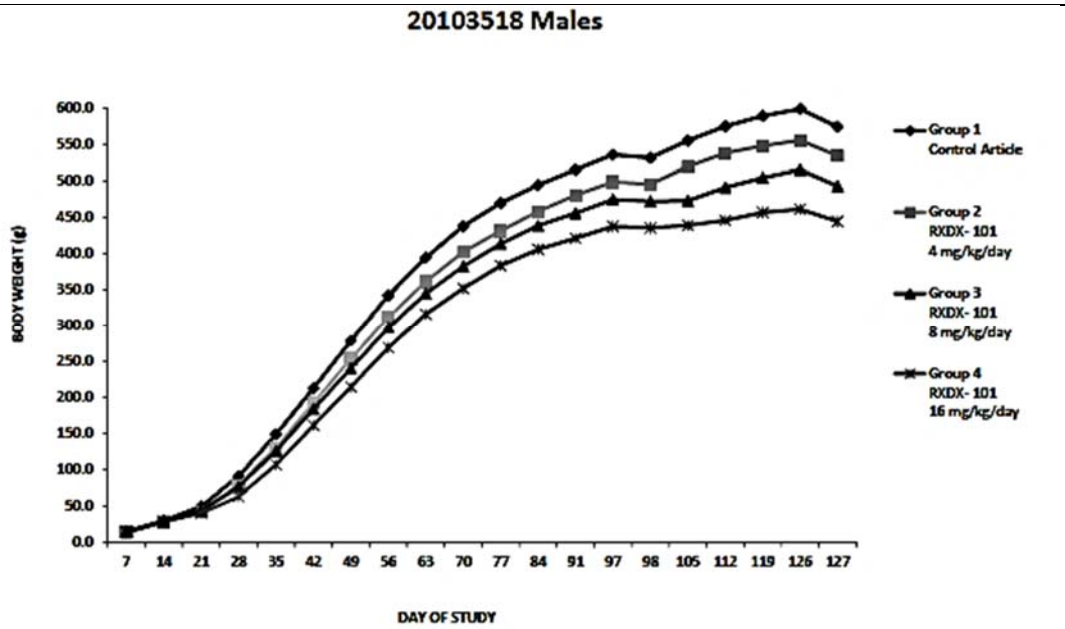
10/sex/group
There were no findings in any of the control animals.

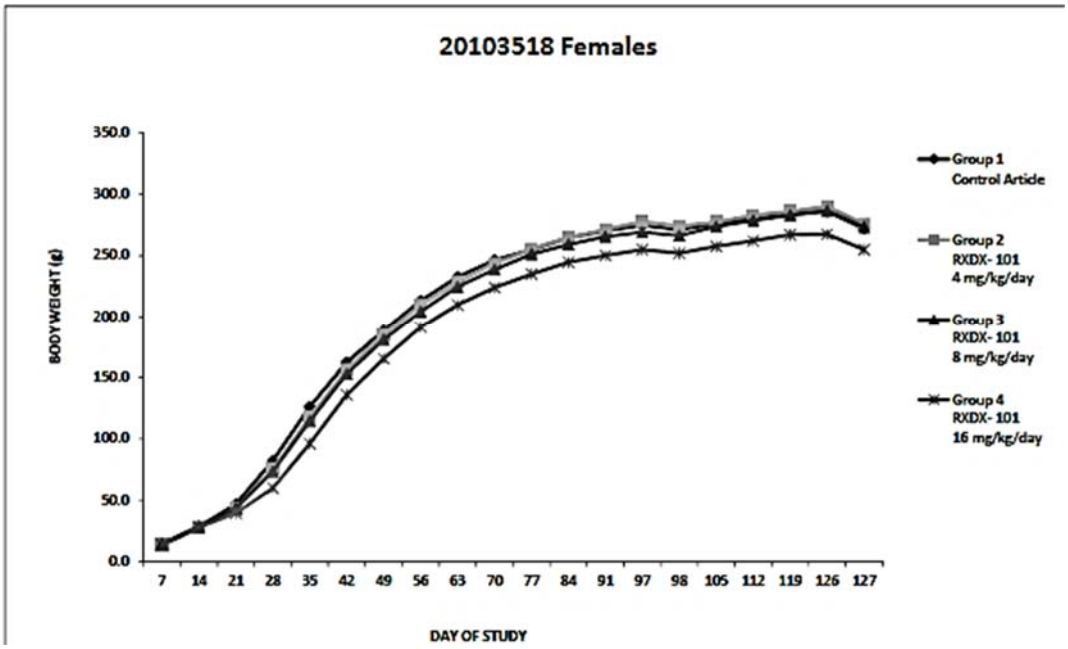
Clinical Signs, Recovery Cohort, Dosing and Recovery Periods (Juvenile Study: Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Activity decreased			7		4	12
Tremors			2			
Convulsions, non-sustained		1	1			
Respiratory rate increased			1			2
Skin, lesion	1					
Fur staining, orange					2	
Breathing, abnormal sounds	1					
Swelling						1
Malocclusion						1
Teeth, broken						1
Eyes, partly closed	19*	20*	20*			
Piloerection	19*	20	20*	20	20	16
Dehydration, suspected	6	6	11*	3	4	10
Abnormal gait			16*			14
Skin, scab	1	2*	4*		1	3*
Fur loss	1**	2*	3*			
Hunched posture	1		1*			2
Fur, thin cover		1**	1**			1**
Salivation			1**			
Repetitive behavior			1**			
Fur staining, red				1**		
Fur, ungroomed					1**	
Activity increased			1**			
Thin			1**			

20/sex/group; distinct subset of animals from the main study cohort.
There were no findings in any of the control animals, except for skin scabs (2 in M, 2 in F), and thin fur cover (2 in F).
No star: event that occurred only before Day 98;
* Event present during recovery period (≥Day 98) (at all; not necessarily in each animal)
** Event only occurred during recovery period

Body Weights and Feed Consumption	Impaired body weight gain and corresponding decreased food consumption, occurred at the HD for both sexes, and also in LD and MD males (with smaller decreases also occurring in the LD and MD females).





(Excerpted from Applicant's submission)

Femur Length	Slightly shorter femurs were observed in HD males and females (statistically significantly in females) at the end of the dosing period, with partial recovery by the end of the study.

Femur Length (Juvenile Study: Rats)

		Day 98				Day 128			
		Males		**Females**		**Males**		**Females**	
mg/kg/day	Length	RFL	LFL	RFL	LFL	RFL	LFL	RFL	LFL
0	mm	40.43	40.38	35.70	35.62	41.61	41.76	36.28	36.32
4	mm	39.82	39.18	35.51	35.29	41.50	41.61	35.61	35.58
	%Diff	-1.51	-2.97	-0.53	-0.93	-2.27	-0.37	-1.86	-2.04
8	mm	40.40	40.89	35.25	35.23	41.07	41.16	36.25	36.21
	%Diff	-0.07	1.26	-1.26	-1.10	-1.30	-1.44	-0.07	-0.29
16	mm	39.18	39.14	34.09**	34.20**	40.52	40.58*	35.31	35.25
	%Diff	-3.10	-3.08	-4.51	-3.99	-2.62	-2.83	-2.66	-2.95

RFL: Right femur length; LFL: Left femur length; mm: Mean femur length in millimeters; %Diff: percent change in length from concurrent control
Day 98: The day after the Day 7-97 dosing period; Day 128: The end of the recovery period.
* $p \leq 0.05$; ** $p \leq 0.01$

Sexual Maturation: (Balano-Preputial Separation and Vaginal Patency)	A dose-dependent delay in sexual maturation occurred in males and females (statistically significant for all dose groups), which was likely related to delayed growth.

Age at Sexual Maturation (Juvenile Study: Rats)

mg/kg/day	**0**	**4**	**8**	**16**	**Historical Control**
Balano-Preputial Separation (Mean Day) (Mean body weight [g])*	Day 43.9 (232.5 g)	46.7* (235.0)	48.5* (235.2)	50.1* (221.6)	41.3-49.7 (207.5-227.8)
Vaginal Patency (Mean Day) (Mean body weight [g])*	Day 31.9 (106.2 g)	33.3* (106.6)	34.7* (115.0)	36.8* (107.8)	30.1-35.3 (92.4-120.8)

Mean body weight: on the respective day
* $p \leq 0.01$

Ophthalmology:	Mostly unremarkable; some sporadic blepharospasm occurred, possibly related to light sensitivity.
Functional Observation Battery	At the HD, decreased forelimb grip strength, hindlimb grip strength, and landing foot splay occurred (statistically significant in males, females, and males, respectively). Partially closed eyes occurred frequently. Although abnormal gait was not observed on the two instances where the functional observation battery was conducted, HD males and females displayed abnormal gait during daily observations for clinical signs.

Functional Observation Battery Results (Juvenile Study: Rats)

Dose Level (mg/kg/day)	0 (Control)		4		8		16	
Sex	Male	Female	Male	Female	Male	Female	Male	Female
PND 70 ± 3								
Palpebral Closure								
Wide open	20	20	9	20	0	6	1	3
Slightly drooping	0	0	10	0	15	14	5	11
Half-closed	0	0	0	0	5	0	13	5
Completely shut	0	0	0	0	0	0	0	0
Mean score	1.0	1.0	1.5**	1.0	2.3**	1.7**	2.6**	2.1**
Piloerection	0	0	0	0	0	0	0	0
Body Temperature (°C)	36.91	37.95	36.90	37.82	37.06	37.44*	36.95	37.39**
Body Weight (grams)	447.3	256.9	413.3**	247.6	386.6**	242.2*	358.1**	224.3**
PND 111 ± 3								
Palpebral Closure								
Wide open	10	10	5	10	3	9	3	4
Slightly drooping	0	0	5	0	6	1	4	6
Half-closed	0	0	0	0	1	0	3	0
Completely shut	0	0	0	0	0	0	0	0
Mean score	1.0	1.0	1.5*	1.0	1.8**	1.1	2.0**	1.6*
Piloerection	0	0	3	0	2	1	3	2
Forelimb Grip Test (grams)								
Maximum	1103.0	686.5	970.0	800.5	1087.0	727.0	721.0**	662.5
Average	945.8	580.0	836.0	689.3	895.8	562.0	579.3**	610.5
Hindlimb Grip Test (grams)								
Maximum	907.5	757.5	849.5	617.5*	877.5	678.0	795.0	584.5**
Average	854.5	677.0	779.0	569.3	808.0	608.0	727.0	548.5
Landing Foot Splay								
Average (cm)	7.91	6.23	7.64	5.84	6.15*	5.27	6.11*	7.06
Body Temperature (°C)	37.05	37.74	36.87	37.84	36.75	37.47	36.52	37.95
Body Weight (grams)	564.9	288.9	530.8	269.1	490.6**	282.3	442.3**	266.0

* = Statistically significant ($p \leq 0.05$)
** = Statistically significant ($p \leq 0.01$)

(Excerpted from Applicant's submission)

Motor Activity and Auditory Startle Response	Unremarkable
Morris Water Maze	Entrectinib treatment impaired spatial learning and memory, most evident at the HD. When a platform was present, HD animals failed to find it in the allotted time more frequently than did control animals. When the platform was absent, HD animals spent less time searching the location where it had been than did control animals. The observed impairment in memory is consistent with known effects of TrkA signaling deficiencies in humans (Indo et al., 1996).

Morris Water Maze: Control vs. High Dose (Juvenile Study: Rats)

Session	Sex/dose (mg/kg)/# rats	# Rats that did NOT reach 60 sec	# Rats that DID reach 60 sec	Total # of times reached 60 sec	% of time reached 60 sec
Session 1: On-treatment; between Days 80-96; platform present	Male / 0 / 20	9	11	25	16%
	Male / 16 / 19	2	17	52	34%
	Female / 0 / 20	7	13	34	21%
	Female / 16 / 19	2	17	74	49%
Session 2: On-treatment; between Days 80-96; platform present	Male / 0 / 20	18	2	2	1%
	Male / 16 / 19	10	9	22	14%
	Female / 0 / 20	14	6	11	7%
	Female / 16 / 19	12	7	19	13%
Session 1: Recovery; between Days 118-125; platform present	Male / 0 / 10	5	5	10	13%
	Male / 16 / 10	2	8	22	28%
	Female / 0 / 10	4	6	14	18%
	Female / 16 / 10	0	10	47	59%
Session 2: Recovery; between Days 118-125; platform present	Male / 0 / 10	10	0	0	0%
	Male / 16 / 10	9	1	2	3%
	Female / 0 / 10	8	2	2	3%
	Female / 16 / 10	3	7	22	28%

Note: There were 9 attempts per session. Attempt 1 of 9 for each session is not counted in this table.
Note: Maximum attempt time is 60 seconds. Assuming that a time of 60 seconds means the rat did not complete the task by the time limit.

Morris Water Maze: Percent of Time Searching Correct Quadrant (Platform Absent) (Juvenile Study: Rats)

	Males				Females			
mg/kg/day	**0**	**4**	**8**	**16**	**0**	**4**	**8**	**16**
Days 80 - 96	38.0	35.0	32.7	22.89*	29.0	36.7	30.8	30.0
Days 118 - 125	36.6	29.6	30.4	29.4	40.1	32.7	25.8**	22.6**

* $p \leq 0.05$
** $p \leq 0.01$

Hematology and Coagulation	In males and females, entrectinib resulted in partially reversible decreases in red blood cells, hemoglobin, and hematocrit (consistent with findings in adult rats and dogs, and clinical data).

Hematology % Change from Concurrent Control (Juvenile Study: Rats)

		Males			Females		
	mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Parameter	Time point						
RBC	End of dosing	-7.4%	-4.4%	-5.8%	-2.1%	-7.8%	-8.6%
	End of recov.	-1.8%	-5.2%	-1.4%	-0.8%	-3.1%	-3.0%
HGB	End of dosing	-7.1%	-4.5%	-5.8%	-2.1%	-7.8%	-8.6%
	End of recov.	-2.0%	-6.5%	-5.2%	-5.4%	-4.1%	-4.8%
HCT	End of dosing	-6.4%	-5.1%	-5.9%	-3.4%	-7.0%	-7.9%
	End of recov.	-1.9%	-7.8%	-4.8%	-4.9%	-5.6%	-4.5%

End of dosing: Day 98
End of recovery: Day 128

Clinical Chemistry	Increases in creatinine (also observed in humans) were noted in males; this change persisted in the recovery period.

Clinical Chemistry % Change from Concurrent Control (Juvenile Study: Rats)

		Males			Females		
	mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Parameter	Time point						
UN	End of dosing	16.7%	23.3%	43.3%	5.1%	9.5%	21.9%
	End of recov.	6.7%	23.5%	22.1%	-2.2%	-0.5%	7.7%
CREAT	End of dosing	4.3%	26.1%	21.7%	6.7%	3.3%	-6.7%
	End of recov.	6.9%	41.4%	34.5%	0%	2.6%	7.9%
TRIG	End of dosing	-38.0%	-46.5%	-32.4%	-13.9%	-19.4%	-13.9%
	End of recov.	-30.7%	-42.0%	-48.9%	-10.9%	-34.5%	-43.6%
GLU	End of dosing	-11.9%	-11.2%	-19.4%	-5.0%	-0.8%	-9.2%
	End of recov.	3.4%	8.2%	16.4%	-11.0%	-15.1%	-16.3%
ALB	End of dosing	-11.4%	-5.7%	-8.6%	2.7%	-2.7%	-5.4%
	End of recov.	-2.6%	-5.3%	-2.6%	4.9%	-2.4%	-4.9%
Ca	End of dosing	-6.7%	-5.6%	-4.4%	2.3%	-1.1%	0%
	End of recov.	0%	-3.2%	-2.1%	3.1%	-2.1%	-1.0%
AST	End of dosing	1.4%	8.2%	24.7%	2.5%	-3.8%	22.8%
	End of recov.	4.8%	2.4%	-3.6%	19.7%	35.5%	3.9%

End of dosing: Day 98
End of recovery: Day 128

Urinalysis	Unremarkable
Gross Pathology	Mostly unremarkable, except for the following: • HD male #3502, which was found dead: Kidney dilatation, adhesion, enlargement, and masses; liver adhesion; discoloration; abnormal appearance; and urinary bladder calculi • MD male #2802: Kidney dilatation • MD male #2804: Kidney dilatation • LD male #2201: Kidney dilatation • HD male #1303 (TK subset), preterm sacrifice: Kidney and jejunum dilatation; abnormal material accumulation in kidney, colon, and urinary bladder; discoloration of liver, lung, small intestine, and stomach
Organ Weights	Increased spleen weights occurred (statistically significant in males ≥ LD and in females at HD). This finding was accompanied by extramedullary hematopoiesis (more in males than in females).

Spleen Weights (Juvenile Study; Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Absolute weight	8.88% (8.76%)	7.28% (9.45%)	7.40% (9.84%)	2.15% (20.13%)	10.18% (27.90%)	20.20% (17.00%)
Body weight ratio (%)	17.34% (16.59%)	17.07% (33.01%)	25.59% (40.10%)	4.42% (15.69%)	14.06% (28.48%)	32.50% (26.37%)

Note: Values in parentheses are from the recovery period.
Note: Values are expressed as percent change relative to controls

Histopathology (Adequate Battery: Yes)	As shown in Table 16, key histological target organs were the spleen and skin.
Neurohistopathology	In HD males and females, statistically significantly lighter brains occurred; however, these were proportional to lower body weights in those dose groups. At the end of the dosing and recovery periods, there were no entrectinib-related neurohistopathology findings in the sections of the brain, spinal cord, Gasserian ganglia, 5th cranial nerve, eyes, dorsal root ganglia and spinal nerves, peripheral nerves or skeletal muscles examined.

Brain Measurements (nm)

	Males				Females			
mg/kg/day	**0**	**4**	**8**	**16**	**0**	**4**	**8**	**16**
Body weight (g)	555.4 (530.8)	480.2 (486.8)	545.6 (508.2)	452.8* (419.8**)	281.4 (276.4)	278.0 (260.6)	277.2 (279.8)	262.2 (266.8)
Brain weight (g)	2.41 (2.40)	2.29 (2.29)	2.30 (2.29)	2.11** (2.14**)	2.19 (2.02)	2.14 (2.18)	2.11 (2.10)	2.02** (2.03)
% of body weight	0.44 (0.46)	0.48 (0.47)	0.42 (0.46)	0.47 (0.51)	0.79 (0.74)	0.77 (0.84)	0.77 (0.76)	0.78 (0.77)
Cerebrum Length	17.89 (16.91)	17.25 (16.93)	17.11 (16.17)	16.85 (16.38)	17.30 (16.50)	16.85 (16.79)	16.01 (16.37)	16.32 (16.34)
Cerebellum Length	11.96 (11.52)	11.77 (11.63)	11.48 (11.46)	11.71 (11.42)	11.64 (11.63)	11.51 (11.71)	11.60 (11.37)	11.21 (11.58)
Brain Morphometry (µm, Day 98)								
Frontal cortex thickness	1926	NA	NA	1868	1978	NA	NA	1892
Parietal cortex thickness	2210	NA	NA	1939	2134	NA	NA	1985
Caudate-putamen width	3829	NA	NA	3395	3811	NA	NA	3504
Corpus callosum thickness	371	NA	NA	275	328	NA	NA	282
Hippocampus thickness	1594	NA	NA	1602	1554	NA	NA	1550
Cerebellum height	5649	NA	NA	5254	5153	NA	NA	5493

Values at Day 98 (Values at Day 127; end of recovery period)
* $p < 0.05$; ** $p < 0.01$; NA: Not assessed

Toxicokinetics	Peak Cmax exposures and AUC(0-24) for entrectinib and M5 were generally proportional to dose in males and females on PND 7 (Dosing Day 1), and for the 4 mg/kg to 8 mg/kg dose interval on Day 97. Exposure was less than dose proportional between the 8 and 16 mg/kg doses on Day 97. Exposure was generally similar in males and females, except for higher entrectinib exposure in females at the 8 mg/kg and 16 mg/kg doses on Day 97. Entrectinib exposure was higher on Day 7 than on Day 97. Entrectinib accumulation ratios in all treatment groups on Day 97 ranged from 0.285 to 0.745. M5 accumulation ratios in all treatment groups on Day 97 ranged from 0.018 to 0.069.

Toxicokinetic Parameters for Entrectinib (Juvenile Study; Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Postnatal Day 7						
Tmax (hr)	4	8	8	4	12	8
Cmax (µM)	0.456	0.614	1.22	0.341	0.615	1.24
AUC(0-24) (µM*hr)	7.48	11.0	21.6	6.05	10.8	19.8
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Dose exposure multiple*	0.16X	0.23X	0.45X	0.13X	0.23X	0.41X
Postnatal Day 97						
Tmax (hr)	4	4	4	4	4	4
Cmax (µM)	0.288	0.683	0.822	0.398	0.843	1.00
AUC(0-24) (µM*hr)	2.20	5.78	6.29	3.12	8.08	11.1
AUC(0-24) AR	0.285	0.526	0.291	0.516	0.745	0.560
Dose exposure multiple*	0.05X	0.12X	0.13X	0.07X	0.17X	0.23X
Dose exposure multiple compared to human*						
Day 7: both sexes	0.14X	0.23X	0.43X			
Day 97: both sexes	0.06X	0.14X	0.18X			
Average of Days 7 & 97: both sexes	0.10X	0.19X	0.31X			

AR: Accumulation ratio; NA: Not applicable
* Calculated relative to human AUC(0-24,22) of 48 µM*hr (after receiving multiple 600 mg doses of the F2A formulation in Study STARTRK-1)

Toxicokinetic Parameters for M5 Metabolite (Juvenile Study; Rats)

	Males			Females		
mg/kg/day	**4**	**8**	**16**	**4**	**8**	**16**
Postnatal Day 7						
Tmax (hr)	12	8	8	8	12	8
Cmax (µM)	0.025	0.037	0.061	0.024	0.030	0.054
AUC(0-24) (µM*hr)	0.326	0.420	1.08	0.297	0.359	0.882
AUC(0-24) AR	NA	NA	NA	NA	NA	NA
Postnatal Day 97						
Tmax (hr)	NC	4	4	NC	4	4
Cmax (µM)	BLQ	0.046	0.069	BLQ	0.018	0.031
AUC(0-24) (µM*hr)	NC	0.304	0.418	NC	0.062	0.192
AUC(0-24) AR	NC	0.725	0.389	NC	0.173	0.217

AR: Accumulation ratio; NA: Not applicable; NC: Not calculated

Table 16: Selected Histopathology Findings (Juvenile Study; Rats)

	Males				Females			
mg/kg/day	**0**	**4**	**8**	**16**	**0**	**4**	**8**	**16**
Animals examined (dosing/recovery)	10/15	10*/13	10*/15	9/13	10/15	10*/15	10*/15	10/14
BONE MARROW								
Increased cellularity; mild								1
ESOPHAGUS								
Regeneration; myofiber; wall; minimal								1
Infiltration, mononuclear cell; wall; min.								1
HEART								
Cardiomyopathy; minimal	3			7	1			3
Necrosis; vascular, adipose tissue; min.				1				
KIDNEY								
Nephropathy								
--minimal	6			3	3			2
--mild				1				
Dilatation; tubular; minimal	1			3				3
Dilatation; pelvis								
--minimal				1				
--mild				1				
LIVER								
Tension lipidosis; minimal				1				1
Inflammation, granulomatous; minimal								1
SKIN								
Hyperkeratosis; minimal	2R		1, 1R		1R		1, 1R	1
Fibrosis; dermal; minimal	2R	2	4, 2R	2, 3R	1, 3R	3, 5R	6, 6R	1
Hyperplasia; epidermal								
--minimal	4R	2, 1R	4, 3R	3, 4R	1, 6R	3, 7R	7, 7R	2
--mild			1, 1R					
Infiltration, mononuclear cell; dermal; minimal	2R	1R	1	2	1, 3R	1	2, 1R	2R
Infiltration, mononuclear cell; follicle; minimal								1
Crust; mild								
--minimal		1R			1R			1R
--mild			1, 1R					
Single cell necrosis; epidermal; min.			1R					
SPLEEN								
Increased hematopoiesis								
--minimal	2, 1R	4, 5R	4, 1R	4, 3R	1, 1R	2, 1R	1	2
--mild		3					1R	1
Congestion								
--minimal	4, 5R	4, 5R	7, 11R	2, 4R	3, 2R	4, 6R	2, 5R	6, 5R
--mild	2	5, 8R	1, 4R	7, 9R		8R	5, 6R	3, 6R

* Only spleen, skin (inguinal), and bone marrow were examined for the LD and MD groups.

5.5.5. Other Toxicology Studies

The results of a GLP-compliant neutral red uptake (NRU) assay in BALB/c 3T3 mouse fibroblast cells (Study #1087359), an in vitro screen for phototoxicity, indicated that entrectinib has some phototoxic potential, with a Photo Irritation Factor (PIF) of approximately 6 (PIF=60 for the promethazine positive control). A follow-up GLP-compliant in vivo phototoxicity study (Study #1087360) assessed the potential phototoxic effects of entrectinib (0, 50, 100, or 200 mg/kg/day for 3 days) in Long-Evans female pigmented rats (5/group). Grade 1 erythema and edema occurred in one animal at the 200 mg/kg dose. Microscopic examination of the eyes revealed neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium at 200 mg/kg, with and without ultraviolet radiation exposure (UVR), and at 100 mg/kg with UVR. Given the observations in the absence of UVR, changes were considered entrectinib-related but not indicative of significant phototoxicity.

A GLP-compliant skin irritation study (Study #1087357) indicated that entrectinib did not irritate the intact skin of New Zealand White rabbits. A GLP-compliant eye irritation study (Study #1087358) indicated that entrectinib (a single 100-mg application) caused a transient ocular irritation reaction in New Zealand White rabbits, which resolved within one week.

Brain penetration of entrectinib was confirmed in a non-GLP compliant 2-week oral repeat dose toxicology study in rats (Study #1087347) at 24-hour post dose. Entrectinib brain to plasma ratios reached 2.5 and 2.3 for males and females, respectively, when treated with 400 mg/kg of entrectinib daily for 2 weeks.

X _____ X _____

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6 Clinical Pharmacology

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6.1. Executive Summary

The primary data supporting the clinical pharmacology component of the NDA are from adult patients with *NTRK* fusion-positive solid tumors enrolled in Study STARTRK-2 (RXDX-101-02) and Study STARTRK-1 (RXDX-101-01), with supportive data from the pediatric study, STARTRK-NG (RXDX-101-03). In addition, clinical pharmacology studies were conducted to investigate following key clinical pharmacology characteristics: mass balance and metabolism, population pharmacokinetics (popPK) analyses of the effect of covariates on entrectinib systemic exposure, potential prolongation of QT/QTc interval, effect of food or proton-pump inhibitor (PPI) on entrectinib systemic exposure, potential pharmacokinetics (PK) drug-drug interactions (DDI) between entrectinib and a strong inhibitor or a strong inducer of Cytochrome P450 3A4 (CYP3A4), effect of entrectinib on the PK of a sensitive CYP3A4 substrate, exposure-response (E-R) relationship analyses for efficacy and safety.

Entrectinib is primarily metabolized by CYP3A4 to form a major active metabolite M5, with minimal excretion of both entrectinib and M5 into urine. The popPK analyses did not identify clinically significant covariates influencing entrectinib exposure. Entrectinib dose adjustment is not necessary in patients with mild hepatic impairment or in patients with mild or moderate renal impairment. Dose adjustment is recommended when entrectinib is coadministered with strong or moderate CYP3A4 inhibitors. Coadministration of strong or moderate inducers of CYP3A4 with entrectinib should be avoided. Results from a QTc sub-study did not suggest a clinically meaningful mean increase (i.e., 20 ms) from baseline in QTcF with entrectinib treatment.

The efficacy and safety profiles support the proposed entrectinib dosing regimens of 600 mg orally once daily (QD) for adults without regard to food. Objective responses as assessed by BICR were achieved in 31 of the 54 (57.4% [95% CI: 43.2%, 70.8%]) patients treated with entrectinib 600 mg QD in the integrated efficacy evaluable population with *NTRK* fusion-positive solid tumors. The E-R analyses suggest a flat relationship for efficacy but a correlation of entrectinib and M5 exposure with the incidence of severe (≥ Grade 3) AE, especially in patients achieving higher exposure with the 800 mg QD entrectinib dose.

For pediatric patients ≥12 years (adolescents), the body surface area (BSA in mg/m^2)-based dosing regimen of entrectinib (600 mg QD for adolescents with BSA greater than 1.50 m^2, 500 mg QD for adolescents with BSA 1.11 to 1.50 m^2, and 400 mg QD for adolescents with BSA 0.91 to 1.10 m^2) is supported by safety data from the pediatric study, STARTRK-NG, and comparable PK exposure of entrectinib based on popPK analyses. Given the mechanism of action of entrectinib, it is considered appropriate to extrapolate the efficacy from adult patients to adolescents. For pediatric patients <12 years old, a BSA-based dosing regimen of entrectinib cannot be established at this time due to the uncertainty regarding the relative bioavailability data in this submission. (b) (4)

(b) (4)

Recommendations

The Office of Clinical Pharmacology has reviewed the data and information contained in NDA 212726. This NDA is approvable from a clinical pharmacology perspective for adults and adolescents. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from the ALKA-372-001, STARTRK-1 and STARTRK-2 studies. Objective responses assessed by BICR were achieved in 31 of the 54 (57.4% [95% CI: 43.2%, 70.8%]) patients treated with entrectinib 600 mg QD in the integrated *NTRK* efficacy evaluable population.
General dosing instructions for adults and pediatric patients ≥12 years (adolescents)	Adults: 600 mg orally once daily Pediatric patients 12 years and older: recommended dosage is body surface area based as shown below: • BSA greater than 1.50 m^2: 600 mg once daily • BSA 1.11 to 1.50 m^2: 500 mg once daily • BSA 0.91 to 1.10 m^2: 400 mg once daily The STARTRK-NG study provided supportive data for dosing in adolescents.

(b) (4)

[redacted]

Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is needed for patients with mild hepatic impairment. The PK of entrectinib in patients with moderate and severe hepatic impairment is unknown. A PMR will be issued for a hepatic impairment study.
	• No dose adjustment is needed for patients with mild and moderate renal impairment. Although the PK of entrectinib in patients with severe renal impairment is unknown, significant effect of severe renal impairment on entrectinib exposure is not expected based on minimum involvement of renal elimination pathway.
	• For adults and pediatric patients 12 years and older with BSA greater than 1.5 m^2, if coadministration cannot be avoided, reduce the entrectinib dose as follows:
	  o Moderate CYP3A Inhibitors: 200 mg orally once daily
	  o Strong CYP3A Inhibitors: 100 mg orally once daily
	• Avoid coadministration of entrectinib with moderate or strong CYP3A inhibitors in pediatric patients with BSA less than or equal to 1.5 m^2.
	• Avoid concomitant use with strong and moderate CYP3A4 inducers in adults and adolescents.

Bridging between the to-be-marketed formulation and clinical trial formulations	A bioequivalence is demonstrated between the main clinical trial formulation F2A and the to-be-marketed formulation F06 in the pivotal BE study RXDX-101-15.
Labeling	The review team has specific content and formatting change recommendations. Significant modifications to the label made by the FDA include recommended dosage for pediatrics in Section 2.2, languages regarding dose modifications for drug-drug interactions (DDI) in Section2.4 and Section 7, the statement about E-R relationship and cardiac electrophysiology in Section 12.2, and the format and content in Section 12.3.

Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Entrectinib dose in patients with moderate and	Entrectinib is extensively metabolized in liver and forms a major active metabolite M5. There is no pharmacokinetic	Complete planned clinical pharmacokinetic trial to determine an appropriate dose of entrectinib in patients with

	severe hepatic impairment.	data to recommend entrectinib dose for patients with moderate and severe hepatic impairment. The clinical trial can provide understanding for entrectinib dose adjustment for this patient subpopulation.	moderate and severe hepatic impairment.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Entrectinib exhibited dose-proportional increases in exposure (C_{max} and AUC) across the dose range of 200 to 800 mg (see Section 6.3.1 for details). Steady-state was achieved within one week for entrectinib and at second week (Cycle 1 Day 15) for M5. The accumulation of entrectinib was approximately 1.8-fold with the QD dosing schedule.

Absorption

The absolute bioavailability of entrectinib was not determined. The human mass balance study suggested that oral bioavailability of entrectinib is greater than 50%. The mean concentration in plasma reached maximum around 4 hours after oral administration of entrectinib. Entrectinib has pH-dependent solubility, (b) (4) (b) (4) (b) (4). With formulation F06 under fasting condition, there was 23% decrease in C_{max} and 25% decrease in AUC_{INF} when entrectinib was coadministered with lansoprazole. When F2A capsules were administered under fed condition, both C_{max} and AUC_{INF} of entrectinib were similar with or without coadministration of lansoprazole. Food has no significant effect on exposure of entrectinib from F2A or F06 formulations (see detail in Section 6.3.2).

Distribution

Both entrectinib and its major active metabolite M5 are >99% bound to human plasma proteins in vitro and independent of drug concentrations. The blood-to-plasma ratio is 1.3 and 1.0 for entrectinib and its major metabolite, M5, respectively.

Elimination

The geometric mean clearance based on population PK analyses is 19.6 L/hour for entrectinib and 52.4 L/hour for M5. The geometric mean terminal elimination half-life is 20 hours for entrectinib and 40 hours for M5.

Metabolism: Metabolism of entrectinib is primary mediated by CYP3A4 (> 90%) and to a minor extent by UGT1A4 in vitro. Following oral administration of a single 600 mg dose of radio-labeled entrectinib to humans, entrectinib was the major circulating drug-derived entity (69% of total radioactivity) in plasma in the 24-hour period after dosing. While entrectinib metabolite M5 (N-desmethyl metabolite) and M11 (N-glucuronide conjugate) were identified as major circulating metabolites in plasma contributing 12% and 19% of the total radioactivity, respectively.

Excretion: In a human mass balance study with mean recovery of 86% over the 13-day collection period, 83% and 3% of the total administered radioactivity excreted into feces and urine, respectively. Entrectinib and M5 accounted for 36% and 22% of radiolabeled material in the feces, respectively.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Genentech proposed a dosing regimen of 600 mg orally once daily (QD) with or without food (b) (4).

The proposed dosage of 600 mg QD without regard to food is acceptable for adults. For pediatric patients 12 years and older, the following BSA based dosage regimens are recommended:

- BSA greater than 1.50 m^2: 600 mg orally once daily
- BSA 1.11 to 1.50 m^2: 500 mg orally once daily
- BSA 0.91 to 1.10 m^2: 400 mg orally once daily

Swallow capsules whole. Do not open, crush, chew, or dissolve the contents of the capsule.

(b) (4)

Therapeutic Individualization

<u>Specific Populations</u>

Patients with Hepatic Impairment: No dose adjustment is necessary in patients with mild hepatic impairment as both noncompartmental and population PK analyses showed no significant effect of mild hepatic impairment on entrectinib and M5 exposure. No dose recommendation can be provided for patients with moderate or severe hepatic impairment due to lack of data.

Patients with Renal Impairment: No dose adjustment is needed in patients with mild or moderate renal impairment as noncompartmental and population PK analyses showed no

significant effect of mild and moderate renal impairment on entrectinib and M5 exposure. Although the PK of entrectinib in patients with severe renal impairment has not been studied, significant effect of severe renal impairment on entrectinib exposure is not expected based on minimum involvement of renal elimination pathway.

Drug-Drug Interactions

Strong and moderate CYP3A4 inhibitors: For adults and pediatric patients 12 years and older with BSA greater than 1.5 m^2, dose reduction of entrectinib from 600 mg QD to 100 mg QD is recommended for coadministration of strong CYP3A4 inhibitors with entrectinib. Coadministration of a strong CYP3A4 inhibitor itraconazole increased entrectinib AUC_{INF} by 6-fold, compared to entrectinib administered alone. Dose reduction from 600 mg QD to 200 mg QD is recommended for coadministration of moderate CYP3A4 inhibitors. The PBPK analysis predicted 3.4-fold increase in entrectinib AUC at steady state when entrectinib is coadministered with a moderate CYP3A4 inhibitor erythromycin. For pediatric patients 12 years and older with BSA less than or equal to 1.5 m^2, avoid coadministration of entrectinib with moderate or strong CYP3A inhibitors. (see detail in Section 19.4.3)

Strong CYP3A4 inducers: Concomitant use of a strong or moderate CYP3A4 inducer with entrectinib should be avoided in adults and adolescents. Coadministration of a strong CYP3A4 inducer rifampin decreased the C_{max} and AUC_{INF} of entrectinib by 56% and 77%, respectively. Concomitant use of a moderate CYP3A4 inducer efavirenz is expected to decrease the steady-state C_{max} and AUC of entrectinib by 43% and 56%, respectively, based on the PBPK analysis. (see detail in Section 19.4.3)

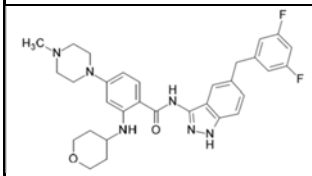
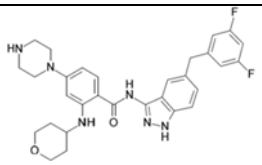
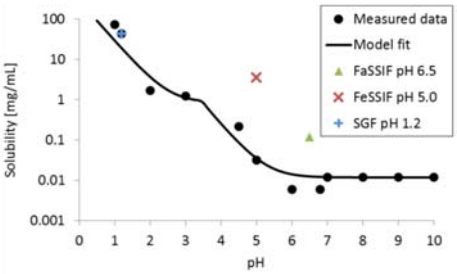
Gastric pH-modifying agents: No dose adjustment is recommended for coadministration of proton pump inhibitors (PPI) with entrectinib. Coadministration of entrectinib with a PPI (Lansoprazole) did not significantly alter the exposure of entrectinib. (see detail in Section 6.3.1)

Outstanding Issues

Other than the PMRs identified by the Clinical Pharmacology review team, the other outstanding issue (b) (4) (b) (4) could not be made due to lack of critical PK data with F06 capsules (b) (4) (b) (4)

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Physical and Chemical Properties		
Chemical Structure and Formula	Entrectinib	M5
	 Molecular formula: $C_{31}H_{34}F_2N_6O_2$ Molecular weight: 560.6 g/mol	 Molecular formula: $C_{30}H_{32}F_2N_6O_2$ Molecular weight: 548.6 g/mol
Solubility	The solubility of entrectinib in aqueous media is pH-dependent.  Abbreviations: FaSSIF=fasted-state simulated intestinal fluid; FeSSIF= fed-state simulated intestinal fluid; SGF= simulated gastric fluid. Filled circles are the measured buffer solubility. The line is the pH versus solubility model used in GastroPlus. Biorelevant solubility measurements are also shown with symbols.	
Pharmacology		
Mechanism of Action	Entrectinib is an inhibitor of TRKA, TRKB, and TRKC (encoded by *NTRK* genes), ROS (encoded by *ROS1* gene). Metabolite M5 is also an inhibitor of TRKA, TRKB, TRKC and ROS with equivalent potency in the in vitro biochemical assay.	
Active Moieties	Entrectinib, and its active metabolite M5 which has clinically relevant contribution to efficacy and safety based on significant metabolite-to-parent AUC ratio (0.41) at steady state in patients.	
QT Prolongation	No large QTc prolongation effect (i.e., >20 ms) of entrectinib was observed in QT assessment of the ECG sub-study of patients (n=113) in Study STARTRK-2 (RXDX-101-02), an open-label, global Phase 2 study at the proposed therapeutic dose, 600 mg once daily (QD). (see details in the IRT review in DARRTS with reference ID 4416352)	
General Information		
Bioanalysis	Entrectinib and its active metabolite M5 were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as an appendix (Section 13.4.1).	

Healthy Volunteers vs. Patients

PK exposure of entrectinib and M5 are considered comparable between healthy volunteers and patients with *NTRK* fusion-positive solid tumor based on the observed geometric means and the range of exposures. As shown in the table below, following a single oral dose of 600 mg with F2A formulation under fed condition, the geometric mean (CV%) of C_{max} and AUC_{0-24} in healthy subjects in Study RXDX-101-07 are comparable to that in patients with *NTRK* fusion-positive solid tumor from Study RXDX-101-01. The variability of PK exposure for both entrectinib and M5 are significantly higher in patients than that in healthy subjects.

Analyte	PK Parameters	Geometric Mean (CV%)	
		Healthy Subjects (n=12)	Patients (n=18)
Entrectinib	C_{max} (nM)	2290 (25%)	2250 (58%)
	AUC_{0-24} (nM*h)	33400 (27%)	31800 (48%)
M5	C_{max} (nM)	392 (29%)	622 (79%)
	AUC_{0-24} (nM*h)	5250 (26%)	10200 (82%)

Drug exposure at steady state following the therapeutic dosing regimen

The geometry means (CV%) of C_{max} and AUC_{0-24} for entrectinib and M5 during the dosing interval of entrectinib 600 mg QD based on data on Cycle 1 Day 14 (n=12) and Cycle 1 Day 28 (n=8) in Study RXDX-101-01 are shown in the table below.

Time	PK Parameters	Geometric Mean (CV%)	
		Entrectinib	M5
Cycle 1 Day 14 (n=12)	C_{max} (nM)	3130 (80%)	1250 (90%)
	AUC_{0-24} (nM*h)	48000 (77%)	24000 (97%)
Cycle 1 Day 28 (n=8)	C_{max} (nM)	2660 (64%)	703 (83%)
	AUC_{0-24} (nM*h)	72800 (42%)	24600 (46%)

Minimal effective dose or exposure

Not available. Entrectinib 600 mg QD was the only dosing regimen studied in the Phase 2 Study RXDX-101-02.

Maximal tolerated dose or exposure

Entrectinib 600 mg QD administered with F2A formulation under fed condition was determined to be the MTD in patients with solid tumors.

Dose Proportionality

Entrectinib showed dose-proportional increase in both C_{max} and AUC after repeat dosing across the dose range of 200 to 800 mg as shown in the table below.

Dose Range	PK Parameters	Number of Subjects	Slope Estimate (90% CI)
200-800 mg	C_{max}	42	1.05 (0.71, 1.40)
	AUC_{0-24}	32	1.09 (0.69, 1.50)

Accumulation

With the 600 mg QD dosing regimen, mean accumulation of entrectinib exposure (AUC) was 1.55 on Cycle 1 Day 14 and 1.96 on Cycle 1 Day 28, the mean accumulation ratio for M5 exposure (AUC) was 2.84 on Cycle 1 Day 14 and 1.64 on Cycle 1 Day 28.

Variability

Inter-subject variability of entrectinib exposure at 600 mg dose was moderate to high with a CV% of 58% to 80 % for C_{max} and 48% to 158 % for AUC_{0-24} after repeat dosing.

Absorption

Oral Bioavailability

Absolute oral bioavailability of entrectinib has not been determined. The human mass balance study suggested an oral bioavailability > 50%.

Bioequivalent (BE)

In the pivotal BE Study RXDX-101-15, entrectinib F06 capsule formulation was determined to be bioequivalent to entrectinib F2A formulation under fasting condition with geometric mean ratios (GMR) and 90% CI within 80% to 125% as shown below.

F06/F2A	C_{max}	AUC_{last}	AUC_{INF}
GMR (90% CI)	0.933 (0.883, 0.986)	0.914 (0.853, 0.979)	0.914 (0.854, 0.979)
Oral Tmax	Following administration of a single oral dose of 600 mg entrectinib using F06 capsule, the median Tmax is 4 hours (range: 4 - 6 hours).		
Food effect for F06 capsule formulation	In Study RXDX-101-15, food had no impact on entrectinib F06 exposures with GMR and 90% CI bounds within 80% to 125% when entrectinib F06 was administered in a fasted state versus following a high-fat, high-calorie meal as shown below.		
fed/fasted GMR (90% CI)	C_{max}	AUC_{last}	AUC_{INF}
	1.06 (0.989, 1.15)	1.15 (1.07, 1.23)	1.15 (1.07, 1.24)
Gastric pH-modifying agents for F06 or F2A formulation	In RXDX-101-09, 600 mg entrectinib was administered at fasted state with the F06 formulation with or without a proton-pump inhibitor lansoprazole in healthy adult male subjects. There was 23% decrease of C_{max} and 25% decrease in AUC_{INF} with lansoprazole. The effect of gastric pH-modifying agent lansoprazole on PK of entrectinib under fed condition was not evaluated with the F06 formulation but was assessed with the F2A formulation at 800 mg in Study CA14707. There was no significant change of C_{max} or AUC_{INF} with the coadministration of lansoprazole under fed condition.		
with PPI/without PPI GMR (90% CI)	Cmax	AUC_{last}	AUC_{INF}
	F06/fasted: 0.765 (0.676, 0.866) F2A/fed: 0.884 (0.741, 1.06)	F06/fasted:0.743 (0.645, 0.856) F2A/fed: 1.14 (0.896, 1.44)	F06/fasted: 0.745 (0.647, 0.859) F2A/fed: 1.16 (0.901, 1.48)
Substrate transporter systems [in vitro]	Entrectinib is not a substrate of P-gp, BCPR OATP1B1, or OATP1B3. However, M5 is a substrate of P-gp and BCPR.		
Distribution			
Volume of Distribution	The estimated apparent volume of distribution (V/F) was 551 L and 81 L for entrectinib and M5, respectively.		
Plasma Protein Binding	The in vitro human plasma protein binding of entrectinib and its active metabolite M5 was 99.78% and 99.69%, respectively.		
Blood to Plasma Ratio	The mean blood-to-plasma ratio was 1.3 for entrectinib and 1.0 for active metabolite M5.		
Elimination			
Half-life	The terminal half-life of entrectinib estimated using NCA method was approximately 20 hours, while the corresponding estimated half-life of M5 was approximately 40 hours.		
Clearance	Population PK analysis estimated a CL/F of 19.6 L/hour and 52.4 L/hour for entrectinib and M5, respectively (for a typical patient of 70 kg).		
Metabolism			
Primary metabolic pathway(s)	Entrectinib is metabolized primarily by CYP3A4 to form the major active metabolite M5, with minor contributions from several other cytochrome P450 enzymes and UGT1A4. M5 is also primarily metabolized by CYP3A4.		

Inhibitor/Inducer	In vitro, entrectinib and its metabolite M5 exhibited inhibitory potential toward CYP3A4/5, CYP2D6, and CYP2C8/9. A clinical DDI study showed that coadministration of entrectinib did not increase the AUC of midazolam after a single dose 600 mg but increase the AUC of midazolam by 50% after repeat dosing at 600 mg. C_{max} of midazolam were decreased by 34% after a single dose and 21% after repeat dosing of entrectinib. In vitro transporter studies suggested a potential inhibitory effect of entrectinib and M5 on P-gp, BCRP, OATP1B1, and MATE1. A clinical DDI study showed that coadministration of entrectinib single dose 600 mg increased the C_{max} and AUC of P-gp substrate digoxin by 28% and 18%, respectively. Entrectinib exhibited induction potential toward CYP3A4 in vitro. However, the clinical DDI study with midazolam showed no induction.
Excretion	
Primary excretion pathways (% dose) ±SD	In a human mass balance Study RXDX-101-05, after a single oral dose of 600 mg [^{14}C]-entrectinib, 83% of the radioactivity was recovered in feces with minimal excretion (3%) into urine over a 13-day collection period. In the feces, entrectinib and M5 accounted for 36% and 22% of the total radioactivity, respectively.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The clinical pharmacology information along with the efficacy results provided evidence of effectiveness.

The primary evidence of effectiveness for the *NTRK* indication came from 54 adult patients enrolled in Studies ALKA-372-001, RXDX-101-01, and RXDX-101-02 with extracranial solid tumors harboring an *NTRK* fusion. As shown in the clinical and statistics reviews, objective responses assessed by BICR were achieved in 31 of the 54 (57.4% [95% CI: 43.2%, 70.8%]) patients in the integrated *NTRK* efficacy evaluable population treated with entrectinib 600 mg QD using the F2A formulation under fed condition.

Of the 54 patients, *NTRK* gene fusions were identified by local and/or central testing in tumor samples of 52 patients using different next generation sequencing (NGS) assays and in samples of 2 patients using other nucleic acid-based assays. Central results with an RNA-based NGS assay were available for 91% (49/54) patients and were positive in 92% (45/49). For most of the 9 patients with *NTRK* gene fusion status determined by local testing only, DNA-based assays were used. Although the inclusion criteria for the *NTRK* efficacy evaluable population included having an in-frame *NTRK* fusion with a functional kinase domain and without a concomitant second oncodriver (e.g., EGFR, KRAS), these criteria were not systematically assessed or documented across the myriad of tests used for enrollment. A PMC is planned to develop a companion diagnostic (see section 4.4).

The distribution of *NRTK* gene fusions among patients in the efficacy evaluable dataset is provided in the clinical review (Table 37). The most common *NRTK* gene fusions found in >2 patients were *ETV6-NTRK3*, *TPM3-NTRK1*, and *TPR-NTRK1*. One patient had discordant *NTRK*

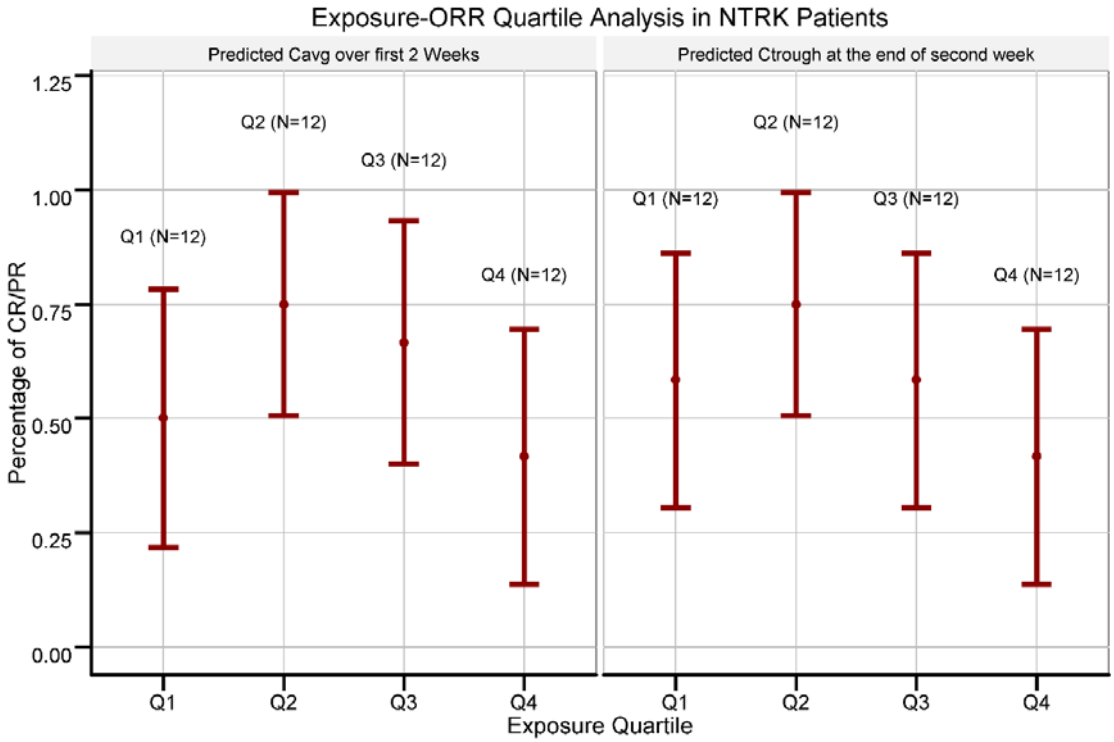
fusions based on local (*CDC42BPA-NTRK1*) and central (*KIF5B-NTRK1*) testing, with the local testing result used in analyses and included in labeling. While development of acquired resistance to entrectinib driven by point mutations in *NTRK* is reported in the literature (Russo 2016, Drilon 2016), no additional clinical information on *NTRK* resistance mutations was provided in the application.

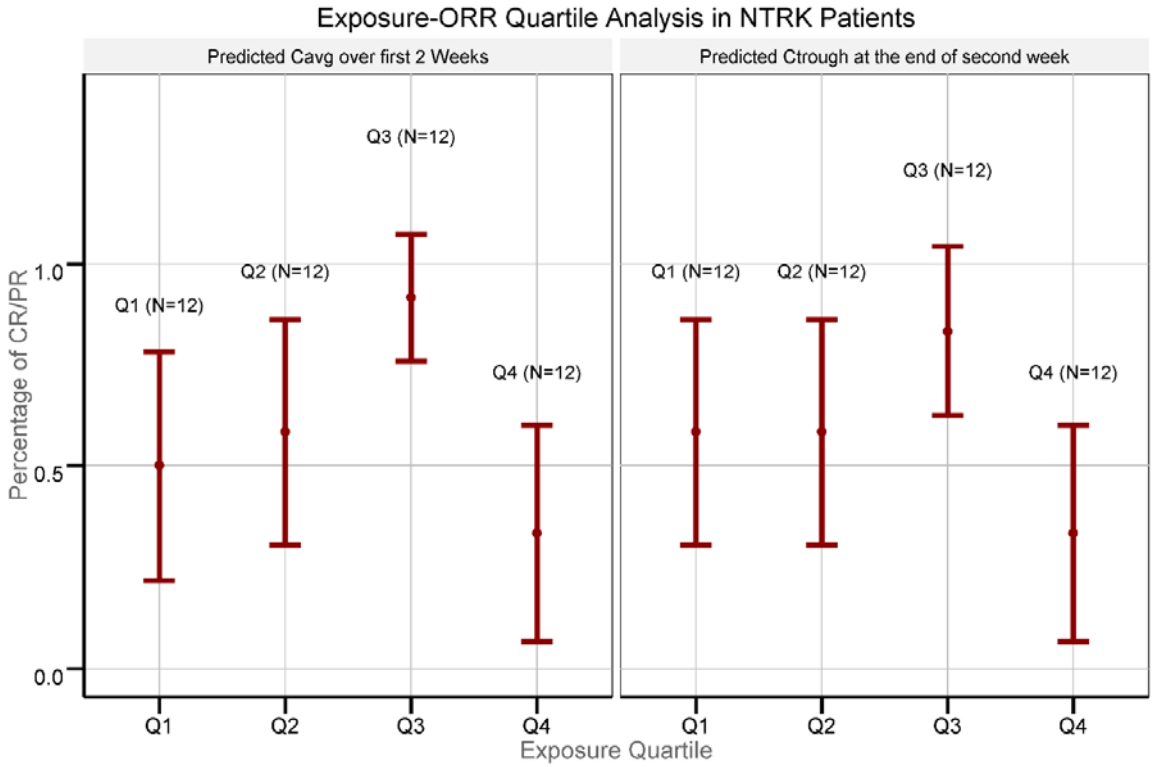
Entrectinib showed clinical activity across *NTRK1-3* gene fusions in patients in the *NTRK* efficacy evaluable population; only 1 patient had an *NTRK2* gene fusion and this patient did not have a tumor response. Based on entrectinib mechanism of action and submitted non-clinical data (see section 5.3), it is reasonable to expect entrectinib to be active against a broad group of activating *NTRK* gene fusions regardless of the fusion partner, which is consistent with the clinical trial experience and supports an indication that is inclusive of activating *NTRK1-3* gene fusions.

Exploratory exposure-response (E-R) analyses were conducted by FDA to compare the relationship in 48 patients with solid tumors harboring an *NTRK* gene fusion. Caution should be taken when interpreting these relationships as they were based on small sample size with one dosing regimen.

In the E-R analysis, there is no clear relationship between entrectinib and M5 exposure and overall response (ORR). The response rates were comparable across the different exposure quartiles (see **Figure 16**).

Figure 16: Relationship Between Entrectinib (Top panel) and M5 (Bottom panel) Exposure and ORR in Patients with *NTRK* Fusion-positive Solid Tumors





Source: Reviewer's Analysis based on "poppk.xpt" and "ars.xpt"

The effectiveness of entrectinib is also supported by the observed decrease in the sum of the longest diameter (SLD) values, including those not considered clinically significant (not meeting criteria for partial response), among patients with *NTRK* fusion-positive tumors treated with entrectinib. Again, there is no clear trend between combined entrectinib and M5 exposure and tumor growth rate (KS) and tumor shrinkage rate (KS) (see Pharmacometrics Report in section 19.4.2). The lack of correlation between PK exposure and the tumor growth and shrinkage parameters may be related to the limited exposure range assessed or the plateau of the pharmacological activity at the recommended therapeutic dose.

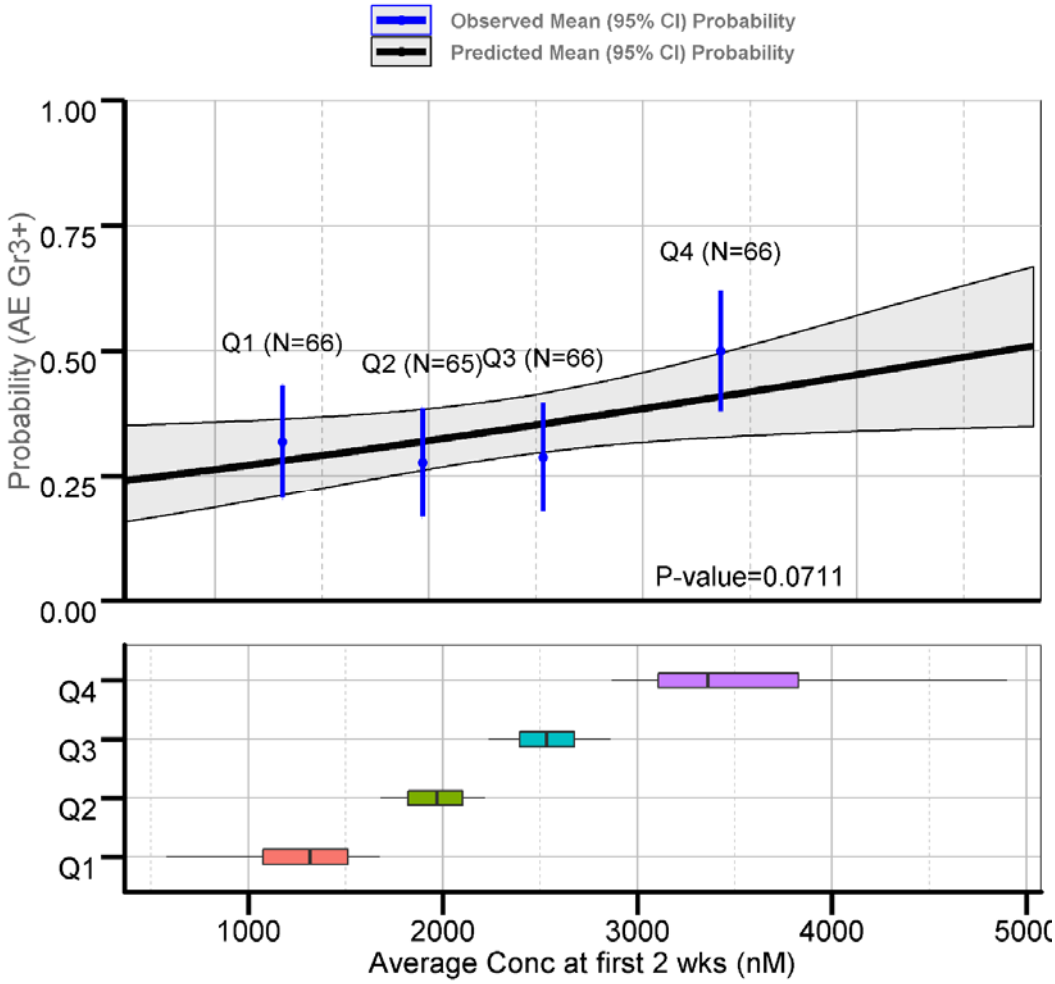
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen is generally supported by the E-R relationships in efficacy and safety. See the previous question for E-R in efficacy.

For tolerability, at 600 mg QD, there were 41% of the 68 patients with *NTRK* fusion-positive solid tumors who had entrectinib dose reduction due to an adverse event. The proposed dose reduction strategy (from 600 mg to 400 mg and then 200 mg QD) in the event of adverse events is acceptable. Dose re-escalation is not recommended due to the lack of supporting clinical data.

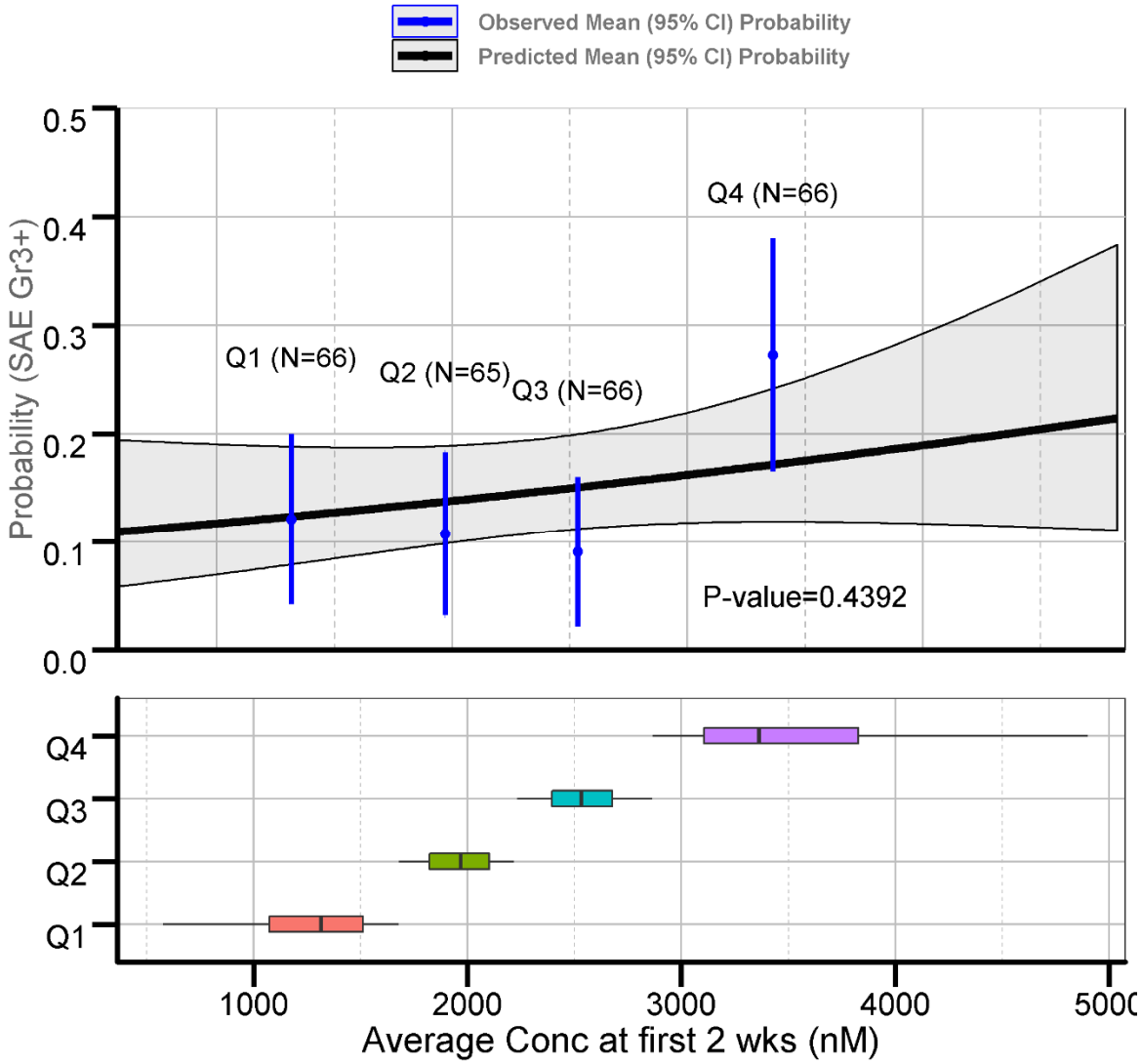
Additional exploratory analyses were also conducted to evaluate the relationship between entrectinib exposure and safety profile. Adverse events (AEs) of interest including NCI CTC Grade ≥3 AE and SAE during treatment. Population PK simulated average concentrations during the first two weeks were selected as the primary exposure metrics in the analysis to overcome the sparse PK sampling and missing data. As depicted in **Figure 17** and **Figure 18**, there are small trends that higher frequency of Grade ≥3 AEs and SAEs are associated with higher exposures (Q4). Similar trends were also observed in patients with higher M5 exposure.

Figure 17: The Relationship between Entrectinib Exposure and Probability of Grade 3+ AE Fit by a Logistic Regression Model



Source: Reviewer's Analysis based on "aex.xpt"

Figure 18: The Relationship between Entrectinib Exposure and Probability of Grade 3+ SAE Fit by a Logistic Regression Model



Source: Reviewer's Analysis based on "aex.xpt"

In addition, no large QTc prolongation effect (i.e., >20 ms) of entrectinib was observed in QT assessment of the ECG sub-study of patients (n=113) in Study STARTRK-2 (see **Table 17**).

Table 17: The Largest Mean Increase in QTcF by Time Shown as Point Estimates and 90% CIs

ECG parameter	Treatment	# of Subjects	Time	ΔΔQTcF(ms)	90% CI (ms)
QTc	600 mg QD	80	Cycle 3 Day 1, 4 h post-dose	-3.9	(-8.2, 0.4)

Source: FDA's QT IRT review (DARRTS with reference ID: 4416352)

Overall, the efficacy and safety data support the proposed dosage of 600 mg QD for the general patient population.

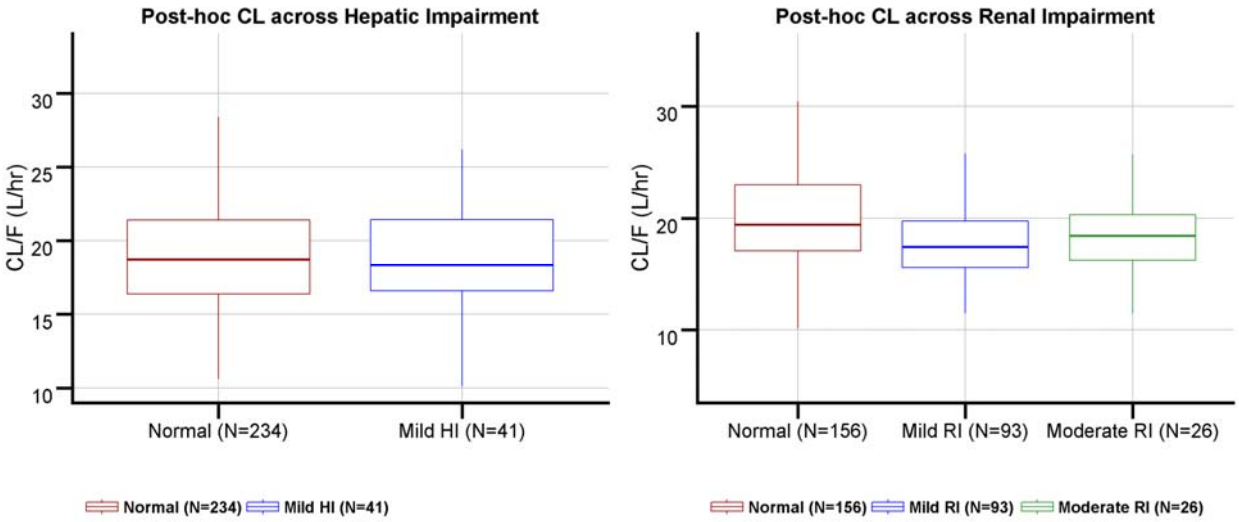
Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Hepatic impairment
Dose reduction is not recommended for patients with mild hepatic impairment.

As depicted in **Figure 19** (Left), the PK profiles of entrectinib and active metabolite M5 in subjects with mild hepatic impairment (total bilirubin ≤ 1.5 ULN, n=41) and those with normal hepatic function (n=234) are comparable. This is consistent with the population PK analysis in which status of mild hepatic impairment has no significant effect on the clearance of entrectinib.

As the impact of moderate and severe hepatic impairment on PK of entrectinib and M5 and safety has not been studied, and hepatic metabolism is the major elimination pathway for entrectinib, a dedicated hepatic impairment study has been planned as a PMR (see Section 6.1).

Figure 19: Comparison of Post-hoc Exposure in Patients with Mild Hepatic Impairment (Left) or Mild to Moderate Renal-impaired Patients (Right) vs. Non-impaired Patients



Source: reviewer's analysis

Renal impairment
Dose reduction is not necessary for patients with renal impairment.

Results from the human mass balance study RXDX-101-05 showed that 83% of the administered radioactivity was recovered in feces, with just a 3% of the total radioactivity recovered in urine. These results suggest that renal clearance pathway plays a minor role in the elimination of entrectinib and its metabolites and significant effect of renal impairment on PK of entrectinib and M5 is not expected.

In the pooled PK analyses, exposure of both entrectinib and M5 were comparable between subjects with mild (CLcr: 60-89 mL/min calculated by Cockcroft-Gault formula, n=93) and moderate (CLcr: 30-59 mL/min, n=26) renal impairment and those with normal (CLcr ≥ 90 mL/min, n=156) renal function (see **Figure 19,** Right).

Pediatric patients

Pediatrics ≥12 years of age
For pediatric patients age 12 years and older (adolescents), the recommended dosage regimens are 600 mg QD for patients with BSA > 1.50 m^2, 500 mg QD for patients with BSA between 1.11 and 1.50 m^2, and 400 mg QD for patients with BSA between 0.91 and 1.10 m^2. The dose recommendation in adolescent patients is supported by the popPK analysis (see detail in Pharmacometrics Report in section 19.4.2).

With the recommended dosing regimen in adolescents, entrectinib exposure in adolescent patients with BSA > 1.5 m^2 is expected to be comparable to adult patients. The predicted exposure in adolescents with BSA > 1.5 m^2 is approximately 10% higher than the exposure in adults either based on estimated weight effect on clearance (scenario 1) or under the assumption of allometric scaling (scenario 2). For adolescents with BSA between 1.11 and 1.50 m^2, the predicted exposure is comparable to adults based on estimated weight effect on clearance (scenario 1), while the predicted average exposure is 20% higher under the assumption of allometric scaling (scenario 2). For adolescents with BSA between 0.91 and 1.10 m^2, the predicted average exposure is 10% lower compared to adults based on estimated weight effect on clearance (scenario 1), while the predicted average exposure is 30% higher under the assumption of allometric scaling (scenario 2) (see **Table 18**). Based on these data, the review team determined that the estimate of 20-30% higher exposure in adolescents with BSA less than 1.5 m^2 compared to adults based on allometric scaling is likely overestimated. It should be noted while the assumption of allometric scaling is, in general, reasonable for pediatric patients less than 12 years of age, this assumption is not supported by the observed PK data of entrectinib in adult patients and additional data will be required to determine a reasonably safe and effective dose in these younger pediatric patients.

Table 18: Predicted PK Exposure in Pediatric Patients 12 Years and Older (PopPK)

Simulation Scenario	Exposure [nM]	WT on CL	Adults[1] (>= 18 yrs)	Adolescents[1] (>=12-<18 yrs & BSA>= 1.5 m^2)	Adolescents[1] (>=12-<18 yrs & 1.1<=BSA< 1.5 m^2)	Adolescents[1] (>=12-<18 yrs & BSA< 1.1 m^2)	RD[2]	RD[3]	RD[4]
1	Cavg	0.31	2254	2336.5	2188.9	1959.9	3.7	-2.9	-13
1	Cmax	0.31	2945.1	3087.7	3035	2912	4.8	3.1	-1.1
1	Cmin	0.31	1556.4	1584.1	1357.4	1064.4	1.8	-12.8	-31.6
2	Cavg	0.75	2123.4	2318.9	2621.4	2769.5	9.2	23.5	30.4
2	Cmax	0.75	2759.8	3047.6	3535.9	3933.3	10.4	28.1	42.5
2	Cmin	0.75	1448.3	1552.6	1671	1614	7.2	15.4	11.4

Note1: Geometric mean based on simulated exposure in 300 virtual adolescent and 300 adult patients with 10 replicates.
Adults (N=300, BSA median (range): 1.88 (1.30-3.00));
Adolescents >=12-<18 yrs & BSA>= 1.5 m^2 (N=226, BSA median (range): 1.73 (1.51-2.70));
Adolescents >=12-<18 yrs & 1.1<=BSA< 1.5 m^2 (N=67, BSA median (range): 1.40 (1.15-1.50));
Adolescents >=12-<18 yrs & BSA< 1.1 m^2 (N=7, BSA median (range): 1.08 (1.04-1.10));

Note2: Relative difference in geometric mean between entrectinib exposure in adolescents with BSA of at least 1.5m^2 compared to adults
Note3: Relative difference in geometric mean between entrectinib exposure in adolescents with BSA between 1.1 and 1.5m^2 compared to adults
Note4: Relative difference in geometric mean between entrectinib exposure in adolescents with BSA less than 1.1m^2 compared to adults
Source: Reviewer's Analysis based on "poppk.xpt"

Pediatrics < 12 years
For pediatric patients less than 12 years, there are insufficient data available to determine a dose with the to-be-marketed formulation that can achieve comparable exposure to adults at the recommended dose of 600 mg QD.

Exposure parameters (C_{max} and AUC_{last}) of entrectinib and M5 in the pediatric Study STARTRK-NG are summarized in **Table 19** by dose levels.

Table 19: Summary of Entrectinib and M5 Exposure Parameters after Single Dose and Repeat Doses with Entrectinib in Pediatric Patients (Study STARTRK-NG)

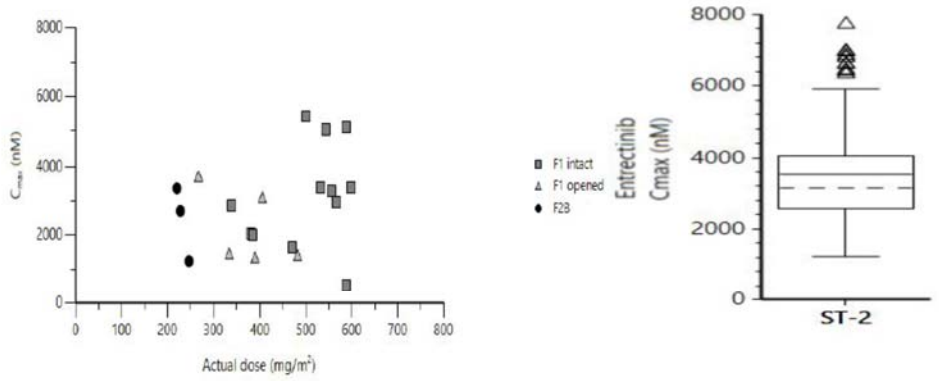
Study Day	Dose (formulation, number of patients)	Geometric mean (CV%) of C_{max} (nM)		Geometric mean (CV%) of AUC_{last} (nM*h)	
		Entrectinib	M5	Entrectinib	M5
Cycle 1 Day 1	400 mg/m^2 (F1, n=9)	1709 (34%)	755 (83%)	20192 (41%)	10435 (79%)
	550 mg/m^2 (F1, n=10)	3217 (57%)	950 (162%)	45455 (57%)	14810 (150%)

Study Day	Dose (formulation, number of patients)	Geometric mean (CV%) of C_{max} (nM)		Geometric mean (CV%) of AUC_{last} (nM*h)	
		Entrectinib	M5	Entrectinib	M5
	750 mg/m^2 (F1, n=3)	4188 (26%)	653 (16%)	54791 (14%)	10305 (1%)
Cycle 2 Day 1	400 mg/m^2 (F1, n=7)	2009 (41%)	748 (72%)	25774 (65%)	9690 (72%)
	550 mg/m^2 (F1, n=8)	2682 (87%)	1103 (83%)	63256 (20%)	24216 (86%)

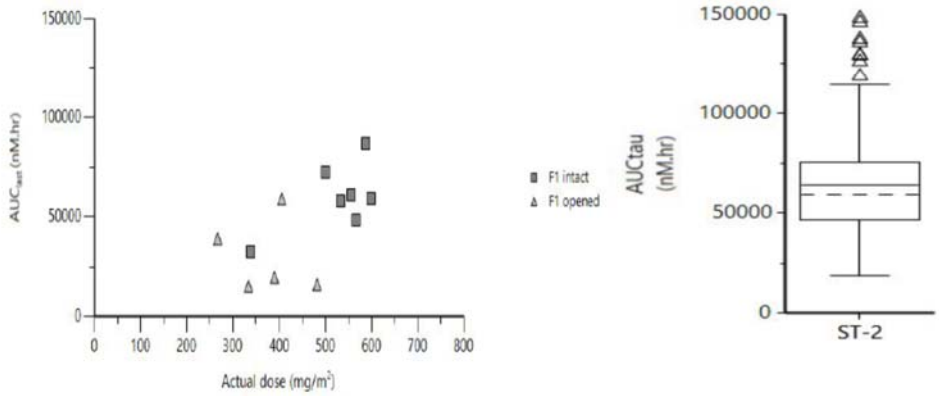
Source: Supplementary results report for Study STARTRK-NG, Table 5 and Table 6

When the observed exposure (C_{max} and AUC_{last}) of entrectinib from F1 formulation in pediatric patients are compared to those from the recommended adult dose of 600 mg with F2A formulation after repeat dosing, as shown in **Figure 20**, steady state C_{max} and AUC_{last} (during the 24 hour dosing interval) from the pediatric dose of 400 mg/m^2 are at the lower end of observed exposure in adults from 600 mg QD with F2A formulation. The steady state exposure from pediatric dose of 550 mg/m^2 with F1 formulation are generally higher than the median exposure observed in adults. In addition, large inter-subject variability of PK parameters is observed in pediatric patients.

Figure 20: Entrectinib Exposure Parameters after Repeat Dosing of 600mg QD Entrectinib to Pediatric Patients in Study STARTRK-NG (Left figures) and Adult Patients in Study STARTRK-2 (Right figures)



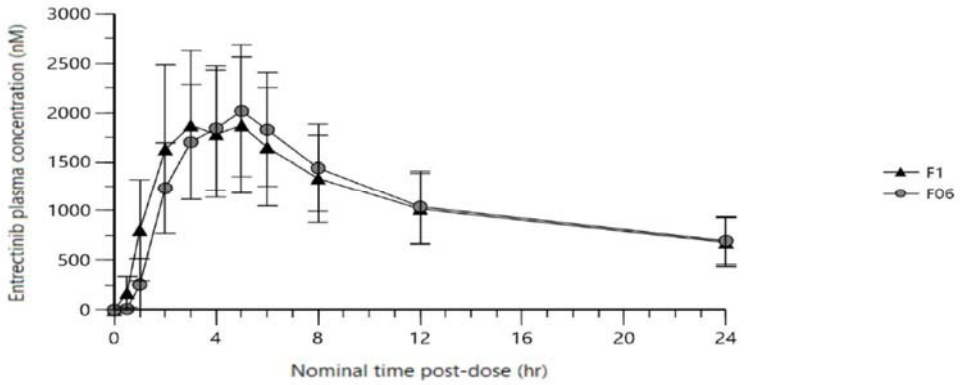
b) AUC_{tau}



Source: Applicant's response to MCC IR, Figure 2

Because there are no PK data available in pediatrics with the to-be-marketed formulation. F06, a PK bridging study was conducted to determine the relative bioavailability of entrectinib F1 and F06 capsule formulations under fed conditions in healthy adult subjects. As shown in **Figure 21**, entrectinib exposure from F1 capsules are comparable to that from F06 capsules following a single dose with a standard light meal (250 Kcal with 25% of those calories from fat) in adults, the GMR (90% CI) for C_{max} and AUC_{INF} were 0.93 (0.82, 1.06) and 0.98 (0.89, 1.08), respectively.

Figure 21: Mean Entrectinib Plasma Concentration vs. Time Profiles from F1 and F06 Capsule Formulations Administered with a Light Meal



Source: Preliminary research report for Study GP41048, Figure 2

Based on the observed PK data in pediatrics with F1 capsules and the relative bioavailability of 0.98 for F1 versus F06, it appears that doses between 400 mg/m^2 and 550 mg/m^2 will be needed in pediatric patients to achieve the adult exposure of entrectinib at 600 mg with F2A since F2A and F06 are bioequivalent.

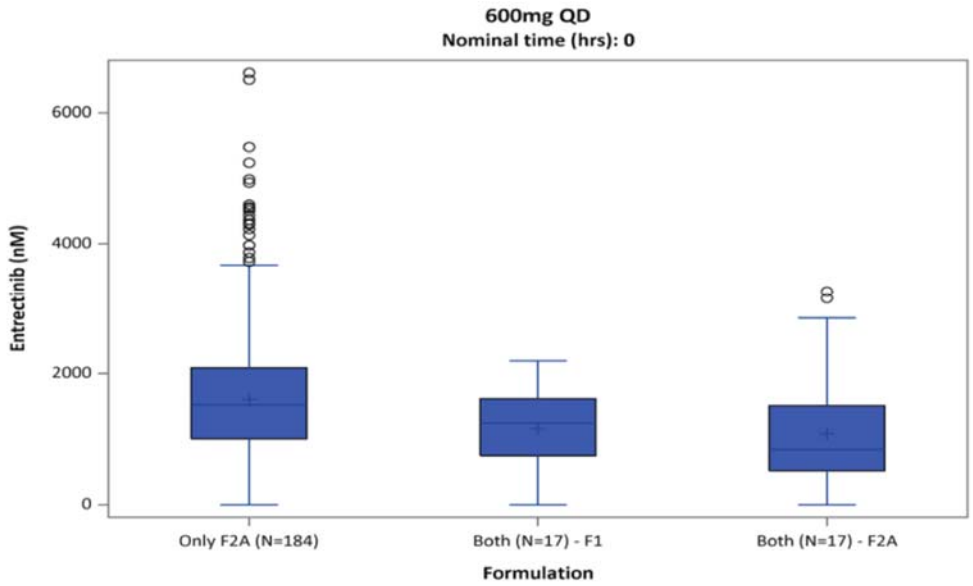
(b) (4)

[redacted]

Based on observed steady state exposure (AUC_{0-24}) of entrectinib, relative bioavailability of F1 versus F2A (bioequivalent to F06) was 91% in adult patients in Study STARTRK-1, similar to the relative bioavailability of 98% estimated in healthy adults in Study GP41048. In Study STARTRK-2, the trough concentrations (C_{trough}) of entrectinib were similar between patients who received F2A only and those patients who received F1 at the beginning of the study and then switched to F2A formulation (**Figure 22**). These data suggest that F1 formulation can achieve similar exposure of entrectinib as that from F2A in adults from clinical trials that had no strict control on meal consumption and concomitant medications (such as PPI). [redacted] (b) (4)

(b) (4)

Figure 22: Trough Concentrations Following 600 mg QD Entrectinib Administration with F1 Formulation and Following the Switch to F2A Formulation (N=17 patients) versus Patients Receiving F2A only (N=184) in Study STARTRK-2



Source: Applicant's response to IR-07, Figure 1

(b) (4)

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

Food-Drug Interaction

Entrectinib can be administered with or without food in the F06 formulation.

When a single dose 600 mg entrectinib in the F06 formulation was administered under fasting condition or with a high-fat, high-calorie meal, a median T_{max} of 4 and 5 hours was observed in the fasted and fed states, respectively. The geometric mean ratio (GMR) and 90% confidence interval (CI) bounds of entrectinib were all within the limit of 80% to 125% when entrectinib F06 was administered in a fasting state or with food as shown in **Table 20**. In addition, food has no effect on the exposure (C_{max} and AUC) of M5.

Table 20: Effect of Food on PK Exposure of Entrectinib in F06 Formulation

Test versus Reference	PK parameter	Geometric LSM		Geometric LSM Ratio (Treatment D/Treatment C) (%)		
		Treatment		Ratio	90% CI (lower)	90% CI (upper)
		C	D			
Treatment D (n=45) versus Treatment C (n=45)	C_{max} (nM)	2230	2370	106	98.9	115
	AUC_{last} (nM·h)	49600	57200	115	107	123
	AUC_{INF} (nM·h)	50300	57900	115	107	124

Treatment C: Entrectinib F06 600 mg, fasted; Treatment D: Entrectinib F06 600 mg, fed
Source: RXDX-101-15 CSR, Table 10

Drug-Drug Interactions (DDI)

Effects of Other Drugs on Entrectinib

Gastric Acid-reducing Agents (ARA)
Dose adjustment is not required for entrectinib in the F06 formulation when it is coadministered with an ARA.

Because entrectinib has pH-dependent solubility as shown in **Table 21**, acidulants such as betaine hydrochloride in the F2A formulation and tartaric acid in the F06 formulation were used in the formulation to overcome this issue.

Table 21: Solubility of Entrectinib in Aqueous Media

Aqueous Media or Buffer	pH of Medium	pH Value (Measured) 1 h/24 h	Solubility at 37°C, 1 h (mg/mL)	Solubility at 37°C, 24 h (mg/mL)
SGFsp	1.2	4.5/4.8	42.2	0.1[a]
Acetate buffer (50 mM)	4.5	4.5/4.5	0.2	0.2
Potassium phosphate buffer (50 mM)	6.8	6.8/6.8	0.0	0.0
Potassium phosphate buffer (50 mM)	8.0	8.0/8.0	0.0	0.0
Deionized water	7.9	7.7/8.4	0.0	0.0
FeSSIF	5.0	5.0/5.2	4.0	3.5
FaSSIF	6.5	6.5/6.5	0.1	0.1

Abbreviations: FaSSIF = fasted–state simulated intestinal fluid; FeSSIF = fed–state simulated intestinal fluid; SGFsp = simulated gastric fluid sine pepsin.

Source: Applicant's M3-2-S-2-3 Table S.1.3-2

When a single 600 mg entrectinib dose in the F06 formulation was coadministered with a PPI lansoprazole 30 mg (QD) under fasting condition, the entrectinib C_{max}, AUC_{last} and AUC_{INF} and were decreased by approximately 24%, 26%, and 26%, respectively, compared with entrectinib alone under fasting condition (**Table 22**). There was also a 17%, 17% and 16% decrease in M5 C_{max}, AUC_{last} and AUC_{INF} with the coadministration of lansoprazole.

Table 22: Effect of Proton-pump Inhibitor Lansoprazole on PK Exposure of Entrectinib in F06 Formulation

Test Versus Reference	PK parameter	Geometric LSM		Geometric LSM Ratio (Entrectinib + Lansoprazole / Entrectinib alone)		
		Entrectinib + Lansoprazole	Entrectinib Alone	Ratio	90% CI (Lower)	90% CI (Upper)
Entrectinib + Lansoprazole (n=19) vs. Entrectinib alone (n=19)	C_{max} (nM)	1770	2310	76.5	67.6	86.6
	AUC_{last} (nM·hr)	40400	54400	74.3	64.5	85.6
	AUC_{INF} (nM·hr)	41200	55300	74.5	64.7	85.9

Source: RXDX-101-09 CSR, Table 5

The effect of lansoprazole on exposure of entrectinib and M5 was negligible under fed condition. When a single 800 mg entrectinib dose in the F2A formulation was coadministered with lansoprazole 30 mg under fed condition, there was only 11% and 6% decrease of mean C_{max} for entrectinib and M5, respectively. There was a 16% and 3% increase in the mean AUC_{INF} of entrectinib and M5, respectively (see **Table 23**).

Table 23: Summary of Entrectinib and M5 PK Parameters under Fed Condition Following Single 800 mg Entrectinib Dose in F2A Formulation Without or With Coadministration of PPI Lansoprazole

Analyte	PK Parameters	Mean (CV%)	
		Without Lansoprazole	With Lansoprazole
Entrectinib	C_{max} (nM)	2530 (20%)	2270 (27%)
	AUC_{last} (nM*h)	79700 (30%)	90700 (31%)
	AUC_{INF} (nM*h)	82800 (31%)	95800 (32%)
M5	C_{max} (nM)	534 (30%)	502 (29%)
	AUC_{last} (nM*h)	23300 (38%)	24100 (16%)
	AUC_{INF} (nM*h)	28700 (40%)	29600 (18%)

Source: Study CA14707 CSR, Table 11-7 and Table 11-9

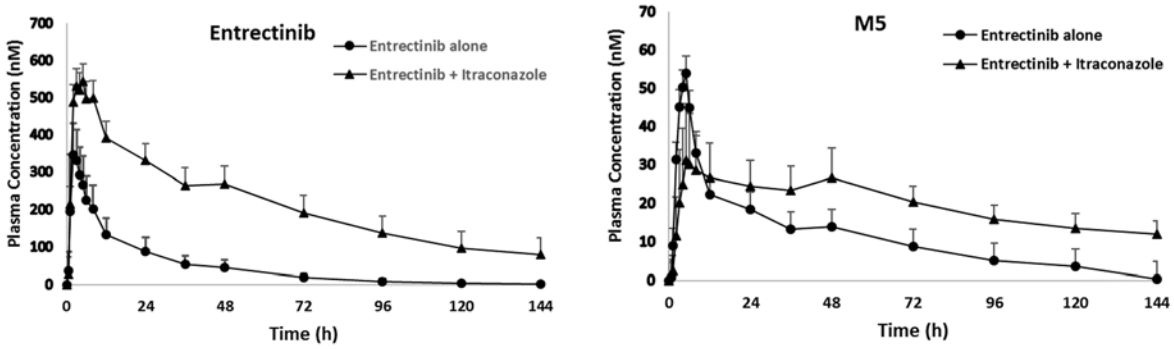
Overall, significant effect of PPI on exposure of entrectinib and M5 with F06 formulation is not expected under fed condition based on data with F2A formulation. Although there were 16% to 26% decreases of entrectinib and M5 exposure with the coadministration of lansoprazole in the F06 formulation under fed condition, the magnitude of exposure change is not considered clinically relevant based on exposure-response relationship described in sections above.

Strong and Moderate CYP3A Inhibitors

Dose reduction is recommended when entrectinib is coadministered with strong CYP3A inhibitors.

When a single dose of 100 mg entrectinib is coadministered with strong CYP3A inhibitor itraconazole, the GMR (90% CI) of C_{max}, AUC_{last} and AUC_{INF} of entrectinib were 1.73 (1.37, 2.18), 5.26 (4.01, 6.91) and 6.04 (4.54, 8.04), respectively. The AUC_{last} and AUC_{INF} of M5 were also increased by 86% and 152%, respectively, while there was a 38% decrease of Cmax for M5 (see **Figure 23**). The metabolite-to-parent ratio (M/P ratio) based on AUC_{INF} for M5 was reduced by coadministration of itraconazole from 0.288 to 0.124. These changes are consistent with simultaneous inhibition of both formation and clearance of M5.

Figure 23: Mean (+SD) Plasma Concentration Profiles of Entrectinib and M5 Following a Single Oral Dose of 600 mg Entrectinib Alone or With Itraconazole



Source: reviewer's analysis

Table 24: Predicted Entrectinib and M5 Exposure at Steady State Following 100 mg Daily Dose Without and With Itraconazole Coadministration

Analyte	PK Parameters	Geometric Mean (CV%)		Geometric Mean Ratio (90% CI)
		Without Itraconazole	With Itraconazole	
Entrectinib	C_{max} (nM)	473 (34%)	1950 (41%)	4.13 (3.90, 4.37)
	AUC_{SS} (nM*h)	7870 (42%)	40200 (46%)	5.10 (4.82, 5.41)
M5	C_{max} (nM)	178 (34%)	174 (39%)	0.98 (0.91, 1.06)
	AUC_{SS} (nM*h)	2150 (45%)	3910 (41%)	1.82 (1.67, 1.98)

Source: Applicant's response to IR-15, Table 2 and Table 3

Genentech also conducted PBPK simulation of drug-drug interaction (DDI) between entrectinib (100 mg QD) and itraconazole (200 mg QD) at steady state. As shown in **Table 24**, the increase of AUC at steady state for entrectinib and M5 are similar to that observed after a single dose, while the increase of C_{max} for entrectinib is more significant after multiple doses. Overall, the observed and predicted DDIs support the dose reduction from 600 mg QD to 100 mg QD when entrectinib is coadministered with strong CYP3A4 inhibitors.

Dose reduction from 600 mg to 200 mg is also recommended for entrectinib when it is coadministered with moderate CYP3A inhibitors. Based on PBPK simulation of DDI between entrectinib (200 mg QD) and erythromycin (500 mg TID) at steady state, as shown in **Table 25**, the steady state AUC for entrectinib and M5 is expected to be increased by 240% and 108%, respectively.

Table 25: Predicted Entrectinib and M5 Exposure at Steady State Following Entrectinib 200 mg Daily Dose Without and With Erythromycin Coadministration

Analyte	PK Parameters	Geometric Mean (CV%)		Geometric Mean Ratio (90% CI)
		Without Erythromycin	With Erythromycin	
Entrectinib	C_{max} (nM)	992 (37%)	2870 (43%)	2.89 (2.75, 3.04)
	AUC_{SS} (nM*h)	16200 (45%)	55000 (46%)	3.40 (3.21, 3.60)
M5	C_{max} (nM)	469 (34%)	568 (44%)	1.21 (1.15, 1.28)
	AUC_{SS} (nM*h)	5230 (45%)	10900 (50%)	2.08 (1.96, 2.21)

Source: Applicant's response to IR-15, Table 5 and Table 6

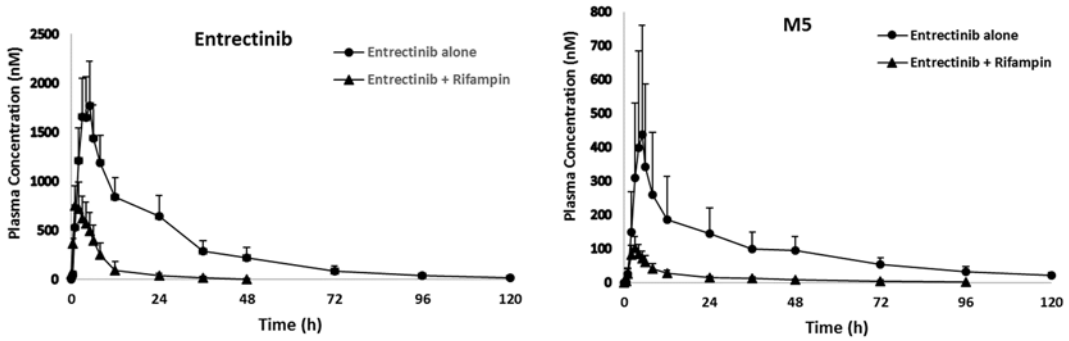
Strong and Moderate CYP3A4 Inducers

Coadministration of strong CYP3A inducers with entrectinib should be avoided.

When a single dose of 600 mg entrectinib was coadministered with multiple doses of rifampin (600 mg QD x 14 days), as shown in **Figure 24**, exposure of both entrectinib and M5 were significantly decreased. The GMRs (90% CI) were 0.44 (0.35, 0.56), 0.23 (0.18, 0.30) for C_{max} and

AUC_{INF} of entrectinib, respectively. The C_{max} and AUC_{INF} of M5 were also 75% and 87% lower with the coadministration of rifampin. Metabolite-to-parent AUC ratio was also reduced from 0.34 to 0.19 with coadministration of rifampin. These changes are consistent with the induction of entrectinib and M5 clearance.

Figure 24: Mean (+SD) Plasma Concentration Profiles of Entrectinib and M5 Following a Single Oral Dose of 600 mg Entrectinib Alone or With Rifampin



Source: reviewer's analysis

The effect of moderate CYP3A inducers on exposure of entrectinib and M5 has not been studied. Genentech conducted PBPK simulation of DDI between entrectinib (600 mg QD) and the moderate CYP3A inducer efavirenz (600 mg QD). At steady state, the C_{max} and AUC of entrectinib is predicted to be 43% and 56% lower with the coadministration of efavirenz, respectively (see **Table 26**). The steady state C_{max} and AUC of M5 is also predicted to be 28% and 47% lower with efavirenz. Based on these results, coadministration of moderate CYP3A inducers with entrectinib should also be avoided.

Table 26: Predicted Entrectinib and M5 Exposure at Steady State Following Entrectinib 600 mg Daily Dose Without and With Efavirenz Coadministration

Analyte	PK Parameters	Geometric Mean (CV%)		Geometric Mean Ratio (90% CI)
		Without Efavirenz	With Efavirenz	
Entrectinib	C_{max} (nM)	2670 (37%)	1530 (47%)	0.57 (0.55, 0.59)
	AUC_{SS} (nM*h)	44000 (44%)	19500 (46%)	0.44 (0.42, 0.47)
M5	C_{max} (nM)	1740 (33%)	1250 (28%)	0.72 (0.70, 0.74)
	AUC_{SS} (nM*h)	18800 (44%)	10000 (37%)	0.53 (0.51, 0.56)

Source: Applicant's response to IR-15, Table 8 and Table 9

Effects of Entrectinib on Other Drugs

CYP3A4 substrate midazolam

Coadministration of a single dose of entrectinib 600 mg with sensitive CYP3A4 substrate midazolam had no effect on the AUC_{INF} of midazolam (**Table 27**). However, C_{max} of midazolam was reduced by 34% than when midazolam was administered alone (**Table 27** and **Figure 25**).

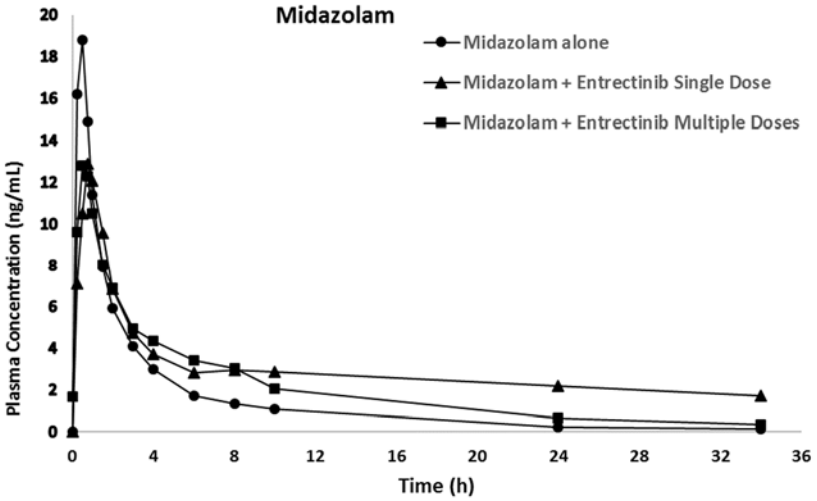
Table 27: Effect of Single or Multiple Doses of Entrectinib (600 mg QD) on the PK Parameters of Midazolam

	PK Parameters	Entrectinib Single Dose	Entrectinib Multiple Doses
Geometric Mean Ratio (90 %CI)	C_{max}	0.66 (0.56, 0.78)	0.79 (0.66, 0.94)
	AUC_{last}	1.21 (0.91, 1.62)	1.42 (1.05, 1.91)
	AUC_{INF}	1.00 (0.87, 1.16)	1.50 (1.29, 1.73)

Source: Study RXDX-101-14 CSR, Table 4 and Table 5

When midazolam was co-administered with 600 mg QD entrectinib dosed for 14 days, the C_{max} of midazolam was reduced by 21% but AUC_{INF} of midazolam was increased by 50% (**Table 27**).

Figure 25: Mean Midazolam Plasma Concentration-time Profiles Following a Single Oral Dose of Midazolam (2 mg) Administered Without or With Single (Day 8) or Multiple (Day 21) Doses of Entrectinib (600 mg QD)



Source: reviewer's analysis

Because entrectinib had no significant inhibition on midazolam metabolism after a single dose, and showed weak inhibition on midazolam metabolism after multiple doses, dose adjustment is not needed for sensitive CYP3A substrates when coadministered with entrectinib.

The results also suggest that there is no significant induction of CYP3A activity with multiple doses of entrectinib.

P-gp substrate digoxin

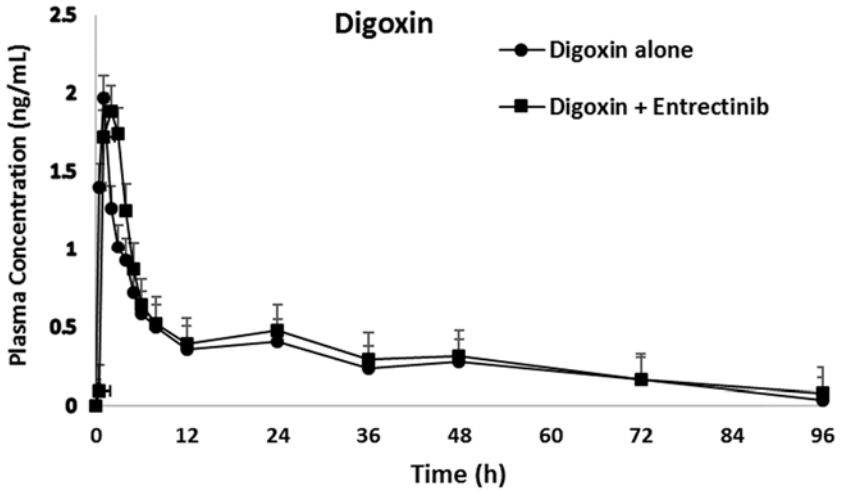
Co-administration of a single dose of entrectinib 600 mg one hour prior to the administration of P-gp substrate digoxin (0.5 mg) resulted in 28% increase in C_{max} of digoxin, the AUC_{INF} of digoxin was also 18% higher than when digoxin was administered alone (**Table 28** and **Figure 26**).

Table 28: Effect of Single Dose of Entrectinib (600 mg) on the PK Parameters of Digoxin

PK Parameters	Geometric Mean (CV%)		Gematric Mean Ratio (90 %CI)
	Without Entrectinib	With Entrectinib	
Cmax (ng/mL)	1.97 (30%)	2.52 (37%)	1.28 (0.98, 1.67)
AUClast (ng/ml*h)	26.8 (17%)	31.9 (21%)	1.19 (1.01, 1.40)
AUCINF (ng/mL*h)	34.2 (14%)	40.4 (17%)	1.18 (1.06, 1.32)

Source: Study RXDX-101-13 CSR, Table 6, Table 16.1 and Table 16.2

Figure 26: Mean (+SD) Plasma Concentration Profiles of Digoxin Following a Single Oral Dose of 2 mg Digoxin Alone or With a Single Dose of Entrectinib 600 mg



Source: reviewer's analysis

The above results indicated that entrectinib has weak inhibition on P-gp. Dose adjustment for P-gp substrate when coadministered with P-gp inhibitor is not needed.

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 29 lists the clinical trials included in the NDA submission. The primary evidence establishing the efficacy of entrectinib in patients with solid tumors harboring an *NTRK* gene fusion is supported by four single-arm trials: ALKA-372-001, RXDX-101-01, RXDX-101-02, and RXDX-101-03 (also referred to as “ALKA”, “STARTRK-1”, “STARTRK-2”, and “STARTRK-NG”, respectively). The integrated safety analysis pooled data obtained across these 4 clinical trials, but efficacy data from STARTRK-NG was not included in the original NDA.

As agreed upon during the pre-NDA meeting with Genentech, seven adult patients with *NTRK*-fusion solid tumors were not included in the efficacy population because they either had primary CNS tumors (n=6), for which Response Assessment in Neuro-oncology (RANO) criteria were used for the radiologic assessment of response, or had non-measurable disease (n=1).

Table 29: Clinical Studies Supporting Safety and Efficacy of Entrectinib in patients with *NTRK*-fusion solid tumors

Study No.	Study Design and Objectives	Doses (Oral)	Safety population	Efficacy Population *NTRK**
ALKA-372-001 Non-US	First-in-human, dose escalation study 3+3 design in adult patients with advanced/metastatic solid tumors *NTRK1/2/3*, *ROS1*, or *ALK* Objectives: DLTs, MTD	100–1600 mg/day	57	1
RXDX-101-01 (STARTRK-1)	Dose escalation study 3+3 design in adult patients with advanced/metastatic solid tumors *NTRK1/2/3*, *ROS1*, or *ALK* Objectives: DLT, MTD, RP2D, ORR	100-800 mg/day	76	3 (*Primary CNS=1*)
RXDX-101-02 (STARTRK-2)	Open label, basket study with advanced/metastatic solid tumors *NTRK1/2/3*, *ROS1*, or *ALK* excluding ALK+NSCLC Objectives: ORR by BICR	600 mg daily	206	57 (*Primary CNS=5; Non-measurable=1*)
RXDX-101-03 (STARTRK-NG)	Open label, dose escalation/expansion study Age 2-22 recurrent or refractory solid tumors and primary brain tumors, including *NTRK1/2/3*, *ROS1*, and *ALK* tumors Objectives: DLT, MTD, RP2D, ORR by BICR	Dosing nomogram based on BSA, ranging from 250 mg/m^2 to 750 mg/m^2	16	0
		Total	**355**	**54 *NTRK***

Key: DLT-dose limiting toxicity; MTD-maximum tolerated dose; ORR-overall response rate
**Included in the brackets are patients excluded from primary efficacy population*

Additional data was submitted from 8 patients (5 adult, 3 pediatric patients) treated with entrectinib under a single-case compassionate use program (Table 30) and from 14 adult patients from Study RXDX-101-14, which evaluated the potential PK interaction between entrectinib and midazolam in patients with advanced solid tumors. These supportive patient data were not integrated with the overall safety population because of their different purpose and limited sample size they would contribute to the analysis. Safety data for healthy subjects from 10 dedicated clinical pharmacology studies were not integrated with the overall safety population due to different population, study design, and limited exposure to entrectinib treatment.

Table 30: Single Case Compassionate Use Program Providing Supportive Safety Information

Patient ID/Country	Age (yrs)	Sex	Tumor Type	Gene Fusion	Treatment Start/End date	Status
Adults Patients						
(b) (6) Canada	65	male	MASC of the salivary gland	ETV6-NTRK1	Started treatment with entrectinib in (b) (6)	Ongoing
(b) (6) Israel	68	female	advanced NSCLC	TPM3-NTRK1*	Started treatment with entrectinib in (b) (6) Discontinued entrectinib in (b) (6)	Discontinued
(b) (6) US	43	female	MASC	ETV6-NTRK3	Started treatment with entrectinib in combination with trametinib in (b) (6) permanently discontinued both entrectinib and trametinib in (b) (6). Died in (b) (6)	Discontinued
(b) (6) US	48	male	advanced NSCLC	SQSTM1-NTRK1	Started treatment with entrectinib in combination with trametinib in (b) (6) Discontinued both entrectinib and trametinib in (b) (6). Died in (b) (6)	Discontinued
(b) (6) US	48	male	MASC of the parotid gland	ETV6-NTRK3	Started treatment with entrectinib in combination with trametinib in (b) (6) Discontinued both entrectinib and trametinib in (b) (6)	Discontinued
Pediatric Patients						
(b) (6) Sweden	2	male	metastatic neuroblastoma	ALK mutation (unspecified)	Started treatment with entrectinib in (b) (6)	Ongoing
(b) (6) US	6	male	high grade astrocytoma	BEND4-NTRK2	Started treatment with entrectinib in	Ongoing
(b) (6) US	1.5	male	infantile fibrosarcoma metastatic tumor	ETV6-NTRK3	Started treatment with entrectinib in Discontinued and died in (b) (6)	Discontinued

ALK = anaplastic lymphoma kinase; MASC = mammary analogue secretory carcinoma; NSCLC = non-small cell lung cancer; NTRK1/2/3 = neurotrophic tyrosine receptor kinase 1/2/3.

- A repeat test in July 2017 did not show NTRK1 gene fusion.

Source: Copied from Summary of Clinical Safety, Module 2.7.4

<u>Clinical Reviewer Comment</u>: The data from the 8 compassionate use protocols were not integrated in the NDA integrated summary of safety (ISS), however each study report was reviewed and the information in these reports did not significantly alter the overall safety conclusions.

There were ten clinical pharmacology studies conducted which enrolled a total of 323 patients, and data from these studies were also submitted to support the safety of entrectinib. Table 31 lists the clinical pharmacology studies submitted to the NDA which provided supportive safety information.

Table 31: Clinical Pharmacology Studies in Healthy Patients that contributed to the Safety Review

Study No.	Objective [a]	Study Design, Control Type	Population n (No. of Patients treated)	Dose, Route, Regimen, and Formulation
CA14707 (US)	Assessment of effect of food, formulation (F1, F2, F2A, F2B), and concomitant lansoprazole on the PK and relative bioavailability of single-dose entrectinib.	Phase I, open-label, randomized, 3-part, 2-sequence, 4-treatment, 3-period study	Healthy adult male and female (of non-childbearing potential) n = 72	Single oral dose fed or fasted, w/ or w/o PPI; (30 mg lansoprazole QD × 8d or 9d) Part 1: Entrectinib 800 mg F1/F2 formulations Part 2: Entrectinib 800 mg F2A Part 3: Entrectinib 800 mg F2B
RXDX-101-04 (US)	To evaluate dose proportionality and compare the relative bioavailability of entrectinib in healthy Japanese and Caucasian subjects after administration of single doses of 400 mg and 600 mg under fasting conditions and 600 mg under fed conditions and to assess the effect of food on the bioavailability of a single dose of entrectinib.	Phase I, open-label	Healthy adult male Japanese and Caucasian n = 24	Single oral dose of 400 mg F2A and 600 mg F2A entrectinib (fed/fasted)

Study No.	Objective [a]	Study Design, Control Type	Population n (No. of Patients treated)	Dose, Route, Regimen, and Formulation
RXDX-101-05 (US)	To investigate the route(s) of elimination and mass balance of entrectinib after oral administration of a single 600 mg (~200 μCi) dose of [^{14}C]-entrectinib. To quantitate the total radioactivity concentration equivalents in plasma, whole blood, urine, and feces and entrectinib concentrations in plasma and urine after oral administration of a single 600 mg (~200 μCi) dose of [^{14}C]-entrectinib. To examine the metabolic profile of entrectinib in humans and to identify major metabolites in biological specimens. To determine the percentage of [14C]-radioactivity associated with cellular components in whole blood over time.	Phase I, open-label, 1 period	Healthy adult male n = 7	Single oral dose of 600 mg [^{14}C]-entrectinib (~200 μCi) as PiC (fasted) plus 246 mg betaine-HCl

Study No.	Objective [a]	Study Design, Control Type	Population n (No. of Patients treated)	Dose, Route, Regimen, and Formulation
RXDX-101-06 (US)	To assess the relative bioavailability of a single oral dose of entrectinib F400 granules vs. entrectinib F1 capsules under fed conditions Secondary: To assess the relative bioavailability of a single oral dose of entrectinib F400 granules when administered with yogurt or directly to mouth under fasting or fed conditions.	Phase I, open-label, 2-cohort, 4-period, 4-treatment	Healthy adult male n = 16	Treatment A: single oral dose of 400 mg entrectinib (F400 granules) in yogurt (fed) Treatment B: single oral dose of 600 mg entrectinib (F400 granules) in yogurt (fed) Treatment C (reference): single oral dose of 600 mg entrectinib (3 x 200 mg F1 capsules) (fed) Treatment D: single oral dose of 600 mg entrectinib F400 granules in yogurt (fasted) Treatment E: single oral dose of 400 mg entrectinib (F400 granules) directly to mouth (fed) Treatment F: single oral dose of 600 mg entrectinib F400 granules directly to mouth (fasted)
RXDX-101-07 (US)	To assess the relative bioavailability of a single oral dose of entrectinib formulations (F05, F06, or F07 versus F2A) under fasting conditions Exploratory: To assess effect of food on a single oral dose of entrectinib (F05, F06, F07, F2A).	Phase I, open-label, comparative, randomized, 4-sequence, 5-period	Healthy adult male n = 48	Single oral dose of 600 mg entrectinib (fasted/fed) using the formulations (F05, F06, F07, F2A)

Study No.	Objective [a]	Study Design, Control Type	Population n (No. of Patients treated)	Dose, Route, Regimen, and Formulation
RXDX-101-08 (US)	To assess the relative bioavailability of a single oral dose of entrectinib F06 Lot A versus F06 Lot B under fasting conditions.	Phase I, open-label, randomized, 2-period, 2-way crossover	Healthy adult male n = 24	Single oral dose of 600 mg entrectinib F06 Lot A (manufactured at registration scale) and F06 Lot B (manufactured at 1/6th of registration scale) (fasted)
RXDX-101-09 (US)	To assess the relative bioavailability of a single dose of entrectinib F06 formulation under fasting conditions, when administered with or without multiple daily doses of lansoprazole.	Phase I, open-label, randomized, , 2-period, 2-way crossover	Healthy adult male n = 19[b]	Single oral dose of 600 mg entrectinib (fasted) F06 formulation with or without 30 mg of lansoprazole delayed-release QD × 9d administered concomitantly.
RXDX-101-12 (US)	To assess the effects of itraconazole as a strong CYP3A4 inhibitor and rifampin as a strong CYP3A4 inducer on the PK of entrectinib.	Phase I, open-label, non-randomized, fixed-sequence, 2-cohort	Healthy adult male n = 20	Cohort 1 Period 1: Single oral dose of 100 mg entrectinib F06 (fasted) Cohort 1 Period 2: Single oral dose of 100 mg entrectinib F06 (fasted) plus itraconazole 200 mg oral QD × 10d Cohort 2 Period 1: Single oral dose of 600 mg entrectinib F06 (fasted) Cohort 2 Period 2: Single oral dose of 600 mg entrectinib F06 (fasted) plus rifampin 600 mg oral QD × 16d F06 formulation fasted

Study No.	Objective [a]	Study Design, Control Type	Population n (No. of Patients treated)	Dose, Route, Regimen, and Formulation
RXDX-101-13 (US)	To evaluate the effect of entrectinib on the single-dose PK of digoxin.	Phase I, open-label, non-randomized, fixed-sequence	Healthy adult male n = 10	Single oral dose of 0.5 mg digoxin with or without single oral dose of 600 mg entrectinib F2A (fasted, 1 hour before digoxin)
RXDX-101-15 (US)	To assess the relative bioavailability of a single oral dose of entrectinib F06 versus entrectinib F2A under fasting conditions. To assess the effect of a high-fat meal on the PK of a single oral dose of entrectinib F06.	Phase I, open-label, randomized, 2-part, 2-period	Healthy adult male n = 83	Part 1: Single oral dose of 600 mg entrectinib (fasted) F06 and F2A in separate periods, respectively. Part 2: Single oral dose of 600 mg entrectinib F06 (fasting) and F06 (fed) in separate periods, respectively.

BID = twice a day; BSA = body surface area; DLT = dose-limiting toxicity; PiC = powder in capsule; MTD = maximum tolerated dose; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily; RP2D = recommended Phase II dose; US = United States. Note: F1, F2, F05, F06, F07, F2A, F2B refer to specific formulations used in clinical development program, respectively.
a Evaluation of safety and tolerability of entrectinib under the respective conditions were secondary objectives of clinical pharmacology studies.
b One subject received lansoprazole, but not entrectinib, i.e. 19 subjects received entrectinib and 20 subjects received lansoprazole.

7.2. Review Strategy

The FDA statistical and clinical review teams conducted a joint review of the efficacy of entrectinib, and the safety of entrectinib was primarily reviewed by the clinical review team.

The safety and efficacy of entrectinib are primarily supported by data from the following four single-arm clinical trials:

- ALKA-372-001, entitled "A Phase 1, Dose Escalation Study of Entrectinib (RXDX-101) In Adult Patients With Advanced/ Metastatic Solid Tumors" (Study GO40783, or "ALKA"),
- RXDX-101-01, entitled "A Phase 1, Multicenter, Open-label Study of Oral Entrectinib (RXDX-101) in Adult Patients with Locally Advanced or Metastatic Cancer Confirmed to be Positive for *NTRK1*, *NTRK2*, *NTRK3*, *ROS1*, or *ALK* Molecular Alterations" (STARTRK-1),
- RXDX-101-02, entitled "An Open-Label, Multicenter, Global Phase II Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements." (Study GO40782, "STARTRK-2"), and
- RXDX-101-03, entitled "A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, with or without TRK, ROS1, or ALK Fusions" (Study CO40778, "STARTRK-NG").

As agreed upon during the October 17, 2018 pre-NDA meeting, the NDA submission contained efficacy results based on data from the first consecutive 54 patients with *NTRK*-fusion solid tumors who were enrolled on the three adult trials. The statistical and clinical review of efficacy focused on the pooled data from the three trials including the clinical study reports (CSR), case report forms (CRF), and statistical analysis plan (SAP); independent analyses using submitted datasets were also conducted. The 75-day safety and efficacy update included 5 pediatric patients with data from duration on drug of at least 6 months.

The clinical review of safety primarily evaluated the safety population in Studies ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG, defined as patients who received at least one dose of study drug, and consisted of 355 patients (58 patients in ALKA, 76 patients in STARTRK-1, 207 patients in STARTRK-2, and 16 patients in STARTRK-NG; although a total of 357 patients were enrolled, 2 patients did not receive entrectenib and were excluded). The review of safety included consideration of the submitted clinical study report, SDTM and analysis datasets, line-listings, CRFs, and case narratives from all 4 trials. The review of safety also included evaluation of single patient protocols (Table 30) for 8 additional patients as well as a brief evaluation of 10 clinical pharmacology trials (Table 31) which enrolled 323 patients.

The statistical and clinical review of safety and efficacy included the following:

- Review of the current literature on *NTRK* fusion protein

- Review of ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG, including CSR, protocol, protocol amendments, SAP, and SAP amendments.
- Review and assessment of Genentech's analyses of entrectinib safety and efficacy in the clinical study reports
- Review of datasets submitted as SDTM, analysis, and SAS transport files
- Review of patient narratives of SAEs and deaths
- Review of minutes of key meetings conducted during entrectinib development for solid tumors
- Review and assessment of the Module 2 summaries including the Summary of Clinical Efficacy, and Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, and proposed labeling modifications for entrectinib
- Review of consultation reports of Office of Scientific Investigations
- Requests for additional information from Genentech and review of their responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

Data Sources

The electronic submission including Protocols, SAPs, CSRs, SAS transport datasets in legacy, SDTM, and ADAM format, and SAS codes for the NDA submission are located in the following network paths:

- Original submission: SDN 1 Application 212726 - Sequence 0001 - 0001 (1) 12/18/2018 ORIG-1 /Multiple Categories/Subcategories

Data and Analysis Quality

Upon further clarifications from Genentech per FDA's information requests (IRs), the reviewer was able to:

- Reproduce Genentech's analysis dataset and analysis results from legacy dataset
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy analyses.

Datasets

There were 3 analysis sets from all 4 supportive studies: ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG. All safety analyses were performed using the integrated safety population, defined as all patients enrolled up to November 30, 2017 who received at least one dose of entrectinib, with data collected up to the clinical data cutoff date of May 31, 2018 in studies ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG. Pooling of safety data was planned as all four studies had similar design, treatment regimens, approach to collection of safety data, and patient population (except for Study STARTRK-NG which enrolled pediatric patients).

The integrated safety population consists of 355 patients, including 338 adult patients with solid tumors and 17 pediatric patients. The analysis sets are described below and in Figure 27:

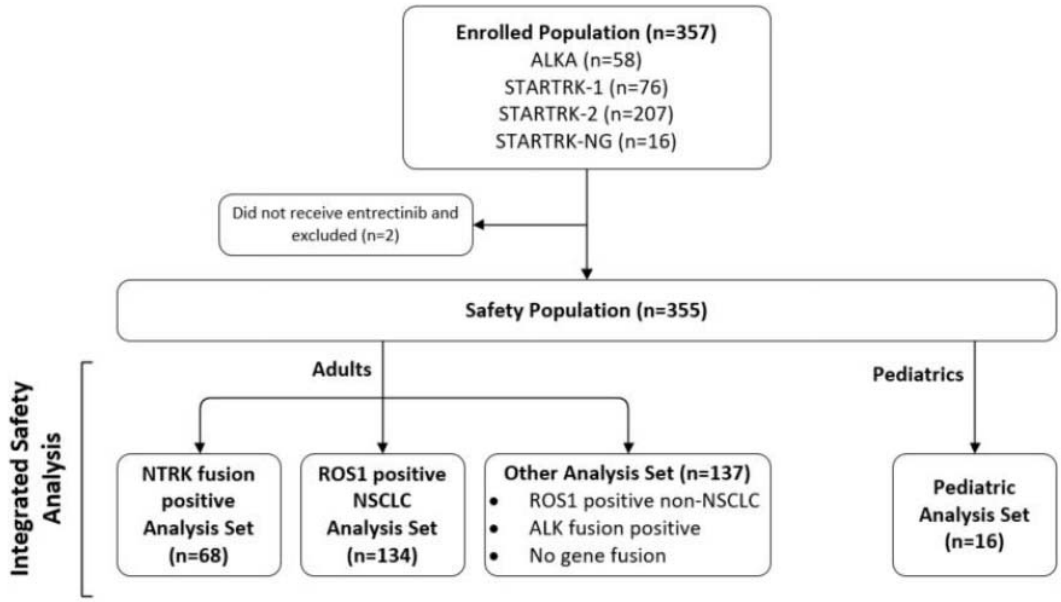
Adult analysis datasets:

- ***NTRK* fusion-positive analysis set (n = 68):** Patients from the ALKA, STARTRK-1, and STARTRK-2 studies in the safety population who have *NTRK* fusion-positive solid tumors
- ***ROS1*-positive NSCLC analysis set (n = 133):** Patients from the ALKA, STARTRK-1, and STARTRK-2 studies in the safety population who have *ROS1*-positive NSCLC
- **Other analysis set (n = 137):** Patients from the ALKA, STARTRK-1, and STARTRK-2 studies in the safety population with either *ROS1*-positive non-NSCLC, *ALK* fusion-positive tumors, or no gene fusion identified

Pediatric analysis dataset:

- **Pediatric analysis set (n = 17):** Includes 15 pediatic patients from STARTRK-NG and 2 pediatric patients from STARTRK-2.
- **75-day safety (n = 26):** safety population [total, inclusive of the pediatric analysis set at original submission] who have either *NTRK* fusion-positive solid tumor or no gene fusion identified)

Figure 27: Patient Population and Analysis Sets for Integrated Safety Analysis*



ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; NTRK = Neurotrophic tyrosine receptor kinase; ROS1 = ROS proto-oncogene 1 receptor tyrosine kinase.

Copied from Summary of Clinical Safety, Module 2.7.4

**Clinical Reviewer Comment: This figure incorrectly indicates that there were 16 patients in the pediatric analysis set. The original safety dataset included in the NDA reflected data from 17 patients less than 18 years of age, including 15 pediatric patients from STARTRK-NG and 2 pediatric patients from STARKTRK-2; therefore, FDA determined that the pediatric analysis set*

comprises 17 patients. It also states that there were 134 patients within the ROS1 positive NSCLC bucket, which is incorrect and is n=133.

Clinical Reviewer Comment: FDA agreed to the composition of the primary efficacy analysis population, consisting of the first 54 consecutive patients with NTRK-fusion solid tumors enrolled across Study ALKA, STARTRK-1, and STARTRK-2 based on Genentech's pre-specified statistical plan that based this sample size on the lower limit of the 95% Confidence Interval (CI) for ORR and power calculations, and use of consecutive enrollment to minimize selection bias.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy of entrectinib for the treatment of patients with *NTRK*-fusion solid tumors was evaluated in a pooled subgroup of adult patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled in Study ALKA, STARTRK-1 (NCT02097810) and STARTRK-2. Efficacy was assessed in the first 54 adult patients with solid tumors with an *NTRK* gene fusion enrolled into these trials. To be included in this pooled subgroup, patients were required to have progressed following systemic therapy for their disease, if available, or would have required surgery causing significant morbidity for locally advanced disease; measurable disease per RECIST v1.1; and at least 6 months of follow-up after the first dose of entrectinib; and no prior therapy with a TRK inhibitor. Patients received entrectinib 600 mg orally once daily until unacceptable toxicity or disease progression. Identification of positive *NTRK* gene fusion status was prospectively determined in local laboratories or a central laboratory using various nucleic acid-based tests. The major efficacy outcome measures were ORR and DOR, as determined by a BICR according to RECIST v1.1. Intracranial response according to RECIST v1.1 as evaluated by BICR. Tumor assessments with imaging were performed every 8 weeks.

Table 29 contains a brief description of each of these studies. For detailed descriptions of each study, including trial design, protocol amendments, data quality and integrity, compliance with Good Clinical Practice (GCP), and financial disclosure specific to the study, see Appendix, Section 19.6 (Description of Relevant Individual Trials Supporting the NDA).

8.1.1. Statistical Analysis Plan for Integrated Summary of Efficacy (ISE)

The efficacy endpoints for the integrated analysis of effectiveness are provided in Statistical Analysis Plan (SAP) version-5 and are summarized below:

Primary Endpoints:
Overall response rate (ORR) and duration of response (DOR) as assessed by blinded independent central review (BICR) using RECIST v1.1.

Secondary Endpoints:

- Clinical benefit rate (CBR) as assessed by BICR using RECIST v1.1
- Progression-free survival (PFS) as assessed by BICR and
- Overall survival (OS)
- Time to CNS progression as assessed by BICR using RECIST 1.1
- In patients with CNS disease at baseline, the following were assessed
    - Overall (systemic) ORR as assessed by BICR using RECIST v1.1

- Intracranial ORR (IC-ORR) as assessed by BICR using RECIST v1.1 in patients presenting with measurable CNS lesions at baseline, as well as patients with measurable and non-measurable CNS lesions at baseline
- Intracranial DOR (IC-DOR) as assessed by BICR and intracranial PFS (ICPFS) as assessed by BICR

Patient-Reported Outcome Endpoints (only for Study STARTRK-2):
Patient-reported outcomes (PROs) were evaluated in Study STARTRK-2 only, and therefore were not considered as part of the integrated efficacy analysis. Patients assessed health-related quality of life (HRQoL) using self-administered validated questionnaires: the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30) and Euro-QoL Group EQ-5D. In addition, patients with NSCLC completed the QLQ-CL13 and patients with metastatic colorectal cancer (mCRC) completed QLQ-CR29.

PRO assessments were performed prior to the first dose of entrectinib on Cycle 1 Day 1, pre-dose on Day 1 of each subsequent treatment cycle, and at the End of Treatment (Refer to Figure 62: Schedule of Assessments for Study STARTRK-2)

QLQ-C30 was developed to assess the quality of life of cancer patients and this questionnaire comprises 30 questions assessing global QOL, functioning, and symptoms of both multi-item and single-item measures. The Lung Cancer Module, QLQ-LC13, consists of 13 questions and the Colorectal cancer module, QLQ-CR29, comprises 29 questions. Euro-QoL Group EQ-5D is a generic, non-cancer specific tool to assess general health status consisting of a descriptive system used to calculate a health utility index score and a visual analog scale (EQ-5D VAS).

Endpoints definition:
ORR: Proportion of patients with confirmed complete response (CR) or partial response (PR) based on RECIST v1.1. The initial documented response was confirmed by repeat imaging obtained a minimum of 4 weeks after initial radiologic documentation or response.

DOR: Time since the start date of first objective response of PR or CR (whichever response was recorded first), and subsequently confirmed, to the date of disease progression or death due to any cause, whichever occurred earlier. For patients without disease progression or death DOR will be censored at the last tumor assessment date.

CBR: Proportion of patients with confirmed CR, PR or stable disease (≥ 6 months since the first dose of entrectinib) based on RECIST v1.1.

PFS: Time from first dose of entrectinib to first documentation of radiographic disease progression per RECIST 1.1 or death due to any cause. PFS data for patients without progression or death were censored on the date of the last tumor assessment. If no tumor assessment was performed after the baseline visit, then PFS was censored at the date of first dose of entrectinib.

OS: Time from the first dose of entrectinib to the date of death due to any cause. Patients who were alive at the time of the analysis, lost to follow-up, or withdraw consent for further follow-up were censored on the last known date that they were alive.

Time to CNS progression: Time from first dose of entrectinib to first documentation of radiographic CNS disease progression or death due to any cause. Radiographic CNS disease progression is defined as an occurrence of a new CNS lesion or progression in any CNS lesion per RECIST1.1 criteria.

IC-ORR: patients with confirmed CR or confirmed PR in only the CNS lesions (target, nontarget, or both, as determined by BICR for each patient) were defined as intracranial responders. IC-ORR is defined as the proportion of intracranial responders. This analysis was performed for patients presenting with measurable CNS lesions at baseline, as well as for patients with only non-measurable CNS lesions at baseline.

IC-DOR: IC-DOR was calculated only for intracranial responders and was measured from the date of first intracranial response to first documentation of radiographic CNS disease progression or date of death due to any cause, whichever occurred earlier. For patients without CNS disease progression and who had not died within 30 days of the last dose of study treatment, IC-DOR was censored at the last tumor assessment date prior to any date of subsequent anticancer therapy, including surgery or radiotherapy to the brain.

Of note, the definition of efficacy endpoints for this integrated analysis was standardized across studies. However, differences in patient-level endpoint results may be observed between the integrated analysis and the individual study analyses results.

Sample Size:
Assuming the true ORR by BICR (ORR-BICR) is 60%, a sample size of 56 patients was estimated to yield a 95% 2-sided CI that excludes a lower limit of 30%. Table 32 provides a summary of the planned per-protocol sample sizes and planned sample size of *NTRK* fusion-positive patients for each of the 3 studies (ALKA, STARTRX-1, and STARTRK-2) that enrolled patients included in the pooled efficacy analysis.

Table 32: Planned Sample Sizes of *NTRK* Fusion-Positive Patients by Study for Efficacy Analyses (per individual study protocols)

Study	Planned Overall Sample Size	Planned Sample Size for *NTRK* Fusion-Positive Patients
ALKA	70	Not Specified
STARTRK-1	15 (dose escalation) 50 (dose expansion)	Not Specified
STARTRK-2	Up to 62 per gene fusion by tumor type basket	Up to 62 per tumor type (e.g., *NTRK* Sarcoma)

Source: Table-2 of Integrated Statistical Analysis Plan, CSR Appendix 1.

Efficacy Analysis Population:
The efficacy analyses were performed using the *NTRK* efficacy-evaluable population, defined as TRK inhibitor-naïve patients with extracranial *NTRK* fusion-positive solid tumors who received at least 1 dose of entrectinib and had measurable disease at baseline as determined per RECIST v1.1 by investigator. The efficacy-evaluable analysis set includes 2 additional subgroup analysis sets based on the presence or absence of CNS disease (no CNS disease and CNS disease analysis sets).

Efficacy Analyses:
ORR, CBR, IC-ORR: Point estimates of the proportion of patients with confirmed CR or PR in the *NTRK* efficacy-evaluable population and the corresponding 2-sided 95% Clopper-Pearson exact CI.

DOR, PFS, OS and IC-DOR: estimated median and the corresponding 2-sided 95% CIs, calculated using the method of Brookmeyer and Crowley. For DOR, the proportion of responders with observed duration of responses ≥ 6 mons, ≥ 12 mons, and ≥ 18 mons were presented. A swimmer's plot were presented to depict each patient's best tumor response and time on study, respectively, including time to first objective response by BICR (if applicable) and DOR

Clinical Reviewer Comment: During the initial breakthrough therapy meeting and the pre-NDA meeting, FDA requested that Genentech (formerly Ignyta) provide a justification for the proposed size of the efficacy population (N=54) supporting this application. FDA concluded that the rarity of solid tumors harboring the activating NTRK rearrangements precluded the conduct of randomized controlled trials and that the size of the efficacy population was adequate to characterize the overall response rate in patients with NTRK-positive solid tumors. Genentech will conduct studies to fulfill postmarketing requirements to verify and further characterize the clinical benefit of entrectinib in patients with NTRK fusion solid tumors.

PRO Analyses:
Statistical Reviewer's comments:

1. *There were very few patients who completed the QLQ-LC13 and QLQ-CR29; therefore, in this review the statistical reviewer has presented the results for only QLQ-C30.*
2. *Note that in a single arm trial, the PRO results are not interpretable. Only a descriptive analysis of PRO outcomes was conducted and all the PRO analysis results were considered exploratory.*
3. *The study protocol further defined the improvement or worsening of global QOL functioning domains, and symptom domains based on 10-point change. There was no agreement between FDA and the applicant on the clinically meaningful threshold (change of >=10-point) for the subscale scores and hence the corresponding analysis is not included in this review.*

Each domain and item in the QLQ-C30 were linear-transformed to standardize the raw score to a range from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/HRQoL represents a high HRQoL; however, a high score for a symptom scale/item represents a high level of severity/problems.

For the PRO-evaluable population, the number of patients expected to complete each questionnaire at each pre-specified time point and the corresponding completion rate (proportion of patients who completed the questionnaire) were presented in a tabular format, and the average score and mean change from baseline for each item in QLQ-C30 were presented graphically.

8.1.2. Pooled Study Results

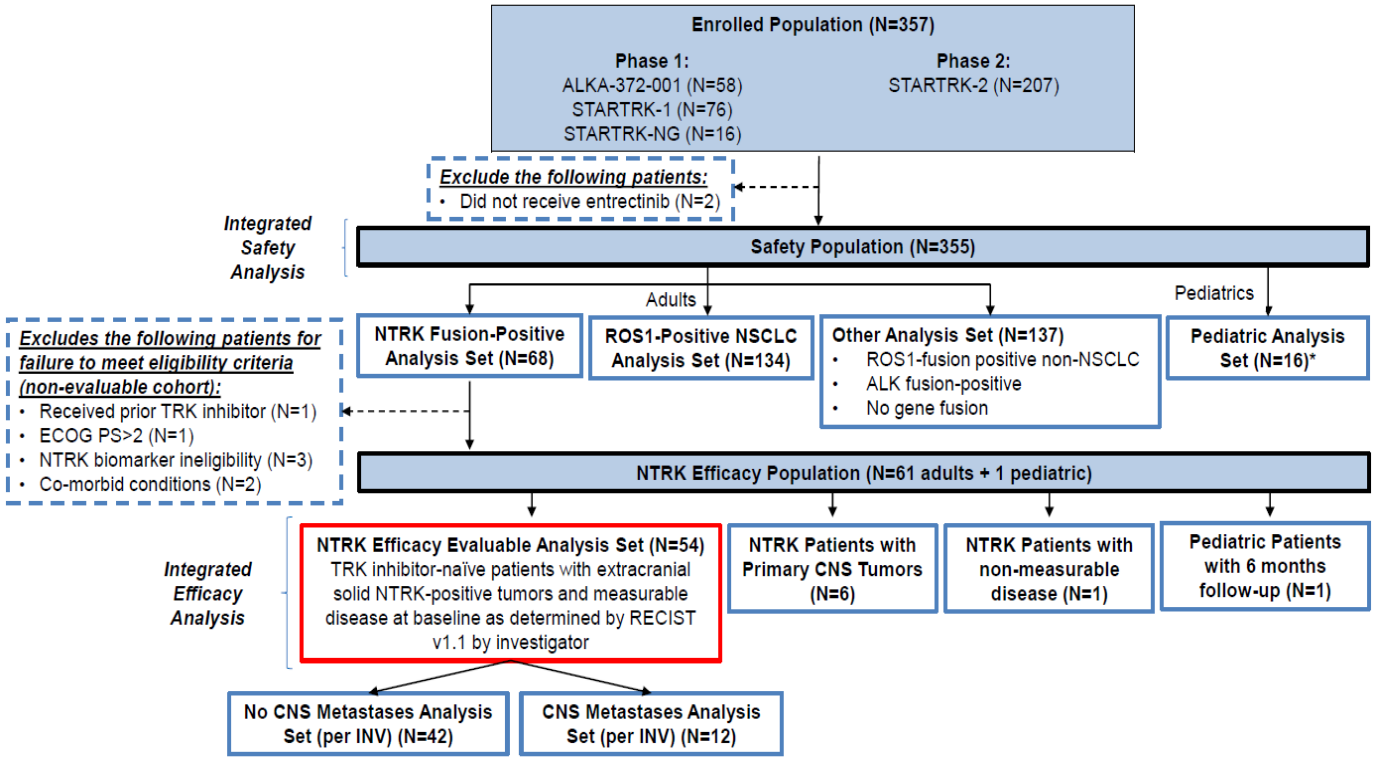
Study population and Patient Disposition

Figure 28 presents all patient populations and analysis sets included in the integrated analyses. A total of 357 patients were enrolled across the four studies ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG, out of which 68 patients had *NTRK* fusion-positive solid tumors with at least 6 months follow-up. Among these 68 patients, 1 patient with non-measurable disease, 6 with primary CNS tumors, and 7 patients based on eligibility criteria (reasons for exclusion are included in Figure 28) were excluded from the *NTRK* efficacy evaluable analysis set; 54 patients in total were included in the *NTRK* efficacy evaluable analysis set. The number of patients from each individual study that comprised the consecutive 54 patients in the efficacy population are as follows: ALKA (n=1), STARTRK-1 (n=2), and STARTRK-2 (n=51).

The *NTRK* efficacy evaluable analysis set was further categorized into the following two analyses sets based on the presence or absence of CNS metastases at baseline, as determined by the investigator,

- CNS Metastases Analysis Set: N=12 and
- No CNS Metastases Analysis Set: N=42

Figure 28: *NTRK* Patient Population and Analysis Sets



Source: Applicant's application orientation meeting slides (Page-16)

** This figure incorrectly indicates that there were 16 patients in the pediatric analysis set. The original safety dataset included in the NDA reflected data from 17 patients less than 18 years of age, including 15 pediatric patients from STARTRK-NG and 2 pediatric patients from STARKTRK-2; therefore, FDA determined that the pediatric analysis set comprises 17 patients. Additionally, the number of actual patients in the ROS1 NSCLC dataset was n=133.*

Table 33 summarizes the patient disposition for the data pooled across the three studies and each individual study. As of the data cutoff date of 31 May 2018, 23 out of 54 patients (42.6%) discontinued the study and the most common reason for discontinuation from study was death (69.6%). Among 31 patients who discontinued the study treatment (57.4%), the majority of the patients had PD (74.2%).

Table 33: Patient Disposition *NTRK* Efficacy Evaluable Analysis Population (pooled and individual studies)

	ALKA (n=1)	STARTRK-1 (n=2)	STARTRK-2 (n=51)	Total (n=54)
Study Status				
Ongoing	0	0	31 (60 8%)	31 (57.4%)
Discontinued from study	1 (100.0%)	2 (100.0%)	20 (39.2%)	23 (42.6%)
Reason for discontinuation:				
- Death	0	0	16 (80.0%)	16 (69.6%)
- Informed consent withdrawn	0	0	4 (20.0%)	4 (17.4%)
- Lost to follow-up	1 (100.0%)	0	0	1 (4.3%)
- Other	0	2 (100.0%)	0	2 (8.7%)
Study drug status				
Discontinued treatment	1 (100.0%)	2 (100.0%)	28 (54.9%)	31 (57.4%)
Reason for discontinuation				
- Due to an AE	0	0	7 (25.0%)	7 (22.6%)
- Informed consent withdrawn	0	0	1 (3.6%)	1 (3.2%)
- Disease progression	1 (100.0%)	2 (100.0%)	20 (71.4%)	23 (74.2%)

Source: Reviewer table by Biostatistics and confirmed by clinical reviewer with IR-33 dated May 10, 2019

Clinical Reviewer Comment: *The disposition of the patients in the efficacy population consistent a refractory solid tumor population, which typically reflects discontinuation from study treatment and from the study due to progressive disease, drug toxicity, and death due to underlying cancer.*

Compliance with Good Clinical Practices

Section 1.9 of the Clinical Overview (Module 2.5) submitted to the NDA states: "All studies were conducted in accordance with the principles of Good Clinical Practice (GCP) (the ICH guidelines on good clinical practice [ICH E6], the US FDA regulations, the Declaration of Helsinki [October 1996], and applicable local, state, and federal laws, as well as other applicable national legal requirements). The study designs also considered statistical principles (ICH E9) and FDA and EMA guidelines on clinical trial endpoints for the approval of cancer drugs (FDA Guidance to Industry, 2007 and EMA/CHMP/205/95 Rev. 5, 2018). The studies were approved by the appropriate Ethics Committees and Institutional Review Boards, were audited for GCP and were source document verified."

Protocol Violations/Deviations

The definition of protocol violation and summary of protocol violations in each individual trial are provided below.

Major protocol deviations were defined as any change, divergence, or departure from the study

design or procedures described in the protocol, as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. These included but were not limited to the following:

- Patients enrolled but not meeting exclusion and inclusion criteria
- Patient developed treatment withdrawal criteria but did not discontinue study treatment (unless there was evidence of clinical benefit as defined by primary physician despite radiological progression)
- Failure to perform procedures related to safety, primary outcome, and key secondary outcomes that could undermine the scientific value of the study
- Administering/taking incorrect treatment or dose as per protocol
- Taking excluded concomitant medications
- GCP protocol deviations such as:
    - o Informed consent not appropriately obtained
    - o Mishandling of study drugs
    - o Noncompliance with principal investigator (PI) responsibilities
    - o Noncompliance with safety/serious adverse event (SAE) reporting.

ALKA:
Eligibility criteria were not met for 39% of the major violations; other major violations were errors in treatment administration (16%), radiologic assessment (11%), which included the timing of assessment (2%), concomitant treatments that were not allowed (2%), informed consent document (ICD) not signed (2%), and issues with documentation (2%).

Clinical Reviewer Comment: Patient (b) (6) *was the only patient in Study ALKA who was included in the primary efficacy population. Patient* (b) (6) *had colorectal cancer (CRC) and received 1600mg/m^2/day of entrectinib, had a partial response (PR) lasting 2.6 months, and then was lost to follow up. In addition to minor protocol deviations, there was a single major protocol deviation for this patient due to a one-day delay in CT assessment of tumor status (performed on C3D2). This short delay in tumor assessment would not materially affect the evaluation of efficacy for this individual patient or the primary efficacy analysis.*

STARTRK-1:
"Important protocol deviations" were defined as a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being.

Overall, 15 (19.7%) patients had important protocol deviations. The most common (occurring in ≥5% of patients) important protocol deviations were in the category of Study Conduct/ Procedures and were primarily in the subcategories of Study Restrictions/Withdrawal Criteria (5 [6.6%] patients) or Inclusion/Exclusion Criteria (4 [5.3%] patients). These important protocol deviations primarily included receipt of prohibited concomitant medication (Phenergan, Levaquin, ciprofloxacin), failure to obtain pregnancy tests at baseline, a shorter washout period

between prior receipt of from crizotinib or radiation therapy and enrollment than specified in the protocol, or incorrect entrectinib dosing (a smaller dose [400 mg instead of 800 mg] was given to patient (b) (6) and a higher dose [600 mg instead of 400 mg] was taken by patient (b) (6)).

Clinical Reviewer Comment: A tabular listing of deviations noted as "non-important" versus "important" was included in the clinical study report (CSR), and an analysis was done with pooled data*. IR-33 dated 10 May 2018 clarified the major protocol violations, and was incorporated into Table 34 below.*

STARTRK-2:
A protocol violation was defined as patient or investigator failure to adhere to significant protocol requirements affecting the inclusion, exclusion, patient safety or primary endpoint criteria. Protocol violations for this study included, but were not limited to, the following:

1. Failure to meet inclusion/exclusion criteria
2. Dose modifications (e.g., wrong treatment or incorrect dose) that are not within the protocol specifications
3. Use of a prohibited concomitant medication
4. Any other deviation that presents significant risk or safety concerns to the patient, e.g., pregnancy on study

Major protocol deviations occurred in 48 (23.3%) patients; these were related to informed consent (15 patients [7.3%]), eligibility and entry deviation (10 patients [4.9%]) and investigational product (IP) compliance (10 patients [4.9%]).

The inspection of the Independent Review process at the CRO identified a study subject whose scans were deemed "no pathologic disease visualized" at baseline and during the study according to two endorsed independent adjudications. At the Investigator's discretion, this study subject continued treatment with entrectinib for approximately twenty months despite absence of BICR-confirmed disease progression. The Office of Scientific Investigations (OSI) and Division of Oncology Products 2 (DOP 2) review teams expressed concern about whether this subject's well-being was properly protected or placed at undue risk given the Independent Review report. This inspectional finding was communicated to the Applicant in an Information Inquiry (IR) on May 9, 2019. Based on the IR responses dated May 17, 2019 and discussions in a teleconference held on May 30, 2019, the Applicant has notified the Investigator of the BICR reports for this subject and considered the event a protocol deviation.

Clinical Reviewer Comment: Although a total of 117 major/important protocol deviations occurred in 88 patients in the safety analysis population in this NDA, Genentech did not consider the protocol violations to have an effect on the safety or efficacy outcomes of the studies. The most frequently reported major protocol violations were those relating to "Inclusion/Exclusion criteria" in 22 of 355 patients and "Issues with informed consent" in 16 of 355 patients.

Although it is challenging to ascertain the impact of protocol violations in single arm trials with small sample sizes, this clinical reviewer agrees with Genentech's conclusion that the protocol deviations described below in Table 34 did not materially alter the safety or efficacy results of entrectinib in this population. See FDA OSI review for details regarding protocol violations.

Table 34: Summary of Major/Important Protocol Violations across all Studies with Entrectinib

Protocol Violation	Overall Safety Analysis Population N=355 n (%)
Patients with major protocol violation (%)	88 (24.8)
Total number of major protocol violations	117
Issues with informed consent	16 (4.5)
Protocol procedures/visits not performed/missing	4 (1.1)
Inclusion/Exclusion criteria violated	22 (6.2)
Incorrect response assessment	6 (1.7)
Out of window visits/procedure	0
Medication errors	13 (3.7)
Other[1]	2 (0.6)

Copied from submission of IR-33 dated May 10, 2018; reviewed with data from CSRs submitted to NDA Module 5.3.5.2

Baseline Characteristics

The demographics and the baseline disease characteristics of the *NTRK* efficacy evaluable analysis population are summarized in Table 35 and Table 36. The types of *NTRK* gene (*NTRK1*, *2*, or *3*) and their corresponding gene fusion partners are summarized in Table 37.

The median age of the patients in *NTRK* efficacy evaluable analysis population was 57 years (range: 21 to 83 years). Fifty-nine percent were female, the majority of the patients were white (80%), and 8% were Hispanic or Latino. The percentage of patients with ECOG performance status of 0 or 1 is comparable (43% and 46% respectively). Ninety-six percent of patients had metastatic disease including 22% with CNS metastases, and 4% had locally advanced disease. Eighty-nine percent of patients had received prior systemic therapy and of these, 20% (n=11) received one prior systemic therapy, 26% (n=14) received two prior systemic therapies, 7% (n=4) received three prior systemic therapies, and 9% (n=5) received four or more prior systemic therapies.

Table 35: Demographics in *NTRK* Efficacy Evaluable Analysis Population

	Entrectinib N=54
Gender	
Male	22 (40.7%)
Female	32 (59.3%)
Age	
Median	57.5
Min, Max	21, 83
Age Group	
< 65	34 (63.0%)
>= 65	20 (37.0%)
Race	
Asian	7 (13.0%)
White	43 (79.6%)
Not Reported	4 (7.4%)
Ethnicity	
n	53
Hispanic or Latino	4 (7.5%)
Not Hispanic or Latino	45 (84.9%)
Unknown	1 (1.9%)
Not reported	3 (5.7%)
ECOG	
0	23 (42.6%)
1	25 (46.3%)
2	6 (11.1%)
Smoking History	
No	30 (56.6%)
Yes	23 (43.4%)
Current	6 (26.1%)
Former	17 (73.9%)

Source: Reviewer generated table from dataset ADL

Clinical Reviewer Comment: *The number of patients enrolled in any specific demographic subpopulation is low, given the rarity of NTRK fusion-positive solid tumors in most primary tumors and the small sample size. There are no outliers that are clinically important in this patient population.*

Table 36: Baseline Disease Characteristics in *NTRK* Efficacy Evaluable Analysis Population

	Entrectinib N=54
Disease Stage	
Metastatic	52 (96%)
Locally Advanced	2 (4%)
Baseline CNS Lesions by Investigator	
Absent	42 (77.8%)
Present	10 (18.5%)
Measurable	2 (3.7%)
Tumor Type	
Sarcoma: MPNST (1), GIST (1), chondrosarcoma	13 (24%)
NSCLC: Adeno and squamous cell (1)	10 (19%)
Salivary Gland (MASC)	7 (13%)
Breast: Nonsecretory (1)	6 (11%)
Thyroid: Papillary, anaplastic	5 (9%)
Colorectal Cancer	4 (7%)
Neuroendocrine	3 (6%)
Pancreatic	3 (6%)
Gynecological: Endometroid, ovarian	2 (4%)
Cholangiocarcinoma	1 (2%)
Prior Radiotherapy of the Brain	
Yes	7 (13%)
No	47 (87%)
# Prior lines of therapy	
0	**20 (37%)**
1	11 (20%)
2	14 (26%)
3	4 (7%)
4 or more	5 (9%)
Any Prior Systemic Therapy	48 (89%)
# Prior systemic therapies	
1	2 (3.7%)
2	10 (19%)
3	8 (15%)
4 or more	28 (52%)

Source: Reviewer generated table from dataset ADL

Clinical Reviewer Comment: *Most of the patients had metastatic disease, which is consistent with incidences of previously approved drugs for a population of patients with refractory solid tumors. A portion of patients had no prior systemic therapy (11%), which is expected because some patients had cancers for which there is no approved standard front-line treatment. Three patients with MASC had not received systemic therapy but underwent surgical resection or radiation prior to study enrollment. The incidences and distribution of tumor histologies enrolled on the trials supporting this application differ from the larotrectinib NDA; this is most likely due*

to the rarity of NTRK gene fusions and because the efficacy populations supporting these applications consisted of a pre-defined number of patients enrolled on a consecutive basis in order to minimize selection bias.

In response to an FDA IR, Genentech provided information clarifying the extent of prior treatment (including neoadjuvant/adjuvant treatment) of patients enrolled across the efficacy population (n=54), and provided additional justification to show that patients who enrolled in the entrectinib trials prior to receipt of systemic chemotherapy for metastatic or unresectable disease had no standard available therapy or satisfactory treatment options. An exploratory analysis of ORR was conducted in patients who received prior systemic therapy for metastatic disease versus those who did not. The ORR was 53% for both populations.

Table 37 provides a summary of the incidence of *NTRK* rearrangements identified in the 54 patients in the efficacy population. The most common *NTRK* fusions involved *NTRK3* (57%) and the second most common *NTRK* fusions involved *NTRK1* (41%). The number of patients with solid tumors with *NTRK2*-fusion proteins (2%) was low.

Table 37: Summary of *NTRK* Gene Fusion Partners

***NTRK* GENE** ***NTRK* GENE Fusion Partner**	**N (%)**
NTRK3	31 (57%)
NTRK3 GENE Fusion Partners	
ETV6-NTRK3	25 (81%)
EML4-NTRK3	2
AKAP13-NTRK3	1
FAM19A2-NTRK3	1
KIF7-NTRK3	1
RBPMS-NTRK3	1
NTRK1 GENE	22 (41%)
NTRK1 GENE Fusion Partner	
TPM3-NTRK1	4
TPR-NTRK1	4
SQSTM1-NTRK1	2
LMNA-NTRK1	2
PEAR1-NTRK1	2
ERC1-NTRK1	1

***NTRK* GENE** ***NTRK* GENE Fusion Partner**	**N (%)**
EPS15L1-NTRK1	1
CGN-NTRK1	1
CDC42BPA-NTRK1	1
PDIA3-NTRK1	1
PLEKHA6-NTRK1	1
CD74-NTRK1	1
TRIM33-NTRK1	1
NTRK2 GENE	1 (2%)
NTRK2 GENE Fusion Partner *SQSTM1-NTRK2*	1

Source: Reviewer generated table from dataset ASL

Efficacy Results – Primary Endpoint

The efficacy analysis results based on a database lock date of May 31, 2018 are reported in this section.

This review includes the data from the first 54 adult *NTRK* fusion-positive patients consecutively enrolled across ALKA, STARTRK-1, and STARTRK-2. Patients enrolled until November 30, 2017 were considered in the primary analysis and the database lock date of May 31, 2018 ensures a minimum 6 months of follow-up for all these patients.

Table 38 summarizes the ORR and DOR results BIRC for the *NTRK* efficacy evaluable analysis population. ORR was 57.4% and considered to be clinically meaningful as discussed and agreed upon in the pre-NDA meeting, as it excludes a lower bound of the 95% CI for ORR of 30%.

Table 38: ORR and DOR Results in the *NTRK* Efficacy Evaluable Analysis Population

	Entrectinib N=54
ORR - BICR	
# Responders	31
Response rate (95% CI)	57.4% (43.2, 70.8)
CR	4 (7.4%)
PR	27 (50%)
DoR	
Median in months (95% CI) Range	10.4 (7.1, NE) 1.9+, 20.3+
# Responders with observed DOR ≥ 6 mons ≥ 12 mons ≥ 18 mons	 17 (55%) 9 (39%) 3 (29%)

Source: FDA statistical reviewer's analysis results

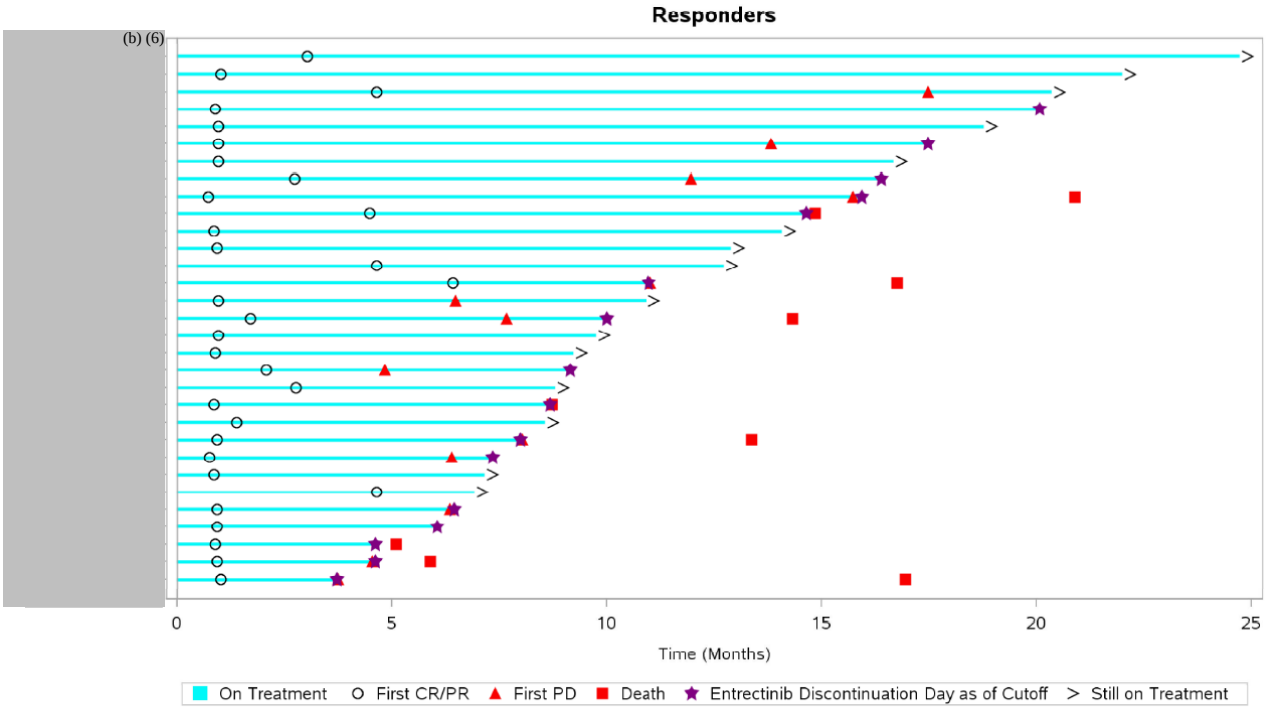
Statistical Reviewer's Comment:

1. *Genentech submitted updated efficacy and safety data based on an additional 5 months follow-up (75-day update) from the time of primary ORR analysis. The updated database lock date was October 31, 2018. The durability of responses was assessed using this data; among the 31 responders, 68% had a DOR of at least 6 months, and 45% had a duration of response of over a year.*
2. *In addition to the pre-specified method to calculate the 95% CI of median DOR, this statistical reviewer calculated the CI using Clopper-Pearson exact method. Using Brookmeyer Crowley method the 95% CI of median DOR was (7.1, NE) and the 95% exact confidence interval was (6, NE).*

Clinical Reviewer Comment: The efficacy results are clinically meaningful in this population with unresectable or metastatic solid tumors that are refractory or have no satisfactory treatment options and will be discussed further in Section 1.3 and Section 8.4.

The graphical illustration of the time line of events in the 31 responding patients is presented in Figure 29.

Figure 29: Plot of Time on Treatment for responders in *NTRK* Efficacy Evaluable Analysis Set



Source: Figure-5 in summary of clinical efficacy document submitted to Module 2.7.3.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints for the integrated assessments are listed below.

- CBR as assessed by BICR using RECIST v1.1
- PFS as assessed by BICR and
- OS
- Time to CNS progression as assessed by BICR using RECIST 1.1
- In patients with CNS disease at baseline, the following will be assessed
  - Overall (systemic) ORR as assessed by BICR using RECIST v1.1
  - IC-ORR as assessed by BICR using RECIST v1.1 in patients presenting with measurable CNS lesions at baseline, as well as patients with measurable and non-measurable CNS lesions at baseline
  - IC-DOR as assessed by BICR and intracranial PFS (ICPFS) as assessed by BICR

The efficacy results for CBR and the time to event endpoints (PFS, OS, and time to CNS progression) are included in this section. ORR results in the subgroup of patients with baseline CNS disease and the intracranial related endpoints analysis results are included in the subpopulation section below.

Table 39: CBR Results in the *NTRK* Efficacy Evaluable Analysis Population

	Entrectinib N=54
# patients who achieved CBR	35
CBR (95% CI)	64.8% (50.62, 77.32)
CR	4 (7.4%)
PR	27 (50%)
SD for at least 6 months	4 (7.4%)

Source: FDA statistical reviewer's analysis results

Statistical Reviewer's Comment:

1. *CBR is not established efficacy endpoint and therefore will not be used for labelling claims.*
2. *Please note that the time to event endpoints are not interpretable in the absence of a control/placebo arm. Although this reviewer included the analysis results for PFS, OS and time to CNS progression, these are not considered definitive analyses to support efficacy.*
   - *PFS: Estimated median is 11.2 months and the corresponding 95% CI are (8.0, 14.9)*
   - *Time to CNS progression: Estimated median is 17.0 months and the corresponding 95% CI are (14.3, NE)*
   - *OS: <30% deaths were observed by the clinical cutoff date which are considered to be immature to include in efficacy interpretations.*

Dose/Dose Response

Not applicable.

Durability of Response

Please see the analysis of duration of response and Table 38 for response durations.

Persistence of Effect

Not applicable.

Efficacy Results –Exploratory COA (PRO) endpoints

As mentioned in Section-8.1.1 (statistical analyses plan for integrated assessments), results based on QLQ-C30 questionnaire for only the patients from STARTRK-2 study are reported in this review. There were only 9 patients with NSCLC that completed the QLQ-LC13 and 3

patients with mCRC tumors that completed the QLQ-CRC29; therefore, the results for these questionnaires are not included in this review.

Table 40 below provides the number of patients who are eligible to complete the questionnaire, number of patients who completed at least one question and completion rate is defined as the ratio of these quantities. The QLQ-C30 questionnaire completion rate was between 71% to 100% for cycles-1 to Cycle-26 and by the end of the treatment the completion rate decreased to 55%.

Table 40: Compliance Rates of QLQ-C30 by Visit in Study STARTRK-2

Visit	# Patients eligible to complete the QLQ-C30 questionnaire	# Patients who completed at one question	Completion Rate
Cycle 1 (Baseline)	51	48	94.1%
Cycle 2	47	43	91.5%
Cycle 3	45	42	93.3%
Cycle 4	43	38	88.4%
Cycle 5	41	37	90.2%
Cycle 6	41	37	90.2%
Cycle 7	36	33	91.7%
Cycle 8	35	33	94.3%
Cycle 9	29	27	93.1%
Cycle 10	27	26	96.3%
Cycle 11	23	23	100.0%
Cycle 12	19	16	84.2%
Cycle 13	16	16	100.0%
Cycle 14	14	14	100.0%
Cycle 15	13	13	100.0%
Cycle 16	12	12	100.0%
Cycle 17	9	9	100.0%
Cycle 18	8	7	87.5%
Cycle 19	7	5	71.4%
Cycle 20	6	6	100.0%
Cycle 21	4	4	100.0%
Cycle 22	3	3	100.0%
Cycle 23	3	3	100.0%
Cycle 24	2	2	100.0%
Cycle 25	1	1	100.0%
Cycle 26	1	1	100.0%
End Of Treatment	20	11	55.0%

Source: FDA statistical reviewer generated table

Statistical Reviewer's comment: Please note that for later cycles there were very few patients who were on study during these cycles (<5 beginning from cycle-20 and only 1 patient at cycles-25, 26). Therefore, the confidence interval bands were not included for cycles 25-26 in the figures in Section 19.5.

Please refer to Section-19.5 for additional PRO analysis.

Subpopulations

List of analysis results that were included in this subsection are provided below to summarize the content in this subsection.

- ORR in subgroups
- Efficacy results in patients with baseline CNS metastases
- Intracranial efficacy results in patients with CNS disease at baseline as confirmed by BICR
- ORR results by Tumor type and by *NTRK* gene fusion partner

ORR in subgroups

Table 41 summarizes the BICR-assessed ORR in the subgroups defined by age (<65 years and ≥ 65 years), gender (male, female), ECOG performance status (0, 1, 2), prior systemic therapy, and based on the number of prior systemic therapies received (0, 1, 2, 3, 4, >4).

Table 41: ORR results by subgroups in *NTRK* Efficacy Evaluable Analysis population

Subgroup	N	# Responders (%)	95% CI of ORR
All	**54**	**31 (57.4%)**	**(43.21,70.77)**
Gender			
Male	22	9 (40.9%)	(20.7,63.7)
Female	32	22 (68.8%)	(50.0,83.9)
Age Group (years)			
<65	34	22 (64.7%)	(46.5,80.3)
≥ 65	20	9 (45.0%)	(23.1,68.5)
ECOG Performance Status			
0	23	13 (56.5%)	(34.5,76.8)
1	25	17 (68.0%)	(46.5,85.1)
2	6	1	NA
Any prior systemic therapy			
Y	48	27 (56.3%)	(41.2,70.5)
N	6	4	NA
Number of prior systemic therapies			
0	20	13 (65.0%)	(40.8,84.6)
1	11	5 (45.5%)	(16.8,76.6)
2	14	9 (64.3%)	(35.1,87.2)
3	4	1	NA
4	4	3	NA
>4	1	0	NA

Source: Statistical Reviewer generated table from Datasets: ASL.

Clinical Reviewer Comment: The efficacy results in subpopulations should be interpreted with caution as the sample size is small, and the data are from single-arm trials.

Efficacy results in patients with baseline CNS metastases
Based on the presence or absence of CNS metastases as determined by the investigator at baseline, the *NTRK* efficacy evaluable analysis population was further categorized into two groups: No CNS metastases analysis set that included 42 patients and CNS metastases analysis set that included 12 patients. Table 42 below summarizes the number of responders and the ORR along with 95% CI for each of these analysis sets.

Table 42: ORR results by baseline CNS metastases disease status

	CNS Metastases at baseline	
	Present (n=12)	Absent (n=42)
# Responders	6	25
Response rate (95% CI)	50.0% (21.09, 78.91)	59.5% (43.28, 74.37)
CR	0	4 (9.5%)
PR	6 (50.0%)	21 (50.0%)
Median DoR (95% CI)	NE (4.2, NE)	12.9 (7.1, NE)

Source: FDA statistical reviewer's analysis results

Intracranial efficacy analysis in patients with CNS disease at baseline:
Among the 12 patients who had CNS metastatic disease at baseline, the following additional endpoints were assessed:

- Overall (systemic) ORR as assessed by BICR using RECIST v1.1
- IC-ORR as assessed by BICR using RECIST v1.1 in patients presenting with measurable CNS lesions at baseline, as well as patients with measurable and non-measurable CNS lesions at baseline
- IC-DOR as assessed by BICR and intracranial PFS (ICPFS) as assessed by BICR

CNS metastatic disease was confirmed by the BICR in 11 out of 12 patients, of which CNS metastases were measurable in 7 patients. A total of 4 of the 7 patients with measurable CNS metastases at baseline as assessed by BICR had not received radiation therapy to the brain within 2 months of study entry. Responses in intracranial lesions were observed in 3 of these 4 patients.

Statistical and Clinical Reviewer Comments: Given the small sample sizes, the efficacy results for intracranial disease need to be interpreted carefully. In the "CNS metastases at baseline" analysis population, the median DOR is not interpretable because there are only 6 responders, and only 3 among these responders had ongoing response as of the clinical data cutoff date. The efficacy results in the CNS subpopulation in uninterpretable as there is a small sample size, and the data are from single-arm trials. Furthermore, data for the responders are confounded by prior XRT in 1 patient and data was missing for 2 patients (see Table 36).

The ORR and DOR results by tumor type and by *NTRK* gene fusion partner are provided in Table 43 and Table 44. For subgroups with <10 patients, only the number of responses or the actual responses are included.

Table 43: ORR and DOR Results by Tumor Type

Tumor Type	Patients N = 54	ORR		DOR
		n(%)	95% CI	Range (months)
Sarcoma	13	6 (46%)	19%, 75%	2.8, 15.1
Non-small cell lung cancer	10	7 (70%)	35%, 93%	1.9*, 20.1*
Salivary (MASC)	7	6	NA	2.8, 16.5*
Breast cancer	6	5	NA	4.2, 14.8*
Thyroid cancer	5	PR	NA	7.9
Colorectal cancer	4	PR	NA	4.8*
Neuroendocrine cancers	3	PR	NA	5.6*
Pancreatic cancer	3	PR, PR	NA	7.1, 12.9
Gynecological cancers	2	PR	NA	20.3*
Cholangiocarcinoma	1	PR	NA	9.3

* Censored
MASC: mammary analogue secretory carcinoma; NA = not applicable; PR = partial response.

Table 44: ORR and DOR Results by *NTRK* Gene Fusion Partner

NTRK Partner	Patients N = 54	ORR		DOR
		n (%)	95% CI	Range (months)
ETV6 – NTRK3	25	17 (68%)	47%, 85%	2.8, 20.3*
TPR – NTRK1	4	4	NA	5.6, 12.9
TPM3 – NTRK1	4	PR, PR	NA	2.8, 15.1
LMNA – NTRK1	2	PR, PD	NA	4.2
SQSTM1 – NTRK1	2	PR, PR	NA	3.7, 18.8*
PEAR1 – NTRK1	2	SD, NE	NA	NA
EML4 – NTRK3	2	SD, NE	NA	NA
CD74 – NTRK1	1	PR	NA	10.4
PLEKHA6 – NTRK1	1	PR	NA	9.3

NTRK Partner	Patients N = 54	ORR		DOR
		n (%)	95% CI	Range (months)
CDC42BPA – NTRK1	1	PR	NA	6.8*
EPS15L1 – NTRK1	1	PR	NA	1.9*
RBPMS – NTRK3	1	PR	NA	4.6
ERC1 – NTRK1	1	SD	NA	NA
PDIA3 – NTRK1	1	SD	NA	NA
TRIM33 – NTRK1	1	SD	NA	NA
AKAP13 – NTRK3	1	SD	NA	NA
KIF7 – NTRK3	1	SD	NA	NA
FAM19A2 – NTRK3	1	PD	NA	NA
CGN – NTRK1	1	NE	NA	NA
SQSTM1 – NTRK2	1	NE	NA	NA

* Censored
PR = partial response; PD = progressive disease; SD = stable disease; NE = not evaluable; NA = not applicable.

8.1.3. Assessment of Efficacy Across Trials

FDA's review of efficacy is based on analyses of ORR and DOR for the first 54 sequentially enrolled patients with *NTRK*-positive solid tumors enrolled across the 3 entrectinib studies (ALKA, STARTRK-1, and STARTRK-2), as described in Section 8.1.1. The clinical data cutoff date for the final ORR and DOR analysis was 31 May 2018.

Primary Endpoints

The primary endpoint for the integrated analysis of effectiveness is ORR according to BIRC assessment. See Section 8.1.5.

Secondary and Other Endpoints

There were no meaningful secondary endpoints specified in the SAP of each study aside from DOR. For exploratory purposes, QoL was evaluated only in patients from Study STARTRK-2 using EORTC QLQ-C30. See Section 8.1.5.

Subpopulations

No subpopulations were identified a priori or in the SAP.

Additional Efficacy Considerations

Although patients with primary central nervous system disease were not included in the primary efficacy population supporting this application, data were provided for 5 adult patients with primary central nervous system disease that received entrectinib across the 3 adult clinical

trials. One patient [redacted] (b) (6)) had a partial response per RANO criteria, 2 patients had SD (1 each per RANO criteria and RANO-Brain Metastases criteria), and three had PD per RANO criteria.

Additionally, preliminary data (not reviewed by FDA and which may not have been independently confirmed) from the STARTRK-NG trial presented by Robinson et al. on July 2, 2019 at the Annual ASCO meeting (Abstract 10009) indicated that in 6 patients with high grade CNS tumors, a CR was observed in 1 patient with an *ETV6-NTRK3* fusion and 3 partial responses were observed in patients with tumors harboring an *TPR-NTRK1*, *EEF1G-ROS1*, or *EML1-NTRK2* fusion; two patients were not yet evaluable for response.

Although limited, these data suggest activity in the CNS. This limited clinical data, together with nonclinical pharmacology data indicating that entrectinib crosses the blood brain barrier achieving levels that would inhibit TRK activity, support the decision not to include in product labeling a limitation of use for patients with primary CNS tumors.

The clinical review team does not anticipate important differences between how the drug was studied in the clinical trials supporting the efficacy of entrectinib and how entrectinib will be used in the postmarket setting that would affect recommendations regarding approval of this application or labeling for entrectinib.

8.1.4. Integrated Assessment of Effectiveness

The clinical and statistical review teams conclude that Genentech has provided substantial evidence of the effectiveness of entrectinib in adult and pediatric patients 12 years of age and older (adolescent patients) with metastatic or unresectable solid tumors that have an *NTRK* gene fusion without a resistance mutation that have no satisfactory alternative treatments or that have progressed following treatment. This application is supported by evidence of a large and clinically meaningful and durable ORR observed in the first 54 patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion enrolled and treated with entrectinib in one of three multicenter, open-label, single-arm clinical trials (ALKA, STARTRK-1, and STARTRK-2). FDA considers ORR of a sufficient magnitude and with a meaningful duration of response as a surrogate reasonably likely to predict clinical benefit in these patients with refractory cancers. Among the 54 patients in the efficacy population, the ORR was 57.4% (95: CI: 43.2%, 70.8%), including 7.4% of patients with a CR and 50% of patients with a PR to entrectinib. Responses were durable. Among the 31 responding patients, 68% had a DOR of at least 6 months, and 45% had a duration of response of over a year. 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, an argument can clearly be made that 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.

Please refer to Section 7 and Section 19.6 (Appendices) of this review for additional details regarding the three clinical trials contributing data to support the efficacy of entrectinib and the efficacy analyses provided in this section.

FDA accepted data pooled from 3 single arm trials due to the rarity of *NTRK* fusion-positive solid tumors, rendering conduct of a randomized trial infeasible. Additionally, given the number of tumor types in which *NTRK* gene fusions can occur, each with different natural histories, "lumping" all tumor types together into a single randomized trial would present significant challenges in trial design and analysis of the data.

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, Genentech will conduct additional single arm studies to obtain data to verify and further characterize the clinical benefit of entrectinib, in an adequate number of patients with common histologic tumor types, including colon cancer and melanoma. Based on the observed ORR and DOR, equipoise no longer exists and verification of clinical benefit in randomized trials would no longer be feasible even in any tumor type at this time; whether such trials may be warranted will be determined as additional clinical data becomes available.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical assessment of the safety of entrectinib is based on data from four single-arm trials: ALKA-372-001, RXDX-101-01, RXDX-101-02, and RXDX-101-03 (also referred to as "ALKA", "STARTRK-1", "STARTRK-2", and "STARTRK-NG", respectively). The pooled safety population, which comprises 355 patients who received at least one dose of study drug (58 patients in ALKA, 76 patients in STARTRK-1, 207 patients in STARTRK-2, and 16 patients in STARTRK-NG; although a total of 357 patients were enrolled, 2 patients did not receive entrectenib and were excluded). The safety monitoring period spanned the time of first administration of entrectinib until 28 days following discontinuation of entrectinib, and for all AEs or related SAEs reported beyond the discontinuation (approximately 28 days [+ 7 days] after the final dose of the last cycle of treatment). All safety analyses was performed for the safety evaluable population and presented by the adult and pediatric safety population analysis sets (Figure 27).

Studies were ongoing during the original NDA submission except for ALKA; therefore, interim clinical study reports were reviewed for STARTRK-1, STARTRK-2, and STARTRK-NG, all of which used a data cut-off date 31 May 2018. Data from the 75-day update included safety data using a data cut-off date of 31 Oct 2018. Narratives of deaths and SAEs from all 4 studies were reviewed for events that occurred through the time of the data cut-off date. The review of safety included consideration of the submitted CSR, SDTM and analysis datasets, line-listings, CRFs, and patient narratives from all 4 trials. The clinical reviewers confirmed Genentech's safety analyses, conducting analyses of primary data using the MedDRA-based Adverse Event Diagnostics (MAED) tool and JMP programs.

Safety data from 10 clinical pharmacology studies (N=323), and 8 single patient protocols (N=8), were also reviewed; however, these data were not included in the integrated summary of safety (ISS) analyses as the former studies enrolled healthy volunteers and the latter did not systematically collect safety data in the same fashion as a clinical trial, making data pooling not appropriate.

Clinical Reviewer Comment: Analyses of safety data from the 75-day safety update performed by Genentech were reviewed and verified by the FDA clinical reviewer. The majority of safety analyses presented below reflect data included in the original NDA submission that used a data cut-off date of May 31, 2018 (N=355). When warranted, clinically important new safety information that was provided in the safety update are also described below.

8.2.2. Review of the Safety Database

Overall Exposure

At the time of the data cutoff for the original NDA and for the 75-Day Update, three trials (STARTRK-1, STARTRK-2, and STARTRK-NG) were ongoing with patients still being treated and new patients being enrolled, and ALKA was completed. Three hundred fifty-five patients across the four trials had been enrolled as of the original NDA data cutoff and were eligible for inclusion in the integrated analysis. The safety data derived from the adult population reflects the safety of entrectinib across multiple dose levels; the majority of adult patients (76%) received the entrectinib 600 mg daily as a starting dose. In the *NTRK* efficacy population (N=54), 94% of patients received the RP2D of 600mg daily. The 3 patients that received below the RP2D received at least 67% of the dose: patients [redacted] (b) (6), [redacted] (b) (6).

In the original dataset (data cut off: May 31, 2018) 259 out of 355 patients (73%) had discontinued entrectinib. For further details regarding patient disposition, please see Section 8.1.5 "Study population and Patient Disposition" and Table 33 of this review.

The median duration of entrectinib treatment was 5.5 months (range: 1 day - 42 months) across the overall safety population of 355 patients treated, with a median of 7 cycles (range 1 - 92) as summarized in Table 45 and a mean cumulative dose of 123405.93 mg received as summarized in Table 46. The overall median dose intensity was 96.89%. With regards to duration of exposure, 61.4% of patients had received entrectinib for >3 months, 48.5% for >6 months, 33.2% for > 9 months, and 23.7% for > 12 months.

<u>Clinical Reviewer Comment</u>: *The median duration of exposure to entrectinib is longer in efficacy-evaluable NTRK fusion population (N=54) compared to the "all-comers" safety population (N=355), and by clinical study, the largest proportion of patients exposed were enrolled in the STARTRK-2 study. These findings were expected as the eligibility criteria in STARTRK-2 selected patients based upon the presence of NTRK fusions (or ROS fusions, in the case of patients with NSCLC) and the hypothesis was the patients with tumors harboring an NTRK-fusion would respond to entrectenib and thus have a longer duration of exposure to entrectinib than patients without the molecular fusion. Patients generally discontinued entrectinib due to disease progression. STARTRK-NG enrolled pediatric patients who tended to have a shorter duration of exposure compared adults, although 2 patients (12.5%) were exposed to entrectinib for over one year. The median dose intensity in STARTRK-NG was similar to the other studies.*

Similarly, the median duration of exposure to entrectinib is longer in the efficacy-evaluable ROS1 fusion population (N=133) compared to the "all-comers" safety population (N=355), and by clinical study, the largest proportion of patients exposed were enrolled in the STARTRK-2 study. These findings were expected as the eligibility criteria required ROS1 fusion and the hypothesis

was the patients with the ROS1-fusion NSCLC would respond to entrectenib, and thus have a longer duration of exposure to entrectinib compared to patients with cancers that did not have ROS-1 fusions. Patients generally discontinued entrectinib due to disease progression.

Notwithstanding the limited size of the safety population, the clinical review team considered the exposure to entrectinib adequate to conduct a risk:benefit assessment, particularly given the observed ORR and DOR. The majority of adult patients (76%) received entrectinib 600 mg daily as a starting dose. There were 4 pediatric dose cohorts in STARTRK-NG; this trial used BSA-based dosing and duration of drug exposure and dose intensity in pediatric patients did not materially differ across the cohorts.

Table 45: Summary Exposure of Entrectinib

Parameter	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Median treatment duration (Months)	7.9 (0.1, 24.7)	8.3 (0.1, 42.1)	2.0 (0.0, 37.0)	1.9 (0.2,12.7)	5.5 (0.0, 42.1)
Median no. of cycles	9.5 (1.0, 49.0)	10.0 (1.0, 92.0)	3.0 (1.0, 70.0)	4.0 (1.0, 16.0)	7.0 (1.0, 92.0)
Median no. of missed doses	1.0 (0.0, 34.0)	1.0 (0.0, 24.0)	0.0 (0.0, 17.0)	2.0 (0.0, 37.0)	1.0 (0.0, 37.0)
Median dose intensity, %*	94.1 (40.5, 105.3)	96.5 (29.8, 133.3)	98.6 (12.6, 388.3)	96.3 (32.6, 115.1)	96.9 (12.6, 388.3)

*Defined as total cumulative dose actually received/total planned dose x 100%. Factors contributing to dose intensity >100% included patients enrolled during the dose finding portion of the Phase I studies who underwent intra-patient dose escalation after determination of the recommended Phase II dose.
Source: Reviewer generated table based on: Module 5.3.5.3 Analysis dataset_AEX. Derivations: BASKGRP3; TRTSDTM: Date/time of first exposure to treatment; TRTEDTM: Date/time of last exposure to treatment; TRTDURM: Duration of exposure (months)

Table 46 summarizes entrectinib exposure for ALKA, STARTRK-1, STARTRX-2, and STARTRX-NG.

Table 46: Entrectinib Exposure by Study and Overall

	ALKA	STARTRK-01	STARTRK-02	STARTRK-NG	Overall
N	57	76	206	16	355
Duration of Exposure					
≥3 month exposure	29 (50.9)	28 (36.8)	156 (76.1)	5 (31.3)	218 (61.4)
≥6 month exposure	18 (31.6)	20 (26.3)	130 (63.4)	4 (25.0)	172 (48.5)
≥9 month exposure	16 (28.1)	18 (23.7)	82 (40.0)	2 (12.5)	118 (33.2)
≥12 month exposure	14 (24.6)	13 (17.1)	55 (26.8)	2 (12.5)	84 (23.7)
Duration of treatment (weeks)					
n	57	76	205*	16	354*
Median	13.65	6.36	31.43	8.21	23.94
Mean	36.06	26.00	36.15	17.38	33.11
Range	2.5, 183.1	0.1, 148.9	0.3, 116.6	0.9, 55.3	0.1, 183.1
Number of cycles received					
Median	6.00	2.00	10.00	4.00	7.00
Mean	15.77	6.86	10.86	5.88	10.57
Range	1.0, 92.0	1.0, 38.0	1.0, 49.0	1.0, 16.0	1.0, 92.0
Cumulative dose (mg)					
n	57	76	205*	16	354*
Median	72800.00	27450.00	115800.00	22550.00	82500.00
Mean	166407.89	98516.45	124938.54	68800.00	123405.93
Range	2200.0, 1411600.0	200.0, 791600.0	1200.0, 367200.0	2400.0, 399200.0	200.0, 1411600
Dose intensity (%)					
n	57	76	205*	16	354*
Median	96.43	100.00	95.45	96.29	96.89
Mean	95.68	94.59	84.57	88.10	88.67
Range	25.0, 3883	33.3, 150.0	12.6, 112.4	32.6, 115.1	12.6, 388.3

Copied from submission to NDA as IR-33 on May 10, 2019, and verified from Module 5.3.5.3 Analysis dataset_AEX.

Relevant characteristics of the safety population:

Given the rarity of *NTRK* fusion solid tumors and *ROS1*-fusion NSCLC, FDA considered the safety database to be adequate to characterize risks in the population who would be treated with entrectinib in the postmarket setting, aside from the pediatric population**.**

The safety population from Studies ALKA, STARTRK-1, and STARTRK-2 primarily consisted of adult patients with solid tumors, and the safety population from STARTRK-NG consisted primarily of pediatric patients (there were 2 patients over 18 years of age). There were no Black patients enrolled on the trials with a solid tumor with an *NTRK*-gene fusion, and the number of patients enrolled in any specific demographic subpopulation is low, given the rarity of *NTRK* fusions in most primary tumors and the small study sample size. ECOG status was predominately 0-1.

Additional exploratory analyses were conducted based on gender, race, performance score, *NTRK*-gene fusion protein, and tumor type. Limitations of these subgroup analyses are the small sample sizes and lack of internal control in all studies. For a summary of demographics across all trials, see Table 35.

Table 47: Demographics

	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult (non *NTRK*, *ROS1*) (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Sex					
Male (%)	46	40	49	62	45
Female (%)	54	60	51	38	55
Median Age (yrs)	58	53	55	10	55
Range	21-83	15-86	15-80	4-20	4-86
Age (yrs)					
<65 (%)	63	76	76	100	75
≥65 (%)	37	24	24	0	25
Ethnicity					
Hispanic or Latino (%)	6	2	3	6	3
Not Hispanic or Latino	86	92	88	81	89
Not stated (%)	6	2.5	1	6	3
Unknown (%)	1.5	4	8	6	5
Race					
White (%)	77	53	72	81	66
Asian (%)	13	38	16	0	23
Black or AA (%)	1.5	5	4	19	4.5
Not reported (%)	9	3	4	0	4.5
ECOG PS (%)					
0	38	39	45	0	41
1	49	50	51	0	50
2	10	8	4	0	7
3	3	0.7	0	0	0.9
4	0	0.7	0	0	0.3

Source: Reviewer generated table based on ADL dataset submitted to NDA 212726 Module 5.3.5.3

Adequacy of the safety database:

The safety population from ALKA, STARTRK-1, and STARTRK-2 primarily consisted of adult patients with solid tumors, and the safety population from STARTRK-NG consisted primarily of pediatric patients (total pediatric patients across all trials N=30; 7% were < 2 years [n = 2], 77% were 2 to < 12 years [n = 23], 17% were 12 to < 18 years [n = 5]). There was insufficient information to establish a safe and effective dose in pediatric patients less than 12 years of age (see Sections 1.3, 6.2, 6.3, 8.4, and 10 for further details).

Overall, the safety database submitted by Genentech was adequate to conduct a risk:benefit assessment, given the observed ORR and DOR, in adult and pediatric patients ≥ 12 years of age. Given the rarity of solid tumors with an activating *NTRK* rearrangement and the observed adverse reaction profile in the context of the entrectinib exposure achieved in the safety population, FDA considered the safety database sufficient to characterize the safety profile of entrectinib in patients ≥ 12 years of age and identify AEs that occur at an incidence of approximately 2%.

Safety monitoring in the entrectinib studies consisted of collection of adverse events (AEs), serious adverse events (SAEs), laboratory tests (standard hematology and blood chemistries), physical observations/measurements (vital signs, electrocardiograms [ECGs], Eastern Cooperative Oncology Group [ECOG] status in adult studies and Lansky or Karnofsky performance status in the pediatric study, eye exams, chest X-rays), and pregnancy test in female patients of childbearing potential.

For all four oncology patient studies, vital signs (blood pressure [systolic and diastolic], heart/pulse rate, and body temperature [except for Study ALKA]) were measured. In addition, respiration rate was measured in Study STARTRK-2 and STARTRK-NG. Vital signs were measured at screening, during each treatment cycle, and at end of treatment visit. Weight and BMI have been integrated and analyzed collectively across all four oncology patient studies. Weight (kg), change from baseline, and percent change from baseline were summarized by cycle.

To monitor for potential corneal-related visual disturbances during treatment with entrectinib, eye examinations were required at screening, during treatment, at the end of treatment, and as clinically indicated. Additionally, neurological functions were assessed as part of physical examinations to monitor potential neurological toxicities during treatment with entrectinib. ECGs were performed in triplicate and assessed by a central reader for STARTRK-1 sites and all U.S. and Japan sites for STARTRK-2. ECGs was performed at screening, throughout treatment cycles, end of treatment visits, and if clinically indicated.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted was organized and of adequate quality to perform a comprehensive review of the safety of entrectinib. Several information requests were sent to Genentech during the review of safety to confirm data, request additional data, request alternative presentations of safety data, or clarify minor discrepancies. On the whole, Genentech provided timely and adequate responses, including additional analyses and clarifications as required. Data was verified and characterized (see final prescribing information for entrectinib).

Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) v15.1, 17.0, 18.0, and 19.0 were used for coding adverse events for the CSRs for Study ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG, respectively.

Genentech coded verbatim AE terms for all 4 studies and the integrated database using MedDRA version 21.0 for the primary analyses (ISS) and the data submitted at the 75-day data safety update. According to the Summary of Clinical Safety (SCS): NDA location Module 2.7.4, treatment-emergent adverse events (TEAEs) were defined as all AEs occurring from initiation of

study drug through 30 days after the last dose of entrectenib, but according to the protocol for ALKA, AEs were defined as all AEs occurring from initiation of study drug through 28 days after the last dose of entrectenib. In response to an IR (IR-29 dated 14 May 2019), Genentech clarified that both ALKA and STARTRK-NG collected AEs from the time of initiation of study drug through 28 days (and not 30 days) after the last dose. Information regarding deaths occurring within 30 days of receiving entrectenib was also collected. Regardless of the differences in AE reporting periods between ALKA and the other 3 clinical protocols, there was one death event which occurred outside of the period of 30 days after the last dose of entrectinib but is included in the analysis of death events. National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE Version 4.03) was used for toxicity grading.

The clinical reviewer assessed the adequacy of Genentech's mapping of AE verbatim terms to MedDRA preferred terms (PTs) for 100% of the four studies' primary AE.xpt datasets. The majority of nonidentical terms were due to spelling differences (e.g., anemia versus anaemia), use of abbreviations instead of full text (e.g., ALT increase versus alanine aminotransaminase increased), and verbatim terms that included descriptors (e.g., abdominal cramping versus abdominal pain). Some verbatim terms were miscoded or FDA did not agree with Genentech's coding such as "giddiness" to "dizziness"; such terms were recoded for accuracy. During the audit of the case report forms, several discrepancies were noted between AE information included in the case report forms and the AE datasets, including missing records. Overall, the MedDRA PTs listed in the dataset adequately represented the verbatim terms from the CRFs.

Safety and tolerability assessment was based on the frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments (hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. Multiple occurrences of the same event for a patient were counted once at the maximum severity reported. All events were followed to their resolution, until the Investigator assessed them as stable or otherwise explained, or until the patient was lost to follow-up, whichever occurred first.

Safety data was available for treatment-emergent AE (TEAE). A treatment-emergent AE (TEAE) was defined as any event arising or worsening after the start of study drug administration until 30 days after the last administration of entrectinib. For the purpose of the AE tables, an event was considered related to entrectinib if the investigator reported that it was possibly, probably, or definitely related in the AE electronic CRF (eCRF) form for the individual study.

Safety data were available for treatment-related SAEs, AE of special interest (AESIs), and all listings of AEs include all events that occurred during or after the first study drug treatment up to the data cutoff date. AESIs included were neurologic toxicity, changes in weight, congestive heart failure, increased creatinine and other renal events, eye disorders, QTc interval prolongation, elevated liver laboratory tests and other liver abnormalities, pneumonitis events, and hematologic events. FDA reviewed each AESO (see Section 8.2.4 for the reviewers conclusions).

Deaths reported during the study treatment period and those reported during the follow-up period after treatment completion/discontinuation and causes of death were summarized. For the integrated safety analysis, deaths due to disease progression were not included in SAE analysis across all four studies.

For laboratory test results, standard normal ranges were used by Genentech to identify values outside the normal ranges. Abnormal laboratory results were graded according to the NCI CTCAE v4.03 except for creatinine, which was revised and graded according to NCI CTCAEv5.0. A shift summary of baseline grade by maximum post-baseline CTCAE grade was included in the analyses. For each laboratory parameter, the baseline laboratory value was defined as the last laboratory value collected on or prior to the date of first dose of entrectinib. Only laboratory parameters common to all 4 studies were included. Potential liver abnormalities were included.

ECG analyses was based on central ECG readings that included the following parameters: heart rate, PR duration, QRS duration, QT duration, QTcB [Bazett's Correction], QTcF [Fridericia's Correction], and RR duration. Local ECG readings for Studies STARTRK-2 and STARTRK-NG included ventricular rate, PR duration, QRS duration, QT duration, QTcB, QTcF, and QTc Unknown. ECGs for Study ALKA included ventricular rate, QT duration, QTc (unspecified) and overall interpretation (normal/abnormal).]

*Clinical Reviewer Comment: Genentech considers it unlikely that the discrepancy in the reporting period of ALKA had an impact in the analysis of adverse events and the clinical reviewers agree. An analysis performed by FDA identified one patient (b) (6)) who died 33 days from the last dose of entrectinib (b) (6)). This patient's death, which was attributed to progressive disease, occurred outside of the 28-day window and was also outside of the 30-day window. Regardless, this patient most likely succumbed to underlying cancer (see Table 51, Table 49 "**Deaths**" below). The discrepancies noted between AE information included in the case report forms and the AE datasets, including missing records, were resolved or were not considered relevant to the overall safety assessment.*

Routine Clinical Tests

Laboratory assessments were performed within 7 days of enrollment for ALKA, 30 days for STARTRK-1, STARTRK-2, and 14 days for STARTRK-NG and on Day 1 of all four studies, at regularly scheduled intervals, and when medically necessary during drug administration. Vital sign measurements were obtained at least once prior to each cycle. Monitoring for cardiac-related toxicities included ECGs prior to each cycle with the exception of ALKA, in which an ECG was performed on D18 of cycle 1 and 3, at the end of therapy, and at the discretion of the Investigator, with the exception of STARTRK-NG in which pediatric patients underwent ECG assessment prior to Cycle 1 Day 1 until Cycle 7 only. (Refer to the Monitoring Plan in Section 19.6 for details).

8.2.4. Safety Results

In the overall integrated safety population, 99% of patients experienced at least one AE, and of those, Grade 3-4 events were experienced in 60%. The most frequently reported AEs (see Table 59) were fatigue (48%), constipation (46%), dysgeusia (44%), dizziness (38%), edema (40%), diarrhea (35%), nausea (34%), dysesthesia (34%), dyspnea (30%), cough (24%), cognitive impairment (27%), peripheral sensory neuropathy and headache (18% each), ataxia (17%) and mood disorders (10%). The most frequently reported Grade 3-4 AEs (see Table 57) were anemia (9%), increased weight (7%), dyspnea (6%), fatigue/asthenia (5%), pneumonia, pulmonary embolism, hypoxia, and AST increased (each 3.4%), cognitive impairment (4.5%), pleural effusion and AST increased (each 3.1%), hypotension/orthostatic hypotension and hypophosphatemia (each 2.8%), neutropenia and syncope (each 2.5%), UTI (2.3%), diarrhea, hypokalemia, hyponatremia, and lipase increased (2.0%).

An overview of the safety profile in patients treated with entrectinib in the overall integrated safety population (n=355) is provided below in Table 48.

Table 48: Overview of Safety Profile in Integrated Safety Population

	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult non*NTRK*, non*ROS1* (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Patients with AE (%)	100	100	99	100	99
Patients with treatment related AE (%)	100	100	98	100	99
Patients with SAE (%)	47	37	40	13	39
Patients with related SAE (%)	10	13	5	6	9
Patients with ≥Grade 3 AE (%)	74	61	56	50	61
Patients with AE leading to discontinuation (%)	13	9	6	6	9
Patients with AE leading to dose reduction (%)	41	34	16	25	28
Patients with AE leading to drug interruption (%)	56	45	43	38	46
Patients with AE leading to death (%)	9	7	4	0	6

Source: Reviewer generated table based on AAE.xpt. Derivation: Variables: BASKGRP3, AEOUT, AEACN, AETOXGR,AESER, AETRTEM (treatment emergent flag) AEACN, AEREL, AESHOP

Deaths

There were 20 patients (6%) who died (Grade 5) due to an AE within 30 days of last dose of entrectinib. The causes of death in >2 patients were acute respiratory failure, cardiorespiratory arrest, dyspnea, meningeal metastases, pneumonia, sepsis/septic shock (Table 50).

Table 49: Overview of Deaths in Entrectinib Trials

Cause of Death	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non*NTRK*, non*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total no. of deaths (%)	22 (32)	29 (22)	37 (27)	5 (31)	93 (26)
Total no. of deaths due to AE	6 (9)	9 (7)	5(4)	0 (0)	20 (6)
Death < 30 days of last dose					
Total	8 (12)	21 (16)	17(12)	2 (13)	48 (14)
PD	4 (6)	15 (11)	11(8)	2(3)	32 (9)
Other	4 (6)	3 (2.2)	1 (0.7)	0	8(2.3)
Unknown	0	3 (2.2)	5 (3.6)	0	8(2.3)
Death > 30 days of last dose					
Total	14 (21)	8(6)	20 (15)	3 (19)	45 (13)
PD	12 (18)	7 (5)	12 (9)	3 (19)	34 (10)
Other	1 (1.5)	1 (0.7)	8(6)	0	10 (3)
Unknown	1(1.5)	0	0	0	1 (0.3)

Source: Reviewer generated table based on Dataset AAE.xpt. Derivation: Variables: BASKGRP3, AEOUT

Clinical Reviewer Comment: *There were no deaths evaluated by the investigator to be attributed to an AE. See comment below after Table 50 and Table 51 for further comment of reviewers attribution.*

Table 50: Adverse Event Resulting in Death

Preferred Term	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non*NTRK*, non*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total number (%)	6 (9)	9 (7)	5 (4)	0 (0)	20 (6)
Acute Respiratory Failure	2 (3)	0 (0)	1 (0.7)	0 (0)	2 (0.6)
Cardio-respiratory Arrest	2 (3)	0 (0)	0 (0)	0 (0)	2 (0.6)
Dyspnea	0 (0)	1 (0.7)	1 (0.7)	0 (0)	2 (0.6)
Meningeal Metastases	0 (0)	2 (1.4)	0 (0)	0 (0)	2 (0.6)
Pneumonia	1 (1.5)	1 (0.7)	0 (0)	0 (0)	2 (0.6)
Sepsis/Septic Shock	1 (1.5)	1 (0.7)	1 (0.7)	0 (0)	3 (0.9)
Cardiogenic Shock	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Cerebral Infarction	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Completed Suicide	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)
Large Intestine Perforation	0 (0)	1(0.7)	0 (0)	0 (0)	1 (0.3)
Pulmonary Embolism	0 (0)	1 (0.7)	0 (0)	0 (0)	1(0.3)
Tumor Lysis Syndrome	0 (0)	0 (0)	1 (0.7)	0 (0)	1 (0.3)

Source: Reviewer generated table based on Dataset AAE.xpt. Derivation: Variables: BASKGRP3, AEOUT, AEDECOD

The reviewer conducted analyses of the narrative summaries and AEs to verify the cause of death described by Genentech for all deaths that occurred within 30 days of the last dose of entrectenib, presented in Table 51.

Table 51: Patient Narratives of Death due to Adverse Event

Patient ID/Study/Dose/ Treatment Dates	Death AE PT	Narrative
(b) (6) /ALKA/Schedule B, 400mg/m^2/day, (b) (6) - (b) (6)	Pulmonary Embolism	67-year-old female patient with *ROS1* NSCLC experienced abdominal pain on treatment D569. CT abdomen revealed fluid collection and diverticulitis. On D579, abdominal pain continued and CT scan chest revealed pulmonary embolism. Patient expired same day.
(b) (6) /RXDX-101/600mg/day, (b) (6) - (b) (6)	Tumor Lysis Syndrome	28-year-old male patient with widespread metastatic sarcoma was hospitalized on treatment D15 for fatigue, lethargy, with decreased urine output. Labs revealed increased ALT, AST, bilirubin, creatinine, uric acid, PT, PTT, INR and anemia. Uric acid was 11.5mg/dl. Entrectinib was discontinued. Patient was stabilized and improved. On D20, patient developed acute respiratory failure, shock and acidosis. Patient was started on dialysis, pressors, and BIPAP. On D23 patient condition deteriorated and expired the same day.
(b) (6) /RXDX-101-01/600mg/day, (b) (6) (b) (6)	Large Intestine Perforation	64-year-old male patient with metastatic *ROS1* NSCLC was hospitalized on treatment on D29 for dyspnea and fever. CXR revealed large pneumoperitoneum, CT abdomen revealed sigmoid diverticulitis and perforation. On D30 patient underwent exploratory laparotomy and weaned off the ventilator. Patient died on D36.
(b) (6) /RXDX-101-01/700mg/day, (b) (6) (b) (6)	Hypoxic Respiratory Failure	50-year-old female patient with metastatic breast cancer became restless, agitated on treatment D7 and pleural effusion was drained. Received her last dose of entrectinib on D8 and arrived at study site lethargic and hypotensive. On D9 was hospitalized for mental status changes, increasing SOB. CXR revealed pulmonary edema, right pleural effusion. Effusion was drained every other day. On D15 patient was transitioned to hospice and died due to hypoxic respiratory failure secondary to metastatic breast cancer.
(b) (6) /RXDX-101-01/ 400mg/m2/day, (b) (6) (b) (6)	Worsening dyspnea, Pulmonary embolism	59-year-old female patient with metastatic *ALK+* NSCLC discontinued entrectinib on D 88 due to disease progression. On D92 was hospitalized for hypoxia during a red blood cell transfusion. CT revealed bilateral pulmonary embolism and bilateral pleural effusion. On D104 patient was discharged. On D114 patient was admitted for serious dyspnea and noted to have increasing pleural effusion Patient

Patient ID/Study/Dose/ Treatment Dates	Death AE PT	Narrative
		condition deteriorated and transitioned to hospice. On D120 patient died due to disease progression.
(b) (6) /RXDX-101-02/600mg/ day, (b) (6) (b) (6)	Pneumonia	58-year-old male patient with metastatic NSCLC with extensive lung metastases was hospitalized for bilateral peripheral edema and hypotension on treatment D14. Noted to have grade 3 pericardial effusion and grade 2 CHF with normal EF. Drug discontinued on D16. On D21, patient underwent pericardiocentesis and the fluid was not malignant. On D37 patient was diagnosed with Grade 4 pneumonia and continued hospitalization. On D43 patient died due to grade 5 pneumonia.
(b) (6) /RXDX-101-02/600mg/ day, (b) (6) (b) (6)	Dyspnea	43-year-old female patient with metastatic NSCLC with extensive mets was hospitalized on D28 for worsening dyspnea (Grade 3). Last dose was D28. Patient died on D55 due to dyspnea and respiratory failure related to underlying metastatic disease.
(b) (6) / RXDX-101-02/ 600mg/ day, (b) (6) (b) (6)	Cerebral Infarction	34-year-old female patient with metastatic NSCLC was hospitalized on D16 for worsening pyrexia and grade 3 neutropenia. On D16 entrectinib was interrupted. On D24 a CT head revealed grade 4 subarachnoid hemorrhage that was drained on D25. On D28 patient experienced grade 4 bilateral cerebral infarction. On D37 patient died due to grade 5 cerebral infarction. The death was attributed to underlying metastatic disease.

Source: Reviewer generated table based on narratives from each CSR submitted to NDA Module 5.3.5.2

One fatal event of large intestine perforation was reported in a patient (b) (6) /RXDX-101-01 with concurrent diverticulitis; the fatal perforation was attributed to the co-morbid condition of diverticulitis.

Patient (b) (6) /RXDX-101 died from tumor lysis syndrome, which is attributed to entrectenib as the patient was not receiving any other concomitant anti-neoplastic treatment. The patient had advanced disease and multiple prior lines of systemic cancer therapy before being treated with entrectenib, and heavy tumor burden at baseline with numerous metastases with increasing size at the time of the event. The investigator assessed the event as not related to entrectinib but related to tumor burden and disease treatment.

One patient committed suicide in the hospital subsequent to confirmation of disease progression. Given the documented CNS effects of entrectinib, this event is possibly/probably attributable to entrectinib.

Two patients reported fatal events of metastases to meninges, both of which were considered by the investigators as related to progression of the underlying disease.

Fatal events of sepsis or septic shock occurred in three patients; these patients had a past medical history of sepsis, previous hospitalization or intensive care unit admission, or cancer as risk factors.

One fatal event of cerebral infraction was reported in a patient with a medical history of deep vein thrombosis and a concurrent event of subarachnoid hemorrhage. The event was considered to be secondary to the patient's underlying hypercoagulable state due to lung cancer.

One fatal case of cardiogenic shock was reported in a patient with NSCLC due to pericardial effusion and pericardial tamponade. The patient developed cardiogenic shock two days after starting entrectinib and died, and it was noted that the patient had suspected pericardial, bilateral pleural, omental and peritoneal carcinomatosis at baseline, as well as diffused lung, liver, and bone metastases. Although entrectinib cause a decrease in ejection fraction, the presence of pericardial metastases make attribution to disease more likely.

Clinical Reviewer comment: The reviewers conducted analyses of the narrative summaries and AE listings to verify the cause of death provided by Genentech for all deaths attributed to a TEAE or that occurred within 30 days of the last dose of study therapy regardless of attribution. The majority of Grade 5 AEs were reported in the context of worsening of underlying diseases or complications of the underlying malignancy. None of the 20 deaths due to AE were assessed by the investigator as being related to entrectinib. While the reviewers agree that the majority of deaths are unlikely to be related to entrectinib, due to the single arm nature of these studies and temporal relationship between the onset of death and initiation of entrectinib in some cases, it is possible that there is a causal relationship for entrectinib in some of these deaths. Additionally, FDA does not agree with the attribution of certain fatal events as noted above. Therefore, the package insert will include information regarding all Grade 5 AEs (deaths).

Serious Adverse Events

The protocols defined a serious adverse event (SAE) as an adverse event that meeting one of the following criteria, in accordance with 21 CFR 312.32(a):

- Resulted in fatality (i.e., the adverse event actually causes or leads to death)
- Was life threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death)
- Required or resulted in prolongation of inpatient hospitalization
- Resulted in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Caused a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Was a significant medical event in the Investigator's judgment (e.g., that jeopardized health of the patient or required medical/surgical intervention to prevent one of the outcomes listed above)

The SAE definition did not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.

The analyses of SAEs presented by Genentech are based on the adverse event dataset and include the overall analysis safety population using the data included in the NDA submission for patients who reported an AE that met any of the serious criteria, whether or not the event was judged to be related to study drug.

SAEs occurred in 39% patients; the most frequently reported SAEs (in >1 % of patients) by MedDRA System Order Class (SOC) were: respiratory and mediastinal disorders (13%), infections (10%), nervous system and psychiatric disorders (10%), cardiac disorders (4%), general disorders (4%), gastrointestinal (4%) and vascular disorders (2%) (Table 52). The most frequently reported AEs by preferred term (PT) were dyspnea (4%), pneumonia (3.9%), pleural effusion (3%), pulmonary embolism (2%), acute respiratory failure (2%), and pyrexia (2%). SAEs were less common among pediatric patients compared to the adult population.

The majority of the SAEs in the “respiratory thoracic and mediastinal disorders” SOC were reported in patients with primary lung cancer or with secondary lung metastasis. The most frequently reported (≥ 2% of patients) PTs in this SOC included dyspnea (3.7%), pleural effusion (3.4%), and pulmonary embolism (2.3%), as pneumonia was listed under the “infections and infestations” SOC, described below.

The most frequently reported PTs (≥ 2% of patients) in the “infections and infestations” SOC was pneumonia (3.9%). Other respiratory infections included upper respiratory tract infection (0.6%), lung infection (0.6%), lower respiratory tract infection (0.3%). The majority of respiratory infections were reported in patients with primary lung cancer or with secondary lung metastasis.

SAEs in the nervous system disorders SOC occurred in 10% of patients, and the most frequently reported PT was cognitive disorder (1.4%). Other SAEs in this SOC (occurring in ≥ 2 patients) included syncope (0.8%), ataxia (0.6%), and dizziness (0.6%), which were consistent with the CNS activity of entrectinib and the known association of TRK receptor involvement in the nervous system. Other nervous system SAEs (occurring in ≥ 2 patients) included hydrocephalus (0.8%) and seizure (0.8%); the patients with these events were noted to have brain metastases at baseline.

No particular pattern by timing or duration of AE were observed in the type and frequency of SAEs reported with the exception of fractures (discussed further below). A smaller proportion (12.5%) of pediatric patients experienced SAEs compared to adults; however given the limited number of patients, a conclusion cannot be made regarding whether there are differences in the safety profile based on age. There was no specific SAE with an incidence that was ≥ 4%.

Table 52 provides a summary of the per-patient incidence of SAEs regardless of causality by SOC and PT in order of decreasing frequency.

Table 52: Serious Adverse Events by System Organ Class and Preferred Term (>1% total incidence)

SOC/Preferred Term	*NTRK* Adult n=68 (%)	*ROS1* NSCLC Adult n=133 (%)	Other Adult non*NTRK*, non*ROS1* n=137 (%)	Pediatric n=17 (%)	All n=355 (%)
Total n (%)	32 (47)	50 (37)	53 (39)	2 (13)	137 (39)
Respiratory and Mediastinal disorders	11 (16)	16 (12)	17 (12)	2 (13)	46 (13)
Dyspnea	2 (2.9)	6 (4.5)	5 (3.6)	0	13 (3.7)
Acute respiratory failure/respiratory distress	3 (4.4)	0	4 (2.9)	0	7 (2)
Pleural Effusion	3 (4.4)	5 (3.7)	3 (2.1)	2 (13)	12 (3.4)
Pulmonary embolism	2 (2.9)	3 (2.2)	3 (2.1)	0	8 (2.2)
Infections and Infestations	11 (16)	13 (10)	11 (8)	1 (6)	36 (10)
Pneumonia	2 (2.9)	2 (1.5)	10 (7)	0	14 (3.9)
Sepsis	2(2.9)	1 (0.7)	6 (4.4)	0	9 (2.5)
Nervous System Disorders and Psychiatric Disorder	8 (12)	16 (12)	11 (8)		35 (10)
Cognitive disorder	1 (1.5)	2(1.5)	2 (1.4)		5 (1.4)
Syncope	0 (0)	2 (1.5)	1 (0.7)		3 (0.8)
Ataxia	1 (1.5)	1 (0.7)	1 (0.7)		3 (0.8)
Dizziness	1 (1.5)	1 (0.7)	0		2 (0.6)
Mental status changes/confusion	1 (1.5)	2 (1.5)	3 (2.1)		5 (1.4)
Depression	1 (1.5)	0	0		1 (0.3)
Cardiac Disorders	5 (7)	6(4.5)	2 (1.4)		13 (3.7)
Vascular disorder	2 (2.9)	3(2.2)	2 (1.4)		7 (2)
Hypotension	2 (2.9)	3(2.2)	1		6 (1.7)
Gastrointestinal Disorder	0	4 (3)	10 (7)		14 (4)
General Disorders and administration site	2 (2.9)	6 (4.4)	7 (5)		15 (4.2)
Pyrexia	0	4 (3)	3 (2.1)		7 (2)

Source: Reviewer generated table based on dataset AAE.xpt. Derivation Variables: BASKGRP3, AESER, AETERM,AEBODYSYS, AEDECOD

Patient narratives for selected SAEs (not inclusive of patient deaths, Grade ≥ 3 AEs, in which the reader should refer to those sections in 8.2.4) are presented in Table 53.

Table 53: Selected Patient Narratives for Serious Adverse Events

Patient ID/Study/Dose/ Treatment Dates	SAE AE PT	Narrative
(b) (6) /ALKA/Schedule A, 200mg/m^2/day, 400mg/m^2/day	Pneumonia Grade 3 Confusion Grade 3	60-year-old male patient with NSCLC was admitted on treatment D341 for pneumonia and Grade 1

Patient ID/Study/Dose/ Treatment Dates	SAE AE PT	Narrative
(D114), 800 mg/m^2/day (D318) (b) (6)		confusion. On D348 was discharged and on D365 was noted to have Grade 3 confusion and admitted for low BP and confusion. Drug was interrupted between D365 to D389. On D370, confusion and pneumonia had resolved and patient was discharged and entrectinib was resumed on D390.
(b) (6) /ALKA/Schedule B, 600mg/day; (b) (6)	Hydrocephalus Grade 3	41-year-old female with metastatic GBM was hospitalized on D20 for decreased level of consciousness. CT revealed hydrocephalus and progression of GBM and had a valve placed. Last dose of Entrectinib was D20. Patient died on D30 due to progression of disease. Hydrocephalus did not resolve.
(b) (6) /ALKA/Schedule B, 400mg/m2/day; (b) (6) - (b) (6)	Syncope Grade 3	67-year-old male with metastatic NSCLC was hospitalized on D385 for an episode of post-micturition syncope the day prior. Patient continued the drug until D456, and had no additional episodes of syncope.
(b) (6) / RXDX-101/, 600mg /day; (b) (6)	Hyponatremia Ventricular extrasystoles	55-year-old female with metastatic HNSCC was admitted on D19 for worsening dyspnea, generalized edema, fever and urinary incontinence. Labs revealed a sodium of 127 mmol/L (normal at baseline) and hypomagnesemia. EKG revealed ventricular extrasystoles. Patient was stabilized and discharged on D23. On D33 her sodium was 139mmol/L and entrectinib was restarted at reduced dose of 400 mg/day. On D43 patient experienced ventricular extrasystoles with no symptoms and entrectinib was discontinued.
(b) (6) / RXDX-101/, 800mg/day; (b) (6)	Hip Fracture	72-year-old female with metastatic ovarian cancer experienced fatigue starting D12, and on D14 entrectinib was skipped due to intolerable fatigue. On D31 patient fell and x-ray revealed a right hip stress fracture. On D32, underwent right hip arthroplasty and intramedullary rod placement. Biopsy of right femoral head revealed no tumor, marrow edema, mild fibrosis, fat necrosis, osteoclastic activity and reactive new bone formation.
(b) (6) / RXDX-101/, 600mg/day; (b) (6)	Altered mental status Ataxia Febrile Neutropenia	67-year-old female with *ALK+* NSCLC experienced significant weight gain, dizziness on D7 and drug was interrupted. On D8 patient was admitted with mental status changes and ataxia. On admission was noted to be febrile. Head CT was normal. With symptomatic treatment with intravenous fluids and interruption of entrectinib, the mental status changes and ataxia resolved on D10. On D14 entrectinib was restarted at 200 mg/day without recurrence of similar symptoms. On D380 patient was hospitalized for neutropenic fever and treated with antibiotics and drug was

Patient ID/Study/Dose/ Treatment Dates	SAE AE PT	Narrative
		interrupted. WBC recovered on D382. Patient was taken off study on D499 for disease progression.
(b) (6) / RXDX-101-02/, 600mg/day; (b) (6)	Dizziness	43-year-old male with metastatic MASC experienced Grade 1 dizziness on D115 that worsened to Grade 2 on D131 and Grade 3 on D154, with Grade 2 ataxia. Patient was noted to have Grade 3 syncope on the same day. CT head was negative, Holter was negative for arrhythmias. On D 169 drug was interrupted and on D171 dizziness resolved. Entrectinib was restarted on D176 at a reduced dose (400mg). Grade 1 dizziness remained ongoing.

Source: Reviewer generated table based on narratives submitted to each CSR NDA Module 5.3.5.2

Clinical Reviewer Comment: *In general, this reviewer considers the attributions of the SAEs by the investigator generally accurate. The majority of SAEs appear to be either wholly or in part attributed to the underlying cancer diagnosis and disease progression, or common complications of cancer therapy, with those SAEs possibly related to the drug described above. Because attribution may be unreliable in single arm trials, these data are described in the package insert for entrectinib.*

Treatment Interruptions, Dose Reductions and/or Discontinuations Due to Adverse Effects

Of the 259 patients (73%) off-treatment at the time of database cutoff (31 May 2018), the most common reason for discontinuation was disease progression (n=197, 76%) with 12% of patients (n=30) discontinuing due to an AE.

Table 33 summarizes the reasons for discontinuation of entrectinib for the 54 patients in the *NTRK* efficacy population using the data cutoff date for the original NDA submission, for all efficacy-evaluable patients with *NTRK* fusion tumors enrolled across the four trials and for the overall safety analysis population (both with and without documented *NTRK* fusion tumors).

AEs requiring discontinuation of study drug treatment across all entrectinib trials occurred in 9% of patients (Table 54). The most common reasons for treatment discontinuation (in ≥ 1% of patients by SOC) were respiratory and mediastinal disorders (2%), cardiac disorders (2%) and infections (1%). Table 54 summarizes AEs leading to discontinuation of entrectinib in all patients.

Table 54: Adverse Events Leading to Drug Discontinuation in ≥ 1% Patients

SOC/Preferred Term	*NTRK* Adult (n=68)	*ROS1* NSCLC Adult (n=133)	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric (n=17)	All (n=355)
Total %	13	9	6	6	9
Respiratory and Mediastinal disorders					
Total	3	2	0.7	6	2.0
Dyspnea	0	0.7	0	6	0.6
Acute respiratory failure	3	0	0	0	0.6
Pneumonitis	0	0.7	0	0	0.3
Pulmonary edema	0	0	0.7	0	0.3
Pulmonary embolism	0	0.7	0	0	0.3
Cardiac Disorders					
Total	4.4	1.5	1.5	0	2.0
Cardio-respiratory arrest	2.9	0	0	0	0.6
CHF	1.5	0	0	0	0.3
A Fib/Extrasystoles	0	0	0.7	0	0.3
Myocarditis	0	0.7	0	0	0.3
Cardiogenic shock	0	0.7	0	0	0.3
Pericardial Effusion	0	0.7	0	0	0.3
Infections and Infestations					
Total	3	0.7	0.7	0	1.1
Pneumonia/Lower RTI/Lung infection	1.5	0.7	0.7	0	0.8
Sepsis	1.5	0	0	0	0.3
General disorders and administrative site conditions					
Total	1.5	0.7	1.5	0	1.1
Fatigue	1.5	0	0.7	0	0.6
Malaise	0	0	0.7	0	0.3
Peripheral edema	0	0.7	0	0	0.3

Source: Reviewer generated table based on Dataset AAE.xpt. Derivation Variables: BASKGRP3, AEOUT, AETERM,AEBODYSYS, AEDECOD; A Fib=atrial fibrillation, RTI=respiratory tract infection

AEs requiring treatment interruption occurred in 46% of patients. The most common reasons for dose interruption (in >2% of patients) were increased creatinine (4%), fatigue (4%), anemia (3%), diarrhea and pyrexia (each 3%), dizziness (3%), nausea (2%), dyspnea (2%), pneumonia (2%), cognitive disorder (2%), and neutropenia (2%). Table 55 describes leading to dose interruption that occurred in at least 1% of patients that received entrectinib.

Table 55: Adverse Events Leading to Treatment Interruption in ≥ 1% of Patients

Preferred Term	*NTRK* Adult n=68	*ROS1* NSCLC Adult n=133	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric n=17	All n=355
Total %	56	45	43	38	46
Increased creatinine/AKI	6	4	1.5	12.5	3.9
Fatigue	7	1.5	4	6	3.7
Anemia	9	0	4	0	3.1
Diarrhea	3	2	3	6	2.8
Pyrexia	3	2	4	0	2.8
Dizziness	1.5	5	0.7	0	2.5
Nausea	4	1.5	2	0	2.3
Dyspnea	3	3	1.5	0	2.3
Pneumonia	3	2	3	6	2.3
Cognitive disorder	0	4.5	0.7	0	2.0
Neutropenia	0	0.7	1.5	6	2.0
AST increase	3	1.5	1.5	0	1.7
Pleural Effusion	1.5	3	0.7	0	1.7
Vomiting	0	1.5	3	6	1.4
ALT increase	3	1.5	0.7	0	1.4
Lipase increase	0	0.7	3	0	1.4
UTI	1.5	1.5	1.5	0	1.4
Peripheral edema	1.5	2	0	0	1.1
Ataxia/fall/gait disturbance	4	2	3	0	1.1
Confusional state/Mental Status change	1.5	0.7	3	0	1.1
Decreased appetite	1.5	0	1.5	0	1.1
Hypotension	0	0	0.7	0	1.1
Hypoxia	4	0	0	0	0.8

Source: Reviewer generated table based on dataset AAE.xpt. Derivation Variables: BASKGRP3, AEOUT, AETERM,AEBODYSYS, AEDECOD

AEs requiring dose reduction was seen in 28% of patients (Table 56). The most common reasons for dose reduction were dizziness (3.9%), increased creatinine (3.1%), fatigue (2.3%), anemia (1.7%), increased weight (1.4%), neurological disorders (ataxia, cognitive changes, peripheral sensory neuropathy, gait disturbance, mental status changes) in 1% of patients.

Table 56 shows AEs that led to dose reductions in at least 1% of patients.

Table 56: Adverse Events that Led to Dose Reduction in ≥ 1% of Patients

Preferred Term	*NTRK* Adult (n=68)	ROS1 NSCLC Adult (n=133)	Other Adult non*NTRK*, non*ROS1* (n=137)	Pediatric (n=17)	All (n=355)
Total %	41	34	16	25	28
Dizziness	4.4	6	2.2	0	3.9
Increased creatinine	6	4	0.7	6	3.1
Fatigue	6	2	0.7	0	2.3
Anemia	7	0	0.7	0	1.7
Increased weight	1.5	0.7	0.7	6	1.4
Ataxia/ Gait disturbance/balance disorder	3	3	1.5	0	1.0
Cognitive disorder	1.5	2	0	0	1.0
Peripheral sensory neuropathy/paresthesia/peripheral neuropathy	3	4	1.5	0	1.0
Gait disturbance	3	0.7	0.7	0	1.0
Arthralgia	0	1.5	1.5	0	1.0
Confusional state/mental status change/somnolence/depressed level of consciousness /depression/agitation/disturbance in attention	1.5	4	1.5	0	1.0

Source: Reviewer generated table based on dataset AAE.xpt. Derivation Variables: AEACN, BASKGRP3, AEDECOD, USSUBJID

Dose interruptions and dose reductions due to AE occurred in 55% of patients. The most frequent adverse reactions (≥ 2%) that resulted in interruption were increased creatinine (6%), neutropenia (5%), fatigue (5%), dizziness (5%), anemia (4%), diarrhea (3%), pyrexia (3%), nausea (3%), dyspnea (3%), cognitive disorder (3%), pneumonia (2%), ataxia (2%), AST increase (2%), confusional state (2%), hypotension (2%) and pleural effusion (2%) and increased weight (2%).

Clinical Reviewer Comment: The reasons for discontinuation of entrectinib are primarily attributable to progressive disease, which is often seen in clinical trials in oncology. The reasons for discontinuation due to AE are summarized in Table 54 and the total incidence (9%) is relatively low and similar to other drugs approved for a refractory cancer population. It is difficult to reliably assess attribution of any specific event to entrectinib given the single arm nature of the trials providing safety data. Dose modifications are outlined in the package insert for the most common and serious AEs.

Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of SAEs also be considered significant AEs. These laboratory abnormalities are described in the Laboratory Findings section of this review.

In addition, the ICH E3 guidance considers other potentially important abnormalities, such as severe AEs (i.e., adverse events of ≥ Grade 3 severity as graded by the NCI CTCAE criteria that do not meet the definition of a serious AE) as potentially significant.

Grade 3-4 AEs

Grade 3 or 4 adverse reactions occurred in 60% of patients; the most common (≥2%) were lung infection (6%), increased weight (7%), dyspnea (6%), fatigue (5%), cognitive impairment (4.5%), syncope (2.5%), pulmonary embolism (3.4%), hypoxia (3.4%), pleural effusion (3.1%), hypotension (2.8%), diarrhea (2%), and urinary tract infection (UTI) (2.5%). One patient developed Grade 4 myocarditis after one dose of entrectinib, confirmed by myocardial biopsy and cardiac magnetic resonance imaging (MRI), which resolved after discontinuation of entrectinib and administration of high-dose corticosteroids. Grade 3-4 laboratory abnormalities will be discussed in "Laboratory Findings." See the clinical reviewer comment below regarding attribution of adverse events.

Interpretation of the causality of adverse events related to increased weight was challenging due to the single arm design of the entrectinib clinical trials and presence of confounding factors. Two percent had an adverse reaction of increased appetite (none were Grade 3-4). Additionally, 2.3% percent of patients had an adverse event of decreased weight with 0.6% having Grade 3 weight loss, and 13% of patients had an adverse reaction of decreased appetite, 0.3% of which was Grade 3. See "**Weight gain**" in Section 8.2.5 AESI below for further details.

Table 57: Grade 3-5 AEs in ≥ 2% of patients in Safety Population

Preferred Term	Grades 3-5
N =355	%
Anemia	9
Neutrophil Count Decreased	7
Hypophosphatemia	7
Weight increased	7
Lung Infection	6
Dyspnea	6
Fatigue/Asthenia	5
Cognitive Impairment	4.5
Alanine aminotransferase increased	2.9
Hypotension	2.8
Aspartate aminotransferase increased	2.7
UTI	2.3
Diarrhea	2

Source: Reviewer generated table from dataset AAE submitted to NDA Module 5.3.5.3 (ISS) variables AETOXGR, USUBJID, and AEDCOD.

Clinical Reviewer Comment: Grade 3-4 adverse events are discussed throughout the review. The related preferred terms fatigue and asthenia were combined to calculate the incidence of significant fatigue, which has a similar incidence compared to other drugs approved for the treatment of solid tumors. Lung infections were inclusive of multiple PTs: lower respiratory tract infection, lung infection, pneumonia, respiratory tract infection, and the incidence reflects the underlying population of patients with NSCLC, lung metastases, and cancer, which confers susceptibility to infection due to prior chemotherapy and decreased immunity. Dyspnea and hypoxia were also seen in the setting of lung infections and patients with NSCLC. Pulmonary embolism could also be attributed to patients' underlying cancer, which increases the risk of embolic events. Adverse events of increased and decreased weight occurred in patients treated with entrectinib and a causal relationship for entrectinib is biologically plausible based on its mechanism of action of TRK inhibition. However, due to the single arm nature of the entrectinib

trials, cofounding factors such as comorbidities, and small sample size, it was difficult to ascertain the extent to which the changes in weight observed were related to entrectinib or other factors. In some cases, it is also difficult to decipher if the increased weight was due to decreased food consumption/caloric intake vs. fluid retention and respiratory issues (about half of the patient narratives describe fluid retention due to respiratory issues like pneumonia in the setting of NSCLC while the other appear to be pure increased weight). Increased food consumption and increased weight was observed in toxicology studies of entrectinib in rats, which is consistent with the observed effects of Trk inhibition in animals and humans with deficiencies in TrkB signaling. Thus, it is likely that the observed increased weight in some patients was related to entrectinib. Changes in weight are also discussed in the section of this review discussing AESI. Cognitive effects, further discussed in the AESI section of this review, appear to be due to the mechanism of action of the drug, given that entrectenib crosses the blood:brain barrier. Hypotension, which is also discussed in in the AESI section of this review, was often observed concomitantly with other AEs such as dehydration, diarrhea, vomiting, acute infections, and cardiac events. Some cases of hypotension occurred with syncopal episodes.

Treatment Emergent Adverse Events and Adverse Reactions

The overall safety database (N=355) was analyzed at each level of the MedDRA hierarchy for common AEs. The tables in this section summarize the incidence of treatment-emergent adverse events (TEAEs), defined as AEs that occurred from the time of the first dose until 30 days (28 days for ALKA: see prior comment in Section 8.2.3) following the last dose of entrectinib. Almost all patients in the safety analysis population (99%) had at least one AE during treatment with entrectinib. Sixty-one percent of patients had 1 or more AEs that were severe (CTCAE Grade 3 or greater); 60% had Grade 3-4 AEs. See Table 48 and Table 58 for further details.

Table 58: Summary of Adverse Events

	***NTRK* Adult (n=68)**	***ROS1* NSCLC Adult (n=133)**	**Other Adult non*NTRK*, non*ROS1* (n=137)**	**Pediatric (n=17)**	**All (n=355)**
Patients with AE (%)	100	100	99	100	99%
Patients with SAE (%)	47	37	40	13	39
Patients with ≥Grade 3 AE (%)	74	61	56	50	61

Source: Reviewer generated table modified from Table 48.

The reviewers analyzed common TEAEs in the overall safety analysis dataset submitted in the original NDA based upon system organ class (SOC), high-level term (HLT), high-level group term (HLGT), and referred term (PT) levels of the MedDRA hierarchy.

TEAEs were most common in the following SOCs: nervous system disorders (84%),

gastrointestinal disorders (82%), and general disorders and administration site conditions (78%).

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders.

Table 59 provides a summary of the per-patient incidence (PPI) of AEs by SOC for AE with a PPI of ≥ 10%.

Table 59: Adverse Events by Preferred Term ≥ 10% Incidence

Adverse Event	Entrectinib 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
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

Adverse Event	Entrectinib N=355	
	All Grades (%)	Grade ≥ 3 * (%)
Metabolism and Nutritional		
Increased Weight	25	7
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 hypoaesthesia, palmar-plantar erythrodysaesthesia, oral paresthesia, genital hypoaesthesia
[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
[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

Source: Modified draft label July 2, 2019 from applicant; package insert. Reviewers verified data from Datasets AAE from NDA Module 5.3.5.3 (ISS Analysis legacy datasets)

Clinical Reviewer Comment: composite terms that were negotiated with Genentech are defined in the footnotes to the above table.

Laboratory Findings

During the review, FDA requested additional information from Genentech to evaluate the cause of the high frequency of laboratory abnormalities in the laboratory dataset including both low and high values outside of the normal range (IR-23, 22 March 2019). Genentech performed a review of the abnormal laboratory values and stated that the majority of the apparent abnormal laboratory readings noted in the dataset occurred as a result of reporting variations in laboratory units, or transcription errors. Genentech additionally clarified that the majority of abnormal laboratory readings were discovered to be within the normal ranges provided by the site upon further investigation. A few patients with abnormal laboratory values had concomitant medications or comorbidities that could potentially have contribute to the abnormal laboratory values.

The majority of patients who experienced post baseline shifts in hematology parameters had shifts to Grade 1 or 2. Few patients had clinically relevant shifts (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) with the most common being Grade 3 anemia (9%) and Grade 3 neutropenia (7%).

The majority of patients who experienced post baseline shifts in chemistry parameters had shifts to Grade 1 or 2. Few patients had clinically relevant shifts (defined as change from Grade 0, 1 or 2 at baseline to Grade 3 or 4 post-baseline) with the most common being Grade 3 hypophosphatemia (12%), Grade 3 hyponatremia (4%) and Grade 3 hypoalbuminemia (3%).

In the integrated safety population based on the adverse event dataset, hyperuricemia reported as an adverse event occurred in 9% (32/355) of patients. The majority of these events (26/32, or 81% of events) were Grade 1, meaning the patient had an elevation of uric acid with no physiologic consequence. No Grade 2 or Grade 3 hyperuricemia events were reported. Grade 4 elevation in uric acid was reported in 6 patients (1.7%), none of which were categorized serious events (although one case of Grade 4 hyperuricemia that can be reasonably attributed to entrectinib occurred in a patient with tumor lysis syndrome, who ultimately died). All except one Grade 4 hyperuricemia resolved at the time of the data cutoff date. The median time to increase in uric acid was 0.9 months (range: 1 day to 14 months). Among 32 patients with an adverse event of hyperuricemia, 34% (11/32) required interventions to reduce uric acid levels, 6% (2/32) required dose reduction, 6% (2/32) required dose interruption, and no patient discontinued entrectinib due to hyperuricemia. Hyperuricemia resolved in 73% of patients following initiation of uric acid-reducing medication without interruption or dose reduction of entrectinib.

The incidence of hyperuricemia as a laboratory abnormality per CTCAE v4.03 was reviewed by Genentech and FDA reviewers. Hyperuricemia was defined per CTCAE v4.0 and v4.03 as follows:

- Grade 1: uric acid > ULN -10 mg/dl (0.59 mmol/L) WITHOUT physiological consequences
- Grade 3: uric acid > ULN -10 mg/dl (0.59 mmol/L) WITH physiological consequences
- Grade 4: uric acid >10 mg/dl; >0.59 mmol/L; life-threatening consequences.

In order to differentiate Grade 3 elevations in uric acid (which require a physiologic consequence) from Grade 1 elevations in uric acid, Genentech reviewed the laboratory ALB dataset for hyperuricemia and cross referenced the adverse event AAE dataset and concomitant medications (ACM dataset) . Patients who had a peak post-baseline uric acid value of >ULN - 10 mg/dL (0.59 mmol/L) were considered to have a Grade 3 elevation of uric acid if both of the following criteria were met:

- Presence of a concurrent AE of “hyperuricemia” or “blood uric acid increased” reported with an onset date within +/- 30 days of lab abnormality
- Concomitant treatment with allopurinol within 30 days on or after the AE onset

At the data cutoff date for the NDA dataset (31 May 2018), there were 259 patients who had a baseline and post-treatment laboratory blood uric acid measurement. A total of 110 of 259 (42%) patients had a normal baseline uric acid level and at least one post-baseline uric acid level that was greater than the upper limit of normal but less than 10 mg/dL (0.59 mmol/L). Of these 110 patients, there were 11 patients reported as having an adverse event of “hyperuricemia” or “blood uric acid increased” in the AE dataset; all were non-serious events. Hyperuricemia was considered to have an adverse physiological consequence for 3 of the 11 patients with an adverse event of hyperuricemia due to initiation of treatment with allopurinol in response to the event; the remaining 8 patients did not require initiation of urate-lowering drugs or dosage modification of entrectinib. Therefore, Genentech defined 3 patients as having a Grade 3 change as the highest post-baseline increase in uric acid per CTCAE version 4.03 and 107 patients as having a Grade 1 elevation in uric acid levels as the highest post-baseline increase.

There were 17 patients (7%) with a normal uric acid level at baseline and at least one post-baseline uric acid value of >10 mg/dL (0.59 mmol/L), which is categorized as Grade 4 elevation of uric acid per CTCAE version 4.03. A total of 9 of these 17 patients had a concurrent adverse event of hyperuricemia recorded. In addition, there were 7 patients who had Grade 3 uric acid levels at baseline who developed Grade 4 elevation of uric acid on study. None of these events were serious or life threatening. Based on the above evaluation, there were 134/259 (52%) patients with hyperuricemia of any grade and a total of 27/259 patients (10%) that met the criteria for Grade 3 (n=3) or Grade 4 (n=24) hyperuricemia.

The majority of patients who experienced post-baseline shifts in liver laboratory parameters (AST increased, ALT increased, and bilirubin increased) had shifts to Grade 1 or 2. Few patients had clinically relevant shifts in liver laboratory parameters (defined as change from Grade 0, 1

or 2 at baseline to Grade 3 or 4 post-baseline). Grade 3 increase in ALT occurred in 3% of patients and Grade 3 increase in AST also occurred in 3%. The median time to onset of increased AST was 0.5 months (range: 1 day to 29.5 months). The median time to onset of increased ALT was 0.5 months (range: 1 day to 9.2 months). Increased AST leading to dose interruptions or reductions occurred in 10.5% and 1.8% of patients, respectively. Increased ALT leading to dose interruptions or reductions occurred in 10% and 2% of patients, respectively. No patients discontinued ROZLYTREK due to increased AST or ALT. There were no Hy's Law cases identified among the 355 patients in the safety database.

Overall, the incidence of liver laboratory abnormalities reported as AEs was higher in the pediatric analysis set compared to the overall adult population, primarily driven by a higher rate of increases in AST and ALT. Five (1.4%) patients in the integrated safety population had concurrent elevations ALT or AST (>3x ULN) and elevated total bilirubin (>2x ULN). Upon medical review, baseline liver metastasis or other confounding factors (such as medical history of liver disease or disease progression with new liver lesions) were reported in all 5 patients; as such, none of the liver enzyme abnormalities observed was suggestive of drug-induced liver injury (i.e., met the criteria for Hy's Law).

Table 60: Laboratory Abnormalities (>20%) Worsening from Baseline in Patients Receiving Entrectinib in ALKA, STARTRK-1, STARTRK-2, and STARTRK-NG

Laboratory Abnormality	Entrectinib NCI-CTCAE Grade N= 355[1]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Anemia	67	9
Lymphopenia	40	12
Neutropenia	28	7
Chemistry		
Increased creatinine[2]	73	2.1
Hyperuricemia[3]	52	8
Increased AST	44	2.7
Increased ALT	38	2.9
Hypernatremia	35	0.9
Hypocalcemia	34	1.8
Hypophosphatemia	30	7
Increased lipase	28	10
Hypoalbuminemia	28	2.9
Increased amylase	26	5.4
Hyperkalemia	25	1.5
Increased alkaline phosphatase	25	0.9
Hyperglycemia[4]	NE[3]	3.8
AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase		

Laboratory Abnormality	Entrectinib NCI-CTCAE Grade N= 355[1]	
	All Grades (%)	Grade 3 or 4 (%)

[1] Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available which ranged from 111 to 346 patients.
[2] Based on NCI CTCAE v5.0
[3] Based on NCI CTCAE v4.03 using laboratory dataset (ALB), adverse event dataset (AAE) and concomitant medication dataset (ACM)
[4] NE=Not evaluable. Grade 1 and 2 could not be determined per NCI CTCAE v5.0, as fasting glucose values were not collected.

Source: draft package insert label 2 July 2019. Reviewers verified data with dataset 1lb in NDA Module 5.3.5.3

Clinical Reviewer Comment: Because of the need for monitoring and intervention, hyperuricemia was included in the Warnings and Precautions (W&P) section of the entrectinib product label. If the incidence of truly life-threatening reactions is 1%, the database was too small (259 patients with baseline and follow up uric acid levels) to ensure that a life-threatening adverse event of hyperuricemia would have been observed. Additionally, 34% of the 32 patients with hyperuricemia adverse reactions required medical intervention to reduce uric acid levels; while the mechanism by which entrectinib results in increased uric acid levels is not known, one patient died of tumor lysis syndrome accompanied by Grade 4 uric acid elevation.

Increased ALT and AST was observed in this safety experience. Because the overall incidence is high (44% increased AST and 38% increased ALT), hepatotoxicity is a known risk of drugs inhibit the same target (TRK inhibitor; larotrectinib and ALK inhibitor; crizotinib), which have hepatotoxicity in the W&P sections of their respective product labels, and due to need for monitoring and potential dose medication, hepatotoxicity will also be included in the W&P section of the entrectinib product label.

Vital Signs

In the vital signs dataset, weight, body mass index, body surface area, height, heart rate, and blood pressure, both systolic and diastolic, were recorded. In the AE dataset, tachycardia, bradycardia, hypo- and hypertension, and weight increase and decrease were reported based on vital signs.

Clinically notable changes in vital signs included increased weight and hypotension, as discussed elsewhere in this review (Section 8.2.5 "**AESI**"). At the data cut- off date of May 31, 2018, AE of increased weight was reported for 25% (88/355) of patients. The majority of increases in weight were of Grade 2 severity (11% of patients), followed by Grade 1 (8% of patients). Increased weight increased of Grade 3 severity was reported in 6.5% of patients. Of the 88 patients with an AE of increased weight, most experienced increase in weight within 60 days of starting entrectenib. In the overall integrated safety population, 18% patients experienced AEs of hypotension, of which 3% experienced Grade 3 hypotension. SAEs of hypotension were reported in 1.7%. A total of 4.5% patients experienced AEs of hypertension, of which 5 patients

experienced Grade 3 hypertension. All events of hypertension were non-serious.

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Electrocardiograms (ECGs)

In Study STARTRK-2, ECGs were performed in triplicate and assessed by a central reader for all U.S. and Japanese sites. For all other sites, ECGs were performed locally and in singlicate. The protocols had baseline ECGs at screening. These ECG data could be collected up to 30 days prior to the first dose. The FDA reviewer examined the timing of ECG data collected at predose on Cycle 1 Day 1. The clinical reviewer confirmed that most predose samples were collected pre-dose and that the postdose samples were obtained ~4 h after dosing as planned per protocol. Overall, ECG data collected predose on Cycle 1 Day 1 could be used as the baseline for QT assessment.

QT

FDA's interdisciplinary review team for QT studies (QT-IRT) conducted a review of data. No large QTc prolongation effect (i.e., >20 ms) of entrectinib was observed in FDA's QT assessment of the ECG sub-study of patients (n=113) in Study STARTRK-2 (RXDX-101-02), an open-label, global Phase 2 study at the proposed therapeutic dose, 600 mg once daily (QD). The data was analyzed using a bytime central tendency analysis as the primary analysis, which did not suggest that entrectinib is associated with large mean increases in the QTc interval at times corresponding to $C_{max,ss}$ and $C_{trough,ss}$.

The data did not support an exposure response analysis because the exposure range is narrow and the PK/ECG sampling schedule could not be used to evaluate possible PK/PD hysteresis. One patient had QTcF > 500 ms and 4 patients had change in QTcF of > 60 ms. Genentech provided an integrated assessment of QTc categorical outliers across all 4 studies. Across these studies, patients were exposed to a range of doses from 100 mg to 2600 mg/day. According to Genentech's analysis, 11 of the 355 patients reported a maximum QTcF interval post-baseline >500 ms or maximum QTcF increase from baseline > 60 ms, as determined by single or triplicate measures. Genentech identified 2 patients (1.1%) who had a maximum QTcF interval post baseline >500 ms and a maximum QTcF increased from baseline > 60 ms. For both patients, no clinically relevant cardiac AEs were reported, serum electrolytes were within normal ranges, and they were not taking known QT prolonging medications. In addition, there was 1 patient who experienced grade 1 ventricular extrasystoles and had QTc prolongation >500 ms.

See "**QT Interval prolongation"** under Adverse Events of Special Interest for the clinical review of QT prolongation.

Immunogenicity

No safety issues related to immunogenicity were identified for entrectinib.

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest (AESI)

The selected AEs were defined on the basis of previous clinical experience, mechanism of action and safety profile from drugs with similar targets to provide a more comprehensive understanding of the safety profile of entrectinib.

AEs of special interest (AESI) were identified based on information from publications describing the neurobiology of TRK and predictions of potential toxicities with TRK inhibition, the preclinical toxicology program, and clinical experience with entrectinib. For an analysis of ALT/AST increases, anemia, and increased creatinine, see the Section above on Laboratory Findings.

Neurologic AESI

A broad spectrum of CNS adverse reactions can occur in patients receiving entrectinib, including impairment in cognitive function or mood, dizziness, and sleep disturbances. PTs combined to make up the composite term of cognitive impairment for inclusion in entrectinib product labeling were: amnesia, aphasia, cognitive disorder, confusional state, delirium, disturbance in attention, hallucinations, visual hallucination, memory impairment, mental disorder, mental status changes.

Among the 355 patients who received entrectinib across clinical trials, 96 (27%) experienced cognitive impairment; in 77% of these patients, symptoms occurred within 3 months of starting entrectinib. Cognitive impairment included cognitive disorders (8%), confusional state (7%), disturbance in attention (4.8%), memory impairment (3.7%), amnesia (2.5%), aphasia (2.3%), mental status changes (2%), hallucinations (1.1%), and delirium (0.8%). Grade 3 cognitive adverse reactions occurred in 4.5% of patients. Among the 96 patients with cognitive impairment, 13% required a dose reduction, 18% required dose interruption and 1% discontinued entrectinib due to cognitive adverse reactions. Table 61, submitted by Genentech in response to IR-25 (5 April 2019), provides a high-level overview of neurotoxicity by time to first onset of a CNS adverse reaction.

Table 61: Summary of Time to First onset of CNS Adverse Reaction

Time to first onset of CNS Adverse Reaction	Total adult (N= 338)	Pediatric (N = 17)	Total (N=355)
Number of patients (n)	92 (100%)	1 (100%)	93 (100%)
< 3 months	70 (77%)	1 (100%)	71 (77%)
≥ 3months and < 6 months	11 (12%)	0	11 (12%)

Time to first onset of CNS Adverse Reaction	Total adult (N= 338)	Pediatric (N = 17)	Total (N=355)
≥ 6months and < 9 months	3 (3.3%)	0	3 (3.3%)
≥ 9 months and < 12 months	2 (2.2%)	0	2 (2.2%)
≥ 12 months +	5 (6%)	0	5 (5%)

Source: copied from IR-25 dated 5 April 2019. Verified with dataset AAE submitted to NDA Module 5.3.5.3 (ISS)

Among the 355 patients who received entrectinib across clinical trials, 36 (10%) experienced mood disorders. The median time to onset of mood disorders was 1 month (range: 1 day to 9 months). Mood disorders occurring in ≥1% of patients included anxiety (4.8%), depression (2.8%) and agitation (2%). Grade 3 mood disorders occurred in 0.6% of patients. One completed suicide was reported 11 days after the last dose of entrectinib. Among the 36 patients who experienced mood disorders, 6% required a dose reduction, 6% required dose interruption and no patients discontinued entrectinib due to mood disorders.

Dizziness occurred in 136 (38%) of 355 patients. Among the 136 patients who experienced dizziness, Grade 3 dizziness occurred in 2.2% of patients. Ten percent of patients required a dose reduction, 7% required dose interruption and 0.7% discontinued entrectinib due to dizziness.

Among the 355 patients who received entrectinib across clinical trials, 51 (14%) experienced sleep disturbances. Sleep disturbances included insomnia (7%), somnolence (7%), hypersomnia (1.1%), and sleep disorder (0.3%). Grade 3 sleep disturbances occurred in 0.6% of patients. Among the 51 patients who experienced sleep disturbances, 6% required a dose reduction and no patients discontinued entrectinib due to sleep disturbances.

The incidence of CNS adverse reactions was generally similar in patients with and without CNS metastases; however, the incidence of dizziness (38% vs. 31%), headache (21% vs. 13%), paresthesia (20% vs. 6%), balance disorder (13% vs. 4%), and confusional state (11% vs. 2%) appeared to be increased in patients with CNS metastases who had received prior CNS irradiation (N = 90) compared to those who did not (N = 48).

Neurotoxicity was largely reversible. At the time of the clinical cut-off date of May 31, 2018, 60% patients who reported neurotoxicity recovered and 4.3% patients were recovering from neurological AEs.

Neurotoxicity rarely led to withdrawal of treatment: 1 patient discontinued entrectinib due to neurotoxicity. This patient experienced Grade 1 hallucination early on during treatment, and his mental status progressively declined until he was diagnosed with Grade 3 cognitive disorder. Entrectinib was initially interrupted and later withdrawn due to the event per the treating physician's decision. This patient's narrative (b) (6) included in the STARTRK 2 CSR, was reviewed and confirmed.

Neurotoxicity requiring intervention was generally managed with dose interruption and/or dose reduction of entrectinib, and very few patients required other interventions, such as concomitant medications and neuro-oncology follow-up. Of the patients with neurotoxicity, 8% received concomitant medications to treat the adverse reaction.

Clinical Reviewer Comment: Neurotoxicity appears to be a class effect for TRK inhibitors and entrectenib had been shown to cross the blood:brain barrier in preclinical models. The Division of Neurology products (DNP) was consulted and provided advice regarding analysis of the CNS adverse reaction data and appropriate language for describing these adverse reactions in the package insert, including the agreed upon PTs for the composite terms of cognitive impairment and mood disorders. The incidence of dose reductions and interruptions of entrectinib due to a CNS AE was 3.4% and 2.5%, respectively. Product labeling for entrectinib includes information in the Warnings and Precautions section advising patients and healthcare providers of these risks, and includes instructions that patients experiencing a CNS adverse reaction should not to drive or operate hazardous machinery. The dosage modification section of product labeling includes instructions for withholding entrectinib, followed by reintroduction at the same or reduced dose following resolution of the AE, or permanent discontinuation of entrectinib, based on severity.

Congestive Heart Failure

In the integrated safety population (N=355), congestive heart failure events were reported in 12 (3.4%) of patients, including Grade 3 (2.3%). An overview of congestive heart failure AEs by PT was undertaken and showed that ejection fraction (EF) was decreased in 4 patients (1.1%), with a Grade 3 EF decrease in 2 patients (0.6%). The PTs that were noted in the narratives included pulmonary edema (1.1%), cardiac failure and congestive cardiac failure (each 0.8%), acute right ventricular failure, cardiogenic shock and chronic ventricular failure (each 0.3%).

Most heart failure events were Grade 3 (2.3% of patients) in severity. Serious events were reported in 7 (2.0%) patients. All of the 7 patients who experienced serious events of congestive heart failure presented with dyspnea or fluid overload; 4 patients experienced a decrease in EF. Five of the 7 patients were treated with systemic diuretic therapy. Entrectinib was interrupted in 3 patients, reduced in 1 patient, and withdrawn in 3 patients. Five of 7 patients with serious congestive heart failure events recovered. Per the summary of clinical safety, of the 12 patients with congestive heart failure events, 7 patients had a past medical cardiac history at baseline and/or concurrent conditions that may have predisposed them to congestive cardiac failure events. Overall, congestive heart failure events were generally manageable with entrectinib dose interruption or reduction.

One Grade 5 adverse event of cardiogenic shock was reported in a patient with NSCLC (Patient (b) (6)) due to pericardial effusion and pericardial tamponade. The patient developed cardiogenic shock two days after starting entrectinib and died. It was noted that the patient had suspected pericardial, bilateral pleural, omental and peritoneal carcinomatosis at baseline, as

well as diffused lung, liver, and bone metastases. This patient was not included in the analysis of cardiac events because Genentech did not consider the adverse event to be drug related, and instead attributed the AE to underlying disease.

One Grade 4 AE of eosinophilic myocarditis was reported in a 40 year old male (Patient (b) (6) (b) (6)) with metastatic NSCLC after receiving treatment with one dose of entrectenib at 800mg/m^2. See Table 62 for patient narratives for further details.

Table 62: Patient Narratives for Cardiac Adverse Events of Special Interest

Patient ID Study ID	Date of Treatments	Narrative
(b) (6) ALKA	(b) (6) (D69)	52-year-old female with metastatic NSCLC treated with 600mg/m^2 of entrectinib was hospitalized on D69 with serious cardiac tamponade. Pericardiocentesis revealed malignant pericardial effusion.
(b) (6) STRTRK-1	(b) (6) (D2)	40-year-old male with metastatic NSCLC started treatment with 800mg/m^2 of entrectinib. On D1, EKG revealed possible Q waves in inferior leads, asymptomatic, troponin of 0.06ng/ml (N: 0-0.31). On D2 patient had diarrhea that resolved the same day. On D3, patient woke up with nausea, grade 3 vomiting, angina, and dizziness. EKG revealed ST elevation, troponin of 0.46ng/ml (range 0.31-0.64). Cardiac catheterization revealed no significant CAD and echo revealed grade 4 myocarditis, normal LVEF. Biopsy of right heart revealed eosinophilic myocarditis. Patient required pressors and a balloon pump, and high dose steroid with IV solumedrol. On D6 a cardiac MRI revealed EF of 72%. Patient recovered and was discharged from hospital on D7. Last dose of entrectinib was (b) (6)
(b) (6) STRTRK-2	(b) (6) (b) (6) (D15)	58-year-old male. On D14, Grade 2 peripheral edema occurred and the patient was treated with Lasix. Grade 3 hypotension was noted on the same day and the patient was hospitalized. On D15, pericardial effusion and grade 2 CHF was noted treated with Lasix, and pressors. On D16 study drug discontinued. On D21 the patient had Grade 1 cough. Echo revealed pericardial effusion with Normal EF. Pericardiocentesis did not have malignant cells. On D37 the patient developed grade 4 pneumonia, hospitalization continued. The patient died on D443. Cause of death was Grade 5 pneumonia.
(b) (6) STRTRK-2	(b) (6) (D43)	76-year-old male with NSCLC was diagnosed on D15 with Grade 3 pneumonia, treated and stabilized. D28 revealed PD. Patient was allowed to continue entrectinib. On D32 pneumonia resolved and was discontinued on D32. On D43 patient died at home due to grade 5 cardiopulmonary arrest. No Autopsy performed.
(b) (6) STRTRK-2	(b) (6) (D2)	57-year-old female with Squamous Cell Carcinoma. On D1 received one dose of 600mg. On D2 patient noted to have cardiopulmonary arrest (CPA) and transported to ER immediately. ECG asystole, PaO2 85%, 36C temp. CPR initiated, intubated. No response. Cause of death CPA.
(b) (6) STRTRK-2	(b) (6) (D264)	55-year-old male with anaplastic thyroid cancer, D22 Grade 3 dyspnea, Grade 3 pneumonia, admitted to ICU. D29: Bilateral pleural effusions and patchy infiltrates, mild hypotension. D30 dyspnea

Patient ID Study ID	Date of Treatments	Narrative
		improved. Anemia treated with PRBCs. On D121 mild aphasia/ stroke. D121 Grade 2 dyspnea, cardiac MRI revealed cardiac metastases. D140 Grade 1 CHF, fluid overload. D216 worsening volume overload, SOB, orthopnea weight gain of 3 Kg, Grade 3 CHF on D217. 2D Echo on D218 normal EF, reduced right ventricle dilation and mass in right ventricle. Dose reduced to 400mg daily on D223. On D225 discharged from hospital and weight was 18 lbs lower than on admission. D263 presented to ER with Grade 3 dyspnea, Grade 4 acute respiratory failure. D265 patient died due to Grade 5 acute respiratory failure.
(b) (6) STRTRK-2	(b) (6) (D141)	33-year-old female with NSCLC. D 37 had Grade 1 peripheral edema. D45 Grade 2 dyspnea, edema worsened to grade 2. Drug interrupted D45 and restarted D51. Dyspnea resolved D57, and edema Grade 1. D72 again grade 1 dyspnea, drug interrupted on D72. D86 dyspnea Grade 2 and chest pain Grade 2, edema Grade 2. Drug reduced to 400mg on D86. On D123 worsening dyspnea, D124 hospitalized Grade 3 cardiac failure. BNP 1014pg/ml. EF 35% with global hypokinesis. D126 G1 CHF discharged. D127 edema resolved. D135 entrectinib restarted 200mg. D141 scans revealed PD.
(b) (6) STRTRK-2	(b) (6) (D413)	60-year-old female with leiomyosarcoma developed Grade 2 chest pain, dyspnea on D352 and Grade 2 orthopnea, PND, Grade 1 peripheral edema on D352. Grade 3 pulmonary edema, BNP of 2603 pg/ml (N<100), ECHO EF 35-40% global hypokinesis, Grade 1 cardiomyopathy and luminal irregularities also occurred on D352. The events resolved on D352, and entrectinib was restarted. On D413 entrectinib was discontinued for pulmonary edema.
(b) (6) STRTRK-2	(b) (6) (D72)	66-year- old male with pancreatic adenocarcinoma, D4 experienced peripheral edema bilateral, D6 Grade 2 dyspnea, D7 Grade 2 orthopnea. Drug interrupted on D7. Hypoxia and troponin that were increased resolved with Lasix. D23 drug restarted at same dose and reduced to 400 mg on D28 for dyspnea and disturbance in attention. On D34 Grade 3 respiratory distress with EKG changes and troponin of 0.27 ng/ml (N: 0-0.04), BNP of 287pg/ml and D Dimer of 483ng/ml. D36 bilateral pleural effusions. ECHO EF of 45%, global hypokinesis and mild MR. On D37 discharged on 2L oxygen. D45 EF was 55-60%, severe MR, mod to severe left atrial enlargement, mild to mod LVH. On D46 restarted on entrectinib 400mg daily. D57 Grade 3 CHF and recommended percutaneous repair of MV. On D65 ECHO EF 55-60% and moderate LA enlargement, severe MR severe mitral regurgitation into the left atrial appendage due to degenerative mitral valve disease, systolic reversal of pulmonary vein inflow from the left lower pulmonary vein and significant systolic blunting in the three other pulmonary veins which was assessed to be likely due to lower systolic blood pressure. Treated medically. D74 presented with CHF Grade 3. Discontinued on D78 and resolved on D 80. Last day of entrectinib was D72. On D113 dyspnea improved to Grade 1. Patient was alive (b) (6) at last f/u and has received two intervening therapies.

Source: Reviewer generated table based on narratives to cardiac events submitted to CSR in NDA Module 5.3.5.2.

Clinical Reviewer Comment: Congestive heart failure (CHF) was added to the W&P section of the entrectinib product label because CHF is a serious adverse event. Although it is challenging to assess relatedness of cardiac events to entrectenib based on the single arm trials and most of the affected patients had a prior medical history of cardiac risk factors , it is unusual to observe clinically detected CHF at an incidence of 2.3% even in clinical trials enrolling patients with refractory cancers. Patient (b) (6) *STRTRK-1, who developed Grade 4 myocarditis, had a biopsy consistent with eosinophilic myocarditis possibly related to entrectinib as this is an unusual adverse event for which no such events are expected in clinical trials. A post marketing requirement (PMR) will be conducted by Genentech to further assess the contribution of entrectenib to cardiac risk and characterize cardiac adverse events. Genentech plans to conduct additional assessments for left ventricular ejection fraction (LVEF) at screening and Cycle 3 Day 1 in clinical trial(s) of entrectinib to better assess cardiac function prior to and during treatment.*

Skeletal Fractures

DOP2 consulted the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding this safety concern identified late in the review cycle based on late-breaking reports of bilateral femoral neck fractures in pediatric patients presented at the annual American Society of Clinical Oncology meeting in June 2019 (Robinson et al.). The identification of these cases prompted a further investigation by FDA into fracture events across the entrectinib program. DBRUP provided assistance in interpretation of the events, recommendations on description of skeletal fractures and provided assistance in the design of the data to be obtained in a PMR to further characterize the fracture risk. See their review for full details.

The mechanism of action of entrectinib involves inhibition of the neurotrophic tropomyosin receptor 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), anaplastic lymphoma kinase (ALK), Janus kinase (JAK)2, and tyrosine kinase non-receptor 2 (TNK2). In addition to their known key role in nervous system development and maintenance, neurotrophins (e.g. nerve growth factor, NGF) and their receptors (e.g., TRKA, TRKB and TRKC) are also involved in skeletal tissue formation and healing. There are nonclinical models that suggested their involvement in chondrogenesis and osteogenesis (Su et al., 2017). A study by Tomlinson et al. (2017) demonstrated that communication between osteoblasts and sensory nerves through nerve growth factor-TRKA signaling is essential for load-induced bone formation in mice, suggesting a key role for TRKA in this process. Entrectinib, a TRKA, TRKB and TRKC inhibitor, may increase the risk of fractures.

In response to an information request by FDA, Genentech evaluated this fracture safety signal by conducting a cumulative review of the clinical trials and company drug safety databases to identify all events of fractures reported in entrectinib-treated patients. That review included patients who were not part of the NDA dataset (which had a cutoff of May 31, 2018) in order to provide a comprehensive analysis of the fracture risk. The search had a clinical cutoff date of

March 8, 2019 for Studies STARTRK-1 and ALKA, March 31, 2019 for Studies STARTRK-2 and STARTRK-NG and May 3, 2019 for the company drug safety database. The analysis included a total of 528 patients (498 adults, 30 pediatric patients) whowere exposed to entrectinib across the 4 clinical studies. The composite term "fractures" used in the search for fracture events included the following MedDRA preferred term (PTs): humerus fracture, foot fracture, ankle fracture, femoral neck fracture, stress fracture, fibula fracture, fracture, rib fracture, spinal fracture, wrist fracture, femur fracture, pathological fracture, tibia fracture, lower limb fracture.

The search retrieved a total of 38 patients with reported events indicative of fractures from the clinical trial database. Upon review of the retrieved events, 4 were determined to be adverse events of joint dislocation (2), meniscus injury (1), and rotator cuff injury (1). These 4 events were therefore subsequently excluded from the fracture analysis.

Of the 34 patients (27 adults and 7 pediatric patients) identified from the cumulative search and review of retrieved events, 15 patients were from outside of the original NDA dataset (11 adults and 4 pediatric patients). Fracture events were considered serious in 15 of the patients (12 adults and 3 pediatric patients). Narratives are provided below.

Narratives submitted for these 34 patients are summarized as follows:

Pediatric Patients:

- 10 year old male patient with left proximal tibia fracture on study day 225 and second left proximal tibia fracture on study day 297 (unclear whether this was a recurrent fracture or new fracture)
- 10 year old female patient with 2nd right metatarsal fracture on study day 130
- 7 year old male patient with right lower limb fracture on study day 54
- 8 year old female patient with tibia fracture on study day 121
- 6 year old male patient with left femur fracture on study day 75 and second left femur fracture after a fall on study day 83 (appears to be a new fracture)
- 4 year old female with bilateral femoral neck fractures on study day 85 with no antecedent trauma
- 9 year old male patient with bilateral femoral neck fractures on study day 221

Adults:

- 22 year old woman with metatarsal fracture on study day 563
- 66 year old woman with ankle fracture on study day 53
- 23 year old woman with tibial stress fracture on study day 42 and additional/recurrent (unclear) tibial stress fractures on study days 100, 281, 366 and 574
- 53 year old woman with humerus fracture on study day 340
- 70 year old woman with bilateral jaw fractures (parasymphysial) on study day 253
- 68 year old woman with unspecified fracture on study day 104; noted to have osteoporosis
- 57 year old man with medial tibial plateau fracture on study day 117; no trauma noted

- 68 year old woman with left humerus fracture on study day 11 and 100 (unclear whether recurrent or new)
- 33 year old woman with left ankle fracture on study day 153
- 38 year old woman with right pathologic femoral neck fracture on study day 38
- 41 year old man with spine fracture on study day 74
- 29 year old man with right humerus fracture on study day 98
- 64 year old woman with rib fracture on study day 85
- 81 year old woman with spinal compression fracture on study 61; noted to have osteoporosis
- 54 year old man with left toe fracture on study day 185
- 72 year old woman with right hip stress fracture on study day 31 after fall; noted to have osteoporosis
- 80 year old woman with right hip stress fracture on study day 7 after mechanical fall; noted to have prior stress fracture of right hip
- 59 year old woman with wrist fracture on study day 114 after a fall
- 67 year old woman with left pathologic femoral neck fracture on study day 262 and right femoral neck fracture on study day 499 after a fall
- 67 year old woman with left ankle and fibula fracture on study day 163 after fall
- 64 year old woman with pathologic left femoral neck and shaft fractures on study day 48 after fall from bed and left proximal tibia stress fracture on study day 49
- 31 year old man with spinal fracture on study day 302
- 27 year old man with pathologic right femur shaft fracture on study day14 after fall
- 60 year old woman with pathologic right humerus fracture on study day 15 after injury; noted to have osteoporosis
- 80 year old woman with lumbar compression fracture on study day 91 after fall
- 51 year old woman with left bimalleolar ankle fracture on study day 121, left foot fracture on study day 138; noted to have osteoporosis
- 68 year old woman with right hip fracture on study day 380 after fall; noted to have avascular necrosis of right hip

In the safety population comprising 338 adult patients included in the adult safety population in the original NDA submission and data from the 30 pediatric patients provided in the updated fracture safety dataset who received entrectinib, 17 (5%) adult patients and 7 (23%) pediatric patients experienced fractures. In adult patients, some fractures occurred in the setting of a fall or other trauma to the affected area, while in pediatric patients, all fractures occurred in patients with minimal or no trauma. In general, there was inadequate assessment for tumor involvement at the site of fracture; however, radiologic abnormalities possibly indicative of tumor involvement were reported in some patients. In both adult and pediatric patients, most fractures were hip or other lower extremity fractures (e.g., femoral or tibial shaft). In a limited number of patients, bilateral femoral neck fractures occurred.

Among adult patients with fractures, median time to fracture was 3.8 months (range 0.3 to 18.5 months). Entrectinib was interrupted in 41% of patients and discontinued in none of the patients who experienced a fracture; in pediatrics, the median time of onset of fracture events was 3.98 months (range: 1.8 months - 7.4 months). By the time of data cut-off, 5 (71%) of pediatric patients and 17 (63%) of adults were reported to have complete healing of their fractures. Entrectinib was interrupted in 44% of patients and was not discontinued in any patient.

The W&P section of entrectenib product labeling will include a recommendation for initiation of an evaluation for fracture in all patients with clinical symptoms suggestive of fracture (e.g., pain, changes in mobility, deformity). The safety of resumption of entrectinib is not known in patients who experience fracture is not known; specifically, there are no data on the effects of entrectinib on healing of known fractures and risk of future fractures.

Clinical Reviewer Comment: based on its mechanism of action, there is a biologic plausibility for a causal relationship for entrectinib in the occurrence of fractures due to the role of TRK in bone health/remodeling. The risk of fractures may be more pronounced in pediatric patients, since the reported fractures in pediatric patients appeared to occur in the absence of trauma and because there were 2 cases of bilateral femoral neck fractures (a 4-year-old female and 9-year-old male), an unusual event in pediatric patients. However, there were confounding factors in many of the cases of fracture, such as pre-existing osteopenia, concurrent steroids use, etc. According to the consult by DBRUP, most fractures did not appear to be due to tumor pathology at the fracture site but data was limited (among the 34 patients with fracture events, none were reported to have had bone biopsies to further evaluate the fracture event). Most patients who experienced a fracture did not appear to have significant underlying risk factors for fracture (only 5 of the adult patients with a fracture were reported to have a history of osteoporosis). While the 5% incidence rate of fractures observed in adults in the entrectinib clinical trials does not appear to exceed the background fracture incidence rate in adults with solid tumors (estimated to be as high as 18%), the 23% incidence rate of fractures observed in pediatric patients was unexpectedly high, as the corresponding estimated background rate is approximately 6%.). Of particular concern is that all fractures in pediatric patients were associated with minimal or no trauma, whereas most fractures in adults occurred in the setting of a fall or other trauma to the affected area. This suggests that entrectinib may have a differential effect on the growing versus mature skeleton. In some adult and pediatric patients, there appeared to be either recurrent or multiple events of fractures. These findings suggest not only a role of entrectinib in fracture, but potentially a detrimental effect of entrectinib on fracture healing.

The W&P section of product labeling for entrectinib will communicate the risk of fractures and Genentech has agreed to conducting a study(ies) to better characterize the risk of fractures in adult and pediatric patients and inform product labeling regarding mitigating this risk. DBRUP recommended the following additional studies:

Nonclinical

These recommended nonclinical studies could help to identify a potential adverse effect of entrectinib on bone metabolism, and perhaps provide information on the mechanism of action of such an effect.

- Conduct a short-term study in young growing rats to determine the effects of entrectinib on longitudinal bone growth and mineralization by static histomorphometry, e.g. in the proximal tibia. (refer to Schenk et al.,1986). Effects on the growth plate, bone and osteoid volume, and trabecular parameters should also be determined in this study.
- Conduct a study of adequate duration (e.g. 2-3 months) to evaluate the effect of entrectinib on bone tissue in young adult rats using bone densitometry, static and dynamic histomorphometry and biomechanical strength testing. Because DXA and areal bone mineral density data may be confounded by entrectinib's potential effects on growth, quantitative computed tomography (QCT) of the long bones may be performed, also because this technique can provide data on both cortical and cancellous bone compartments. Bone mechanical tests should be performed of both cancellous and cortical bone sites, and data on both extrinsic and intrinsic strength parameters, which are independent of bone size, should be obtained. The correlation between bone mineral content (BMC) and bone strength parameters for control vs. treated groups may also provide relevant information.

Clinical Reviewer Comment: In consultation with the nonclinical review team, FDA decided not to require these animal studies because juvenile animal studies have already been performed and the risk of fracture has already been identified in clinical trials, so additional animal studies are unlikely to provide substantive new information that cannot be obtained in the clinical trials, including the PMR.

Clinical

The following assessments should be performed in the ongoing and planned trials of entrectinib in all adult and pediatric patients.

- Initial and serial assessments of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans. DXA should be performed every 6-12 months. The DXA scans should analyze areas where there are standardized DXA placement procedures and normative data available for assessment (i.e. lumbar spine, femoral neck, and total hip). Analyses should be based on scans with standard (supine) patient positioning. Adequate quality control measures should be established for DXA scans performed in the trials (as described by Faulkner et al., 1995). Serial DXA scans in patients who are continuing entrectinib therapy will not be as informative as those in patients who are initiating entrectinib therapy (since initiating patients will have a baseline BMD available for comparison). However, serial DXA scans in patients continuing entrectinib could still provide useful information regarding durability of a potential drug effect on BMD.
- Initial and serial serum bone formation and resorption markers (N-terminal propeptide

of Type I Collagen [P1NP], osteocalcin, bone-specific alkaline phosphatase [BSAP] and carboxy-terminal cross-linked telopeptides of type 1 collagen [CTX-1]). Because levels vary with time of day and in response to meals, these markers should be measured in standardized conditions, preferably in the morning after an overnight fast. Similar to BMD, markers of bone turnover will be more informative in patients initiating entrectinib, but also may provide useful information regarding durability of a potential drug effect.

- Initial and serial measures of calcium metabolism markers (e.g. vitamin D, parathyroid hormone) to evaluate a potential role of entrectinib in calcium metabolism and skeletal homeostasis.

Pediatric Patients:

- Assessment of linear growth at least every 6 months. Height measurements should be conducted according to recommendations in Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children.
- Assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays. With growth impairment, sclerotic lines, usually referred to as growth arrest or "Harris" lines, develop adjacent and parallel to growth plates (Park, 1964; Ogden, 1984). The appearance of these lines may be helpful in assessing possible growth plate effects of entrectinib. These lines typically are not apparent on X-ray until approximately 6 weeks following a triggering event (Jacobson et al., 2012). Therefore, for patients starting entrectinib therapy, initial X-rays should be performed 6 weeks following the entrectinib start date. X-rays should be performed at 6-month intervals and should use a consistent side (left or right) for all scans.
- If there continues to be uncertainty regarding the nature of entrectinib's effects on bone tissue after evaluation of adequate data from the abovementioned assessments, peripheral quantitative computed tomography (pQCT) of the distal radius and/or tibia should be considered, as this assessment would provide more specific information on bone geometry and differential effects on cortical versus trabecular bone compared to DXA. pQCT is not recommended as an initial assessment, however, given the additional burden, radiation exposure and expense associated with this procedure.

Clinical Reviewer Comment: the clinical review team will review the protocol for this PMR, when submitted by Genentech, to ensure that these assessments are incorporated into the study

Vision Disorders

In preclinical studies in rats, microscopic findings of neutrophil infiltrates of corneal stroma and single cell necrosis of the corneal epithelium were and are considered entrectinib-related. In all ongoing clinical studies, eye exams were required at screening, during treatment, at the end of treatment, and as clinically indicated. In the integrated safety population (n= 355), visual disturbances were reported in 21% of patients, including Grade 1 (82%), Grade 2 (14%) and

Grade 3 (0.8%) severity.. The spectrum of AEs related to vision disorders included: blurred vision (9%), photophobia (5%), diplopia (3.1%), visual impairment (2%), photopsia (1.3%), vitreous floaters (1.1%), cataract (1.1%), vitreous detachment (0.8%), vitreous adhesions, blindness, corneal erosion, keratitis and retinal hemorrhage (each 0.3%). Periorbital edema and eyelid swelling also occurred. The majority of cases, patients were able to continue entrectinib.

Clinical Reviewer Comment: the Division of Anti-infective and Ophthalmology Drug Products was consulted for interpretation of visual disorders and to provide advice regarding the description of these events to be included in the Warnings and Precautions Section of product labeling. The ophthalmology consultant advised the Division that severe visual disturbances were unlikely to be related to a direct effect on the eye, and were more likely to be related to CNS metastases or the effect of entrectinib on the CNS, as seen with drugs with an overlapping mechanism of action such as crizotinib. Given the known CNS effects of entrectinib, the temporal relationship between some of the visual disturbances, and positive dechallenge in some cases (described in Table 64 *below) a causal relationship for entrectinib in many of the cases of visual disturbance is likely. Many of the ocular AEs are consistent with entrectinib causing dry eye syndrome, which can usually be treated with ocular demulcents (artificial tears). In addition, there are some ocular adverse events appeared to be related to allergic reactions (e.g., periorbital swelling). The ophthalmology consultant considered that the majority of the remaining ocular events could be attributed to the normal aging process (Table 63).*

Table 63: Vision Changes with Entrectinib and Plausible Cause

MedDRA Preferred Term	N=97	**Plausible Etiology**
EYE DISORDERS		
Total number of patients with an event	97	
Total number of events	171	
Vision blurred	31	Likely related to dry eye condition
Photophobia	18	Likely related to dry eye condition
Diplopia	11	Likely related to dry eye condition
Dry eye	10	Likely related to dry eye condition
Eye pain	9	Likely related to dry eye condition
Visual impairment	7	Likely related to dry eye condition
Cataract	4	Likely age related
Photopsia	4	Associated with vitreous detachments, likely age related
Vitreous floaters	4	Likely age related
Conjunctivitis allergic	3	Potential drug related allergic event
Periorbital oedema	3	Potential drug related event
Vitreous detachment	3	Likely age related
Conjunctival hyperaemia	2	Likely related to dry eye condition
Eye swelling	2	Potential drug related event
Eyelid oedema	2	Potential drug related event

MedDRA Preferred Term	N=97	Plausible Etiology
EYE DISORDERS		
Glaucoma	2	Unlikely to be related
Lacrimation increased	2	Likely related to dry eye condition
Asthenopia	1	Likely related to dry eye condition
Blindness	1	Attributed to radiation necrosis of a left parieto-occipital lobe lesion
Cataract cortical	1	Unlikely to be related
Chalazion	1	Unlikely to be related
Conjunctival haemorrhage	1	Unlikely to be related
Corneal erosion	1	Likely related to dry eye condition
Eye disorder	1	Unknown- single event
Eye irritation	1	Likely related to dry eye condition
Eye pruritus	1	Likely related to dry eye condition
Halo vision	1	Likely related to dry eye condition
Keratitis	1	Likely related to dry eye condition
Lacrimation decreased	1	Likely related to dry eye condition
Meibomian gland dysfunction	1	Likely related to dry eye condition
Metamorphopsia	1	Unknown- single event
Mydriasis	1	Unknown- single event
Pathologic myopia	1	Unlikely to be related
Presbyopia	1	Likely to be age related
Retinal haemorrhage	1	Unknown- single event
Strabismus	1	Unlikely to be drug effect on eye
Trichiasis	1	Unknown- single event
Vitreous adhesions	1	Likely to be age related
Xerophthalmia	1	Likely related to dry eye condition

Source: copied from Dr Wiley Chambers ophthalmology consult.

Table 64: Patient Narratives for Visual Disturbances

Patient ID Study ID	Date of Treatments	Narrative
(b) (6) STRTRK-2	(b) (6) (D69)	67-year-old female with metastatic NSCLC started treatment with 600mg/day of entrectinib, dose reduced to 400mg/day for grade 1 gait disturbance on D 36 reported on D11. On D69, treatment was interrupted for grade 1 diplopia reported on D65. On D74 dose was further reduced to 200mg for persistent gait disturbance and fatigue. On D91 an eye exam was normal and dose was increased to 400mg. On D109 patient was hospitalized for Grade 3 diplopia and eye exam was normal. Entrectenib was held from D109 and diplopia resolved D110. On D113 the dose was reduced to 200mg with no recurrence of diplopia.

Patient ID Study ID	Date of Treatments	Narrative
(b) (6)	(b) (6) (D249)	61-year- old female with papillary thyroid cancer experienced Grade 1 dizziness on D10, Grade 3 muscular weakness. On D27 experienced Grade 1 blurred vision. Drug was interrupted and resumed on D35 at 400mg. On D51 was noted to have new brain lesions and allowed to continue entrectinib. On D163 s/p motor vehicle accident was noted to have Grade 3 blindness in right eye. CT and MRI showed stable left parieto-occipital lesion. Resumed treatment on D168 after Grade 3 blindness improved to Gr 2 blurred vision. D 211 Gr 1 blurred vision worsened to Gr 2. Drug was interrupted and restarted on D 231. On D 246 noted to have progression of disease and last dose of entrectinib was (b) (6). Cause of blindness was radiation necrosis per applicant.
(b) (6) STRTRK-1	(b) (6) (D37)	58-year-old male with metastatic melanoma was started treatment with 600mg/day of entrectinib developed grade 3 peripheral sensory neuropathy on D11 and dose was interrupted and resumed at 200mg/day on D22. On D22 patient experienced grade 1 blurred vision in both eyes and continued to have this 1-2 times a day. On D37 patient was hospitalized for Grade 1 blurred vision (intermittent) in both eyes frequency increasing. Dose was interrupted on D37. MRI revealed a subependymal lesion in the roof of his posterior right lateral ventricle, extending to corpus callosum had increased in size. On D38 symptoms of blurred vision improved. On D44 entrectinib was restarted at 200mg/day. The Grade 1 blurred vision and diplopia resolved on D169.

Source: Reviewer generated table from narratives submitted to CSR in NDA Module 5.3.5.2

QT Interval prolongation

Among the 355 patients who received entrectinib across the clinical trials, 2.8% of patients with at least one post-baseline ECG assessment experienced QTc interval prolongation of >60 ms after starting entrectinib and 1.7% had a QTc interval >500 ms. Based on the review done by FDA's QT-IRT team, in the QT substudy of STARTRK-2, of 113 patients receiving entrectinib 600 mg daily, there was no large increase in QTc change from baseline. Based on QT-IRT review, the data did not support an exposure-response analysis because the exposure range was narrow and the PK/ECG sampling schedule could not be used to evaluate a causal effect of entrectinib on QT prolongation.

Clinical Reviewer Comment: It was the opinion of the QT-IRT team that there is no clear signal that entrectenib causes prolongation of QTc due to limited data. The relevance of sporadic outliers in an uncontrolled study when the limited QT assessment does not support a large drug-effect is unclear. The narratives for 2 patients with both QTc >500 and dQTc >60 ms do not

indicate any confounders [e.g., QT prolonging medications, electrolyte abnormalities] that could explain the isolated QTc prolongation (refer to their review). The clinical studies were not designed to evaluate concentration-QTc relationship and even in their dedicated QTc assessment the data did not support such analysis. Nevertheless, to be conservative, the package insert will include language in Warnings and Precautions section indicating that patients should be monitored who already have or who are at significant risk of developing QTc interval prolongation, including patients with known long QT syndrome, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. QT interval and electrolytes should be assessed at baseline and periodically during treatment, adjusting frequency based upon risk factors such as congestive heart failure, electrolyte abnormalities, or concomitant medications known to prolong the QTc interval. Based on the severity of QTc interval prolongation, entrectenib should be withheld and resumed at the same or reduced dose, or permanently discontinued.

Dizziness

In the integrated safety population (N=355), adverse events of dizziness were reported in 38%. The cases of dizziness were reviewed with consideration to whether alternative etiologies or comorbid conditions present within 7 days of the reported dizziness event suggested an alternative neurologic or cardiovascular cause. Among patients with dizziness adverse events, 1.2% were possibly attributable to cardiovascular disease, 15% had potentially attributable to neurologic etiology, and 4.0% with a history of orthostatic hypotension. However, for the majority (80%), no alternative etiology was identified; thus, these events were probably attributable to entrectinib. The mechanism by which entrectinib may cause these events is unclear. There is biologic plausibility that entrectinib is responsible for these events given TRK receptors' involvement in neuronal development and maintenance of the central and peripheral nervous system neurologic.

Syncope

Adverse events of syncope were reported in 3.9% (14/355) of patients. Syncopal events were generally by rapid onset and were of short duration with a prompt recovery. Among the 14 patients who experienced syncope, four patients had concurrent co-morbid conditions of hypotension and/or dehydration and QT prolongation was a concurrent co-morbid condition in one patient. Relevant co-morbid cardiac disease was document in one patient who had a medical history of cardiac arrest and one patient who had medical history of Prinzmetal's angina.

Ataxia

In the integrated safety population (N=355), AEs of ataxia were reported in 17 (4.8%) patients. The majority of these events occurred contemporaneously with other AEs (e.g. fatigue, mental status change, mood change, memory impairment, dizziness, neuralgia, syncope, somnolence),

which suggests a neurologic etiology. In the context of the CNS penetrance of entrectinib and the identified risks of neurologic adverse events (e.g. syncope, cognitive disorders) with entrectinib, attribution of ataxia in the majority to entrectinib is plausible.

Clinical Reviewer Comment: Refer to DNP's full review of neurotoxicity, inclusive of ataxia.

Gait Disturbance

In the integrated safety population (N=355), AEs of gait disturbance were reported in 24 (7%) patients, overall. The majority of these patients' events were reported contemporaneously with other AEs (e.g. vertigo, insomnia, fatigue, cognitive disturbances, confusion). In the context of the CNS activity of entrectinib and the identified risk of neurologic adverse effects (e.g. syncope, cognitive disorders) with entrectinib therapy, a neurologic etiology of gait disturbance in the majority of the reported related cases is plausible.

Hypotension

In the integrated safety population (N=355), AEs of hypotension and orthostatic hypotension were reported in 63 (18%) patients, collectively. Most events of hypotension or orthostatic hypotension were reported concomitantly with other AEs. Of the 72 hypotensive events that were reported concurrently with other AEs, a majority were reported with AEs which may contribute to the development of hypotension, such as dehydration, diarrhea, vomiting, acute infections, and cardiac events. No single etiology of hypotension is suggested by the data.

Weight gain and Weight Loss

According to FDA nonclinical review team, in the 13-week study, entrectinib-treated male rats demonstrated increased food consumption, which is consistent with literature reporting hyperphagia and obesity in mice that express reduced amounts of TrkB (Xu et al, 2003) and in a human with a missense mutation in *NTRK2*, the gene encoding TrkB (Yeo et al., 2004). Paradoxically, dehydration and impaired weight gain was also observed in juvenile rats.

A consistent increase in food consumption and increased weight was not observed across 1-month and 3-month studies in rats and dogs at low and high doses. Findings may have been confounded by toxicity in some animals (animals that lost weight tended have CNS or GI toxicity). Therefore, the relationship between entrectinib exposure and food consumption or weight gain was less clear for entrectinib in animals. However, based on the mechanism of action, instances of clinical increased weight can reasonably attributed, at least in part, to entrectinib.

Increases in body weight were observed in patients treated with entrectinib. This observation is likely an on-target effect of entrectinib, since TRKB may be important in appetite control (Tsao et al. 2008). In patients who had adverse events of increased body weight, some were also

noted to have fluid retention or edema. Upon review of adverse events of increased weight in the integrated safety population (N= 355), approximately half of the patients had concurrent adverse events (within a 30-day time frame) of increased weight and fluid retention or edema. Based on this observation and available literature, it appears that both increased appetite and fluid retention/edema may potentially contribute to adverse events of increased weight.

At the data cut- off date of May 31, 2018, 25% patients (88/355) had an AE of increased weight. The majority of these AEs were Grade 2 (11% of patients) events, followed by Grade 1 (8% of patients). Grade 3 increased weight occurred in 6.5% of patients. Of the 88 patients who had an AE of increased weight, most experienced increased weight within 60 days of starting entrectinib.

Table 65, containing analyses submitted by Genentech, provides a high-level summary of the time to first onset of an adverse event of increased weight.

Table 65: Summary of Time to First onset of Increased Weight Adverse Events

Time to Onset of Adverse Event of Increased Weight	Total adult (N= 338)	Pediatric (N = 17)	Total (N=35)
	83 (100%)	5 (100%)	88 (100%)
0-30 days	34 (41.0%)	5 (100%)	39 (44.3%)
≥ 30 - <60 days	25 (30.1%)	0	25 (28.4%)
≥ 60- <90 days	10 (12.0%)	0	10 (11.4%)
≥ 90 - < 180 days	9 (10.8%)	0	9 (10.2%)
≥ 180 - < 365 days	5 (6.0%)	0	5 (5.7 %)
365+ days	0	0	0

Source: Table copied from IR-12 from 5 April 2019, and data verified from reviewer with dataset AAE

Among 88 patients with an AE of increased weight, 6% required dose reduction, 2.3% required dose interruption, and one patient (1.1%) permanently discontinued entrectinib.

<u>Clinical Reviewer Comment</u>: *Adverse events of increased weight gain were reported in 25% of entrectinib-treated patients. This is attributable to entrectinib, although more than one mechanism (fluid retention vs. increased food consumption) may be responsible for this adverse reactions, based on the role of TRKB in appetite control and the observed 15% incidence of "increased weight" reported in the product label for larotrectib (VITRAKVI), which also inhibits TRK.*

Impaired weight gain was seen in juvenile rats and adverse events of decreased weight were also reported in patients exposed to entrectenib. Adverse events of decreased weight were reported in 2.3% of patients. The weight changes may be attributable to entrectinib as the TRK pathway is involved in weight and thermal regulation; however, there are confounding factors such as underlying cancer and the catabolic nature of cancer that could also result in weight

loss. In some cases, due to the single arm nature of the studies, small sample size, and underlying cancer and comorbidities, it was difficult to assess the extent to which entrectinib was responsible for changes in weight. Refer to Section describing Grade 3-4 AEs for further details. The majority of AEs of decreased weight were of Grade 1 severity (1.1% of patients), followed by Grade 2 and Grade 3 (0.6% of patients each).

Dyspnea

Adverse events of dyspnea were reported in 30% of patients (106/355). The cases of adverse events of dyspnea were reviewed to evaluate the possible etiology of dyspnea, i.e., pulmonary, cardiac, or another etiology. In approximately half of the 106 cases, dyspnea could not be attributed to another comorbid condition because no alternative etiology or confounding factor could be identified; thus these cases of dyspnea appeared to be related to entrectinib. In the remaining patients, comorbid conditions included concurrent pulmonary disorders (such as respiratory tract infection, pleural effusion, or pulmonary edema) in roughly 50%, cardiac disorders (such as heart failure, or arrhythmia) in 25%, and assorted conditions in the other 25% (e.g., anemia, anxiety, or hypotension).

Similar incidences of AEs reports as dyspnea were reported regardless of underlying diagnosis(i.e., NSCLC vs. other cancers), suggesting that the histologic cancer was not a risk factor for adverse events of dyspnea.

Clinical Reviewer Comment: AESI that were not included in the W&P section of the entrectinib product label included weight changes and clinically relevant adverse reactions occurring in <10% of patients such as dysphagia (10%), fall (8%), pleural effusion (8%), syncope (3.9%), pulmonary embolism (4%), and hypoxia (4%). After assessment of the narratives and review of Genentech's responses to multiple FDA IRs, the reviewers decided that inclusion of these adverse events in the W&P section was not warranted either because a causal relationship between the AE and entrectinib was unclear or inclusion in the W&P section was not necessary given that oncologists are typically skilled in managing a variety of adverse reactions to drugs, including those described above.

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

Not applicable

8.2.7. Safety Analyses by Demographic Subgroups

Geriatric Patients

Of the 355 patients who received entrectinib across clinical trials, 25% were 65 years or older, and 5% were 75 years of age or older. Clinical studies of entrectinib did not include sufficient numbers of geriatric patients to determine whether they respond differently from younger patients.

Pediatric patients

For the purposes of this review and product labeling, the pediatric population comprises patients less than 18 years of age. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients (n=30) compared to adult patients (n=338) were neutropenia (27% vs. 2%), bone fractures (23% vs. 5%), increased weight (20% vs. 7%), thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma-glutamyl transferase (7% vs 0%), and device-related infection (7% vs 3%). Three pediatric patients discontinued entrectinib due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis in one patient each). Due to the small number of pediatric patients, the modest size of the safety database in adults (n=338), the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors.

Clinical Reviewer Comment: An assessment of safety by other demographic subgroups (sex, ethnicity, age, RP2D vs entire efficacy population) did not show any safety signals. However, the data was difficult to interpret based on small sample size. Comparisons of AEs between adults and pediatric patients should be interpreted with caution due to the small sample sizes of these subpopulations.

In addition to the increased incidence of skeletal fractures, cytopenias, and elevated liver enzymes, infections appeared to be more common in the pediatric population; however, pediatric patients are prone to seasonal illnesses such upper respiratory infections and the symptoms that accompany them such as cough, nasal congestion.

As noted above, due to the small number of pediatric patients, the modest size of the safety database in adults (n=338), the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors.

There is insufficient pharmacokinetic and safety information to establish a safe and effective dose in pediatric patients less than 12 years of age, see Sections 1.3, 8.4, and 10 for further details.

8.2.8. Specific Safety Studies/Clinical Trials

There were no additional studies performed to evaluate any specific safety concerns.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Carcinogenicity studies were not conducted or required to support the use of entrectinib in the proposed indication. Entrectinib was aneugenic, but not mutagenic in in vitro genotoxicity studies.

Human Reproduction and Pregnancy

No pregnancies have been reported in female patients exposed to entrectinib. One pregnancy was reported in the partner of a 47-year old male patient who was taking entrectinib. The pregnancy was voluntarily terminated at 5 weeks for unspecified personal reasons.

There were no reports of exposure to entrectinib in lactating patients; it is unknown whether entrectinib is excreted in human breast milk. However, because many drugs are excreted in human milk and because of the potential for serious adverse drug reactions in nursing infants, lactating mothers were not eligible for clinical studies with entrectinib.

Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of entrectinib in pediatric patients aged 12 years and older with solid tumors that have an *NTRK* gene fusion have been established. The effectiveness of entrectinib in adolescent patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumors harboring an *NTRK* gene fusion (ALKA, STARTRK-1, and STARTRK-2) and pharmacokinetic data in adolescents enrolled in STARTRK-NG; the pharmacokinetic profiles in adult and adolescent patients were comparable.

There is limited clinical experience with entrectenib in pediatric patients. The safety of entrectinib in pediatric patients 12 years of age and older was established through extrapolation of safety data in adults supported by safety data from 30 pediatric entrectinib-treated patients enrolled in STARTRK-NG. Of these 30 patients, 7% were < 2 years (n = 2), 77% were 2 to < 12 years (n = 23), 17% were 12 to < 18 years (n = 5); 57% had metastatic disease (n = 17) and 44% had locally advanced disease (n=13); and all patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were neuroblastoma (47%), primary CNS tumors (30%), and sarcoma (10%). The median duration of exposure for all pediatric patients was 4.2 months (range: 0.2 to 22.7 months).

Due to the small number of pediatric patients, limited number of adult patients, the single arm design of clinical studies of entrectinib, and confounding factors such as differences in

susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors. Adverse reactions and laboratory abnormalities of Grade 3 or 4 severity occurring more frequently (at least a 5% increase in per-patient incidence) in pediatric patients (n=30) compared to adult patients (n=338) (using the database lock date of 31 May 2019) were neutropenia (27% vs. 2%), bone fractures (23% vs. 5%), increased weight (20% vs. 7%), thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma-glutamyl transferase (7% vs 0%), and device-related infection (7% vs 3%). Three pediatric patients discontinued entrectinib due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis in one patient each).

From the nonclinical studies, it is mechanistically plausible that entrectinib could have skeletal effects. According to Su et. al. Trk receptors has been observed in injured bone tissues, and neurotrophin may play a role in bone fracture healing (Su et. al. 2018). For pediatric patients on entrectenib in the safety database, there were 2 patients (a 9-year old and a 4-year old) with bilateral leg fractures.

There were no findings of fractures or tooth problems in the animal toxicology studies in entrectinib. There was dose-dependent fetal rat developmental toxicity, especially in bone, seen mainly at a top dose which is less than 3 times higher than the human exposure at the proposed marketing dose. There was delayed growth in juvenile rats including shorter bones, and impaired learning and memory in juvenile rats. See the nonclinical part of this review for further details (Section 5.5).

As described in the skeletal fracture subsection of the AESI section of this review, skeletal fractures appeared to occur at a higher incidence in pediatric patients compared to adult patients and occurred in the absence of a history of trauma, suggesting that pediatric patient may be at higher risk of developing fractures with entrectinib compared to adult patients. Genentech will conduct a PMR study to better characterize the risk of fractures in adult and pediatric patients and identify ways to mitigate this risk.

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

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

The safety and effectiveness of entrectinib in pediatric patients less than 12 years of age with solid tumors who have an *NTRK* gene fusion have not been established.
The safety and effectiveness of entrectinib in pediatric patients with *ROS1*-positive NSCLC have not been established.

<u>Clinical Reviewer Comment</u>: Given the small number of pediatric patients in the safety database, the limited duration of follow-up, and limitations inherent in interpreting longitudinal

growth and development information in single arm trials, additional information is needed to better characterize the safety of entrectinib in pediatric patients, particularly because they may undergo treatment with entrectinib for months or years. Genentech is required to conduct a postmarketing requirement study to assess the long-term effects of entrectinib on pediatric growth and development. Given that entrectinib will be indicated for the treatment of pediatric patients 12 years of age and older with (b) (4) *metastatic cancer who have no satisfactory treatment options, the benefit:risk assessment favors use for use of entrectinib in the adolescent population despite the residual uncertainty regarding late effects of entrectinib, given the serious, life-threatening nature of the disease, based on the indication, and the lower risk of effects on growth and development than in younger patients.*

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There have been no reported cases of overdose in clinical studies with entrectinib. In the entrectinib clinical development program, the highest dose to which patients have been exposed is 2600 mg once daily. There is no information available on higher doses.

Genetech stated that available clinical evidence does not suggest a potential for abuse with entrectenib in a patient population with cancer and this reviewer agrees.

No AEs suggestive of withdrawal and rebound effects have been reported in clinical studies with entrectinib.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Entrectinib has been approved in Japan at the time of this review.

Expectations on Safety in the Postmarket Setting

The review teams determined that a REMS is not required to ensure safe and effective use of entrectinib. Entrectinib will be prescribed by oncologists who are trained how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs. See Section 13 (Postmarketing Requirements and Commitment) for details regarding the postmarketing studies Genentech is required to conduct to further characterize and identify ways to mitigate the serious risks of cardiac toxicity and skeletal fractures, and to characterize potential serious risk of adverse long-term effects of entrectinib on the growth and development, including neurological outcomes, of pediatric patients 12 years of age and older.

8.2.11. Integrated Assessment of Safety

The above safety assessment incorporates data from 4 trials and is therefore integrated.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

There were no major statistical issues that impacted the overall efficacy conclusions. However, the single arm nature of the study does not allow for statistical inferences to be made. In general, when considering integrated assessment strategy using data pooled across multiple studies, the findings need to be assessed with caution due to the underlying heterogeneity in the design of each of the studies included in pooled assessment. In this application, although the dose levels of the study drug considered in each study were different, the pooling of data across 3 studies for efficacy and four studies for safety was considered appropriate for reasons stated in Section 8.1. Time-to-event endpoints were included as the secondary endpoints supporting efficacy in the integrated assessments, but due to the non-randomized nature of the study these endpoints are not interpretable and cannot be used to support the efficacy of the study drug. Similarly, the same limitation applies to the PRO analyses included in this application and described in this review.

8.4. Conclusions and Recommendations

Drug approval based on the presence of a common genetic defect, regardless of primary tumor site of origin and histology (i.e., tissue-agnostic) is a new paradigm; the only previous drugs to be approved under this paradigm is pembrolizumab for the treatment of microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) metastatic solid tumors that has progressed on or for which there is no available therapy, and larotrectinib for the treatment of adult and pediatric patients with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

Approval under this paradigm draws from the strength of scientific evidence that a biomarker identifies a population with common characteristics (e.g., serves as primary oncogenic driver when present) regardless of tumor type, the strength of evidence that drug has the same pharmacologic effects on biomarker across tumor types in nonclinical and clinical studies, and the ability to reliably identify the biomarker across tumor types, when the biomarker-defined population is a subset of a specific tumor type. For entrectinib, there was a strong scientific rationale that the inhibition of TRK would cause tumor shrinkage in tumors with rearranged or mutated *NTRK*. There was strong non-clinical support in multiple cells lines and *NTRK*-fusion partners, and clinically, shrinkage was consistent across several primary tumors. Pooling of *NTRK* rearranged or mutated tumors allowed for a regulatory decision to be made for a tissue agnostic indication.

Based on the first 54 patients with a solid tumor an *NTRK*-fusion enrolled into the single arm-studies ALKA, STARTRK-1, or STARTRK-2, the estimated ORR as assessed by IRC was 57.4% (95% CI: 43.2%, 70.8%). The median duration of response was not reached by the time of the data cut-off date. including 7.4% of patients with a CR and 50% of patients with a PR to entrectinib. Responses were durable. Among the 31 responding patients, 55% had a DOR of at least 6 months, and 39% had a duration of response of over a year. The ORR and DOR is clinically meaningful in patients with advanced cancer who have no other treatment options or who would face morbid surgery. These observed benefits outweigh the risk of toxicity.

The safety review consisted of data from 355 adult and pediatric patients from 4 single-arm studies: Study ALKA, STARTRK-1, STARTRK-2 and STARTRK-NG. In general, the adverse reactions observed with entrectinib were consistent with the mechanism of action and toxicity observed in preclinical studies of entrectinib. The primary risks related to entrectinib are a variety of different neurotoxicities including cognitive, mood, and sleep disorders; congestive heart failure; skeletal fractures; hyperuricemia; transaminase elevation; QT prolongation; and vision disorders. These serious risks are adequately addressed in the Warnings and Precautions and Dosage Modifications sections of entrectinib product labeling. The rate of permanent

discontinuation of entrectinib due to AEs was 9% and most discontinuations were attributed to disease progression the underlying cancer. Overall, the toxicity profile of entrectinib is considered acceptable when considering the anti-tumor effects (e.g., durable responses) in patients with limited treatment options. The major safety risks of entrectinib are toxicities that oncologists frequently manage and are acceptable for a population with a serious and life-threatening condition in the context of the efficacy.

The heterogeneity of *NTRK*-fusion solid tumors is evident in the pivotal clinical trials and described in published literature. Due to the small sample size, there is a degree of uncertainty regarding the magnitude of the treatment effect of entrectinib in any single histologic subtype of solid tumors with an activating *NTRK* fusion. Genentech has agreed to a postmarketing requirement (PMR) to conduct studies that will provide additional data to verify and confirm the clinical benefit of entrectinib, particularly in histologic tumor types such as colon cancer and brain cancer for which the ORR is not well characterized.

(b) (4)

(b) (4). The review team determined that the safety and effectiveness of entrectinib was established in pediatric patients 12 years of age and older (i.e., adolescents) with solid tumors that have an *NTRK* gene fusion. The effectiveness of entrectinib in adolescent patients was established based on extrapolation of data from three open-label, single-arm clinical trials in adult patients with solid tumors harboring an *NTRK* gene fusion (ALKA, STARTRK-1, and STARTRK-2) and pharmacokinetic data in adolescents enrolled in STARTRK-NG. Entrectinib doses based on body surface area in pediatric patients 12 years and older resulted in similar systemic exposure compared to that in adults who received an entrectinib dose of 600 mg. There is limited clinical experience with entrectinib in pediatric patients. The safety of entrectinib in pediatric patients 12 years of age and older was established based on extrapolation of data in adults and data from 30 pediatric patients enrolled in STARTRK-NG. Due to the small number of pediatric and adult patients, the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors. In an expanded safety database that included 338 adult patients and 30 pediatric patients who received entrectinib across clinical trials, the Grade 3 or 4 adverse reactions and laboratory abnormalities that occurred more frequently (≥ 5%) in pediatric patients (n = 30) compared with adults (n = 338) were neutropenia (27% vs 2%), bone fractures (23% vs 5%), thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma-glutamyl transferase (7% vs 0%), device-related infection (7% vs 0.3%), and increased weight (20% vs 7%). Three pediatric patients discontinued ROZLYTREK due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis).

The safety and effectiveness of entrectinib in pediatric patients less than 12 years of age with solid tumors who have an *NTRK* gene fusion have not been established because there was inadequate information submitted to the NDA to determine the safe and effective dose of

entrectinib in this patient population and the safety database is very limited in this population, considering the many potential off-target effects of this multikinase inhibitor on the growth and development of younger (<12 years) patients (b) (4)

(b) (4)

We recommend approval of this application under Subpart H (accelerated approval) pending agreement regarding final labeling and agreement regarding post-marketing commitments and requirements. This approval is based on the observation of durable overall responses in patients with a variety of unresectable or metastatic tumors with *NTRK* fusions who experienced disease progression after prior treatment or who have no satisfactory treatment options and the strong biological rationale and nonclinical data supporting the site agnostic effects of entrectinib in patients with *NTRK* fusions as described in the efficacy section of this review.

Primary Statistical Reviewer
Sirisha L. Mushti, PhD

Statistical Team Leader
Lisa Rodriguez, PhD

Primary Clinical Reviewer
Leigh Marcus, PhD

Clinical Team Leader
Martha Donoghue, PhD

9 Advisory Committee Meeting and Other External Consultations

FDA did not refer this NDA to an advisory committee because no review issues were identified that raised significant public health questions regarding the risk:benefit assessment of entrectinib for the proposed indication.

Three special government employees (SGEs), Dr. Hussein Tawbi, M.D., Ph.D., Director of Melanoma Clinical Research & Early Drug Development and Co-Director of the MD Anderson Brian Metastasis Clinic at UT MD Anderson Cancer Center, Dr. Carlos Rodriguez-Galindo, EVP and Chair, Department of Global Pediatric Medicine of St. Jude Children's Research Hospital, a pediatric oncologist with expertise in rare pediatric cancers, and Mr. Josh Mailman, a patient representative with expertise in issues relating to development of treatments to treat rare cancers, were cleared by the Advisory Committee Oversight and Management Staff (ACOMS) to participate in a divisional assignment to consult on these NDAs.

A separate teleconference was held with each SGE on July 11, 2019 to discuss the applications. During these teleconferences, the SGEs indicated that they considered the risk:benefit assessment favorable for use of entrectinib in the treatment of patients with metastatic or unresectable *NTRK*-fusion solid tumors that had progressed following standard treatment or who did not have satisfactory available treatment. The SGEs also stated that they did not have concerns regarding approval of entrectinib for treatment of adolescent adult patients covered by this indication.

10 Pediatrics

Pediatric Patients ≥ 12 and <18 years

There is limited clinical experience with entrectenib in pediatric patients. The safety and effectiveness of entrectinib in pediatric patients aged 12 years and older with solid tumors that have an *NTRK* gene fusion have been established. The effectiveness of entrectinib in adolescent patients was established based on extrapolation of data obtained in adult patients with solid tumors harboring an *NTRK* gene fusion enrolled in one of three open-label, single-arm clinical trials (ALKA, STARTRK-1, and STARTRK-2), pharmacokinetic data in adolescents enrolled in STARTRK-NG, evidence that the pharmacokinetic exposure in adolescent patients with BSA based dosage regimens are comparable to that in adults at the recommended dose of 600 mg daily based on population PK analyses, and nonclinical data indicating the role of *NTRK* gene fusions as driver mutations in many cancers, regardless of histology, and that inhibition of the kinase inhibits proliferation of cells harboring *NTRK* gene fusions .

The safety of entrectinib in pediatric patients 12 years of age and older was established based on extrapolation of data from adults, safety data in 30 entrectinib-treated pediatric patients, and the comparability of exposure to entrectinib across adults and adolescent (≥12 but <18 years) patients. Of these 30 pediatric patients, 7% were < 2 years (n = 2), 77% were 2 to < 12 years (n = 23), 17% were 12 to < 18 years (n = 5); 57% had metastatic disease (n = 17) and 44% had locally advanced disease (n=13); and all patients had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were neuroblastoma (47%), primary CNS tumors (30%), and sarcoma (10%). The median duration of exposure for all pediatric patients was 4.2 months (range: 0.2 to 22.7 months).

Due to the small number of pediatric and adult patients, the single arm design of clinical studies of entrectinib, and confounding factors such as differences in susceptibility to infections between pediatric and adult patients, it is not possible to determine whether the observed differences in the incidence of adverse reactions to entrectinib are related to patient age or other factors. In an expanded safety database that included 338 adult patients and 30 pediatric patients who received entrectinib across clinical trials, Grade 3 or 4 adverse reactions that occurred more frequently (≥5%) in pediatric patients compared with adults were Grade 3-4 neutropenia (27% vs. 2%), skeletal fractures (23% vs 5%), Grade 3-4 thrombocytopenia (10% vs 0.3%), lymphopenia (7% vs 1%), increased gamma-glutamyl transferase (7% vs 0%), device-related infection (7% vs 3%), and increased weight (20% vs. 7%). Three pediatric patients discontinued entrectinib due to an adverse reaction (Grade 4 pulmonary edema, Grade 3 dyspnea, and Grade 4 pancreatitis in one patient each).

Pediatric Patients < 12 years

The safety and effectiveness of entrectinib in pediatric patients less than 12 years of age with solid tumors who have an *NTRK* gene fusion has not been established. Additionally, for

pediatric patients less than 12 years, there are insufficient data available to determine a dose with the to-be-marketed formulation (F06 capsule formulation) that can achieve comparable exposure to adults at the adult recommended dose of 600 mg orally daily. For further details, see Section 6.3.2.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

On March 11, 2019, FDA requested that Genentech incorporate the labeling information for NDA 212725 and NDA 212726 into a single integrated product label and address additional format and content issues. The table below summarizes changes to the proposed prescribing information for the integrated labeling submitted by Genentech on March 29, 2019. See the final approved prescribing information for ROZLYTREK (entrectinib) accompanying the approval letter for more information.

Table 66: Summary of Significant Labeling Changes

Section	Proposed Labeling	Approved Labeling
Highlights		
General	Format was not consistent with Selected Requirement of Prescribing Information (SRPI).	Revised format in accordance with SRPI.
Indications and Usage	…	Modified based on changes made to Indications and Usage (1).
Dosage and Administration	…	Modified based on changes made to Dosage and Administration (2).
Warnings and Precautions (W&P)	Included W&P for congestive heart failure, QT interval prolongation, cognitive disorders and embryo-fetal toxicity.	Broadened cognitive disorders to central nervous system (CNS) effects, removed syncope, and added vision disorders, skeletal fractures and hyperuricemia based on changes made to W&P (5).
Drug Interactions	…	Modified based on changes made to Drug Interactions (7).
Full Prescribing Information		
Indications and Usage, *NTRK* Gene Fusion-Positive Solid Tumors	Included an indication for adults and pediatric patients.	Restricted to adults and pediatric patients 12 years and older, to patients without a known acquired resistance mutation and to

Section	Proposed Labeling	Approved Labeling
		patients with metastatic disease or in which surgical resection is likely to result in severe morbidity based on FDA analysis of available data.
Dosage and Administration, Patient Selection	Included general statement that an FDA-approved test was not available and referred to section 14 for information on tests used in the trial.	Revised to recommend selecting patients for treatment based on presence of *NTRK* gene fusion in tumor specimens and to state that a FDA-approved test for the detection of *NTRK* gene fusion in solid tumors is not available.
Dosage and Administration, Recommended Dosage	(b) (4) Included tiered dosing based on body surface area for pediatric patients.	Included a separate subsection for each indication based on recommendations in Content and Format of the Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products regarding drugs with multiple indications. Added two headings under the new subsection "Recommended Dosage for *NTRK* Gene Fusion-Positive Solid Tumors": (1) adult patients and (2) pediatric patients 12 years and older with a modified tiered dosing approach for pediatric patients.

Section	Proposed Labeling	Approved Labeling
Dosage and Administration, Dosage Modifications for Adverse Reactions	Included a table describing (b) (4) (b) (4) dose reduction based on body surface area. Included a table describing the recommended dosage modifications for congestive heart failure, QT interval prolongation, cognitive disorders, syncope and anemia or neutropenia.	Simplified table to only include first and second dose reduction based on recommended dosage. Broadened dosage modifications for cognitive disorders to CNS effects, removed dosage modifications for syncope, and added dosage modifications for hyperuricemia and vision disorders based on changes made to W&P.
Warnings and Precautions	…	Reordered based upon frequency and potential severity of outcomes as recommended in Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format. Revised the W&P to describe the incidence in the safety population across clinical trials.
Warnings and Precautions, Central Nervous System Effects	(b) (4)	Expanded W&P to include cognitive impairment, mood disorders, dizziness and sleep disturbances based on FDA analysis of safety population.
Warnings and Precautions, Vision Disorders	Not included.	Added because clinically significant vision disorders occurred in patients, including blurred vision, photophobia, diplopia and visual impairment

(b) (4)

Section	Proposed Labeling	Approved Labeling
		(b) (4)
Warnings and Precautions, Skeletal Fractures	Not included.	Added because clinically significant fractures occurred in adult and pediatric patients.
Warnings and Precautions, Hepatotoxicity	Not included.	Added because clinically significant increased liver enzymes occurred in the safety population.
Warnings and Precautions, Hyperuricemia	Not included.	Added because clinically significant hyperuricemia occurred in the safety population.
Warnings and Precautions, Embryo-Fetal Toxicity	Based recommendations on animal studies and mechanism of action. Included recommendations for females of reproductive potential to use contraception during treatment and for (b) (4) after last dose.	Based recommendations on animal studies, mechanism of action and human data. Lengthened recommendation based on guidance document (see discussion about subsection 8.1 in this table) and added recommendation for males with female partners of reproductive potential.
Adverse Reactions	…	Revised list of clinically significant adverse reactions based on changes to W&P.
Adverse Reactions, Clinical Trials Experience	Included a description of the safety population. …	Revised description of safety population to indicate that the safety population described in Clinical Trials Experience is the same population used to describe the adverse reactions in the W&P and minimize description of pediatric population. Revised the list of serious adverse reactions (including fatal adverse reactions) and

Section	Proposed Labeling	Approved Labeling
	…	the list of adverse reactions that led to dose reduction and permanent discontinuation based on FDA analysis of available safety data. Added a description of grade 3-4 adverse reactions and adverse reactions that lead to dose interruption. Revised adverse reaction table to include columns for all grades and grades 3 to 5, list categories in decreasing frequency based on the rates for the adverse reactions listed in each category and list adverse reactions in each category in decreasing order, added additional terms, and redefined composite terms based 21 CFR 201.57 and FDA analysis of the safety population. Modified list of less common clinically relevant adverse reactions to include other adverse reactions that occurred in <10% of the safety population based on FDA analysis of the safety population. Modified laboratory abnormality table to include additional laboratory abnormalities based on FDA analysis of safety population and list categories in decreasing frequency based on the rates for the
	(b) (4)	
	(b) (4)	

Section	Proposed Labeling	Approved Labeling
		abnormalities listed in each category and list abnormalities in each category in decreasing order based on 21 CFR 201.57 and FDA analysis of the safety population.
Drug Interactions	(b) (4)	Simplified recommendations and referred to Dosage and Administration for specific recommendations.
Specific Populations, Pregnancy	Not included.	Added human data summarizing the effects of mutations in TRK pathway from published literature.
Specific Populations, Lactation	Recommended discontinuing breastfeeding during treatment and for 14 days after the final dose.	Modified recommendations based on entrectinib elimination half-life.
Specific Populations, Females and Males of Reproductive Potential	Recommended using effective contraception during treatment and for (b) (4) (b) (4) after the final dose.	Modified recommendation based on Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry.
Specific Populations, Pediatric Use	Summarized the data supporting the safety and effectiveness of ROZLYTREK in pediatric patients with *NTRK* gene fusion-positive solid tumors.	Included pediatric use statements for the following: (1) pediatrics 12 years and older with *NTRK* gene fusion-positive solid tumors; (2) pediatric patients less than 12 years with *NTRK* gene fusion-positive solid tumors and (3) pediatric patients with *ROS1*-positive NSCLC as required by 21 CFR 201.57. Modified the description of the safety, efficacy and pharmacokinetic data used to support the pediatric

Section	Proposed Labeling	Approved Labeling
		indications based on FDA analysis of the available data.
Specific Populations, Renal Impairment	Stated that no dose adjustment was needed for mild and moderate renal impairment and provided a definition of mild to moderate renal impairment.	Added method used to measure renal function to include sufficient information needed to evaluate renal function and determine need for dosage modification.
Specific Populations, (b) (4) Impairment	Stated that ROZLYTREK has not been studied in patients with hepatic impairment.	Revised dosage modifications based on degree of hepatic impairment and added definition for hepatic function based on FDA analysis.
Clinical Pharmacology, Pharmacokinetics	Included multiple subheadings to describe pharmacokinetics in specific populations.	Consolidated under heading "Specific Populations" based on recommendations in Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products - Content and Format
(b) (4)		
Clinical Studies, *NTRK* Gene Fusion-Positive Solid Tumors	(b) (4)	Replaced (b) (4) (b) (4) with percent of patients with a response at select timepoints, (b) (4) (b) (4)
	Described clinical outcomes in patients with brain metastases	Minimized description of outcomes in patients with brain metastases.
	Not included.	Added a table to summarize efficacy results by *NTRK*

Section	Proposed Labeling	Approved Labeling
		fusion partner.
	(b) (4)	
Patient Counseling Information	Included information for congestive heart failure, QT interval prolongation, cognitive disorders, embryo-fetal toxicity, lactation, administration and missed dose.	Added information for new W&P and drug interactions.

12 Risk Evaluation and Mitigation Strategies (REMS)

The review teams determined that a REMS was not needed to ensure safe and effective use of entrectinib in the indicated patient population. Entrectinib will be prescribed by oncologists who are skilled in monitoring, diagnosing, and managing serious toxicities caused by anti-neoplastic drugs including targeted therapies. Standard practice in oncology dictates that patients be apprised of risks related to treatment prior to receiving anti-neoplastic drugs.

13 Postmarketing Requirements and Commitment

Genentech has agreed to the following postmarketing requirements (PMR) and commitments (PMC):

PMRs Subject to the Reporting Requirements Under 21 CFR 314.510 Subpart H

- Submit the final report, including datasets, from the first 54 patients with *NTRK*-fusion solid tumors enrolled across ALKA, STARTRK-1 [NCT02097810] and STARTRK-2 [NCT02568267] studies to verify and describe the clinical benefit and further characterize the duration of response in patients who achieved a complete or partial response to entrectinib. All responding patients will be followed for at least 2 years from the onset of response or until disease progression, whichever comes first. Duration of response will be assessed by independent central review.

- Submit the final report, including datasets, from ongoing and proposed trials conducted 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; are metastatic or would require surgical resection that would result in severe morbidity; and have no satisfactory alternative treatment or that have progressed following treatment.

  A sufficient number of patients will be evaluated to 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.

PMRs Subject to the Reporting Requirements Under 505(o)

- Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the cardiac risks and sequelae in patients exposed to entrectenib with reasonable precision; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification

and monitoring. The design of the trial should include sufficient cardiac monitoring to achieve these objectives.

- Conduct clinical trial(s) of entrectinib in a sufficient number of pediatric patients 12 years of age and older with *NTRK*-fusion solid tumors to evaluate the potential serious risk of adverse long-term effects of entrectinib on growth and development, including neurological outcomes with reasonable precision. Patients will be monitored for growth and developmental milestones using age-appropriate screening tools and undergo neurological examination at appropriate intervals. Evaluations will include neurological exams with neurocognitive assessment, Karnofsky/Lansky score, growth as measured by height, weight, height velocity, and height standard deviation scores (SDS), age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner Stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

- Submit integrated safety analyses and supporting data from an adequate number of patients enrolled in clinical trial(s) designed to characterize the risk of fractures and its sequelae in patients exposed to entrectenib with reasonable precision; to identify risk factors for development of these sequelae; and to support labeling recommendations to mitigate the risk of skeletal fractures. The design of the trial should include sufficient bone monitoring to achieve these objectives, including but not limited to initial and serial assessment of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans, and markers of bone formation, bone resorption, and calcium metabolism.

Clinical Pharmacology

- Complete a pharmacokinetic trial to evaluate the effect of moderate and severe hepatic impairment on the pharmacokinetics and safety of Rozlytrek (entrectinib) compared to subjects with normal hepatic function in accordance with the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*," available at: https://www.fda.gov/media/71311/download.

Nonclinical

Determine functional activation or inhibition of off-target receptors, transporters, and/or channels that, at a concentration of 10 µM, showed greater than 50% inhibition by entrectinib or M5 in the secondary pharmacology studies submitted to NDA 212725 and 212726. As part of an integral safety assessment, include EC_{50} or IC_{50} data for target receptors, transporters, and channels that are still significantly affected at concentration less than 1 µM, particularly those involved in suicidal intent and behavior, as described in Muller et al., 2015.

Postmarketing commitments

- Commit to providing adequate analytical and clinical validation results from clinical trial data to support labeling of the F1CDx test to detect *NTRK* rearrangements for identifying patients who may benefit from entrectinib. The analytical validation should consist of precision, limit of detection, and accuracy studies for *NTRK* indications. The clinical validation should be supported by a clinical bridging study comparing F1CDx and the clinical trial enrollment assays.

14 Division Director (DHOT)

John Leighton, PhD
Director, Division of Hematology, Oncology, and Toxicology

15 Division Director (OCP)

Nam Atiqur Rahman, PhD
Director, Office of Clinical Pharmacology

16 Division Director (OB)

Rajeshwari Sridhara, PhD
Director, Office of Biometrics

17 Division Director (Clinical)

I concur with the recommendations of the review team, cited here and in the Quality review, that the application should be approved for the proposed indication and recommended dose, based on the demonstration of an effect on overall response rate that is large in magnitude [ORR 57% (95% confidence interval: 43%, 71%)] and durability [68% of the 31 responders with DOR ≥ 6 months and 45% with DOR ≥12 months, providing substantial evidence of a clinically meaningful effect on ORR. Considering that the estimated annual incidence of 1500-5000 new cases of *NTRK* fusion-positive tumors in the United States, the heterogeneity of affected tumors and that there is no available therapy for the indicated population (larotrectinib was approved under the provisions of 21 CFR 314 Subpart H), the conduct of randomized clinical trials to demonstrate improvements in survival are not feasible. The benefits of durable responses in this population with a serious and life-threatening disease and no alternative therapy outweigh the serious risks of entrectinib, which include congestive heart failure, a variety of neurocognitive impairment, mood disorders, and other central nervous system (ataxia, dizziness, dysesthesia,) effects, skeletal fractures, hepatotoxicity, QT prolongation, a variety of effects impairing vision, and hyperuricemia requiring medical intervention, as well as common (≥ 20%) but less serious toxicities of fatigue, constipation, dysgeusia, edema, diarrhea, nausea, weight gain, cough, vomiting, pyrexia, and arthralgias.

The major scientific issues with this application were the limited number of patients studied and short follow-up such that the treatment effect is imprecisely characterized and the assumption that *NTRK* gene fusions are the primary or sole oncogenic driver across all tumor types requires additional data to verify. Additionally, the limited data available in pediatric patients suggested that, unlike other drugs, the pharmacokinetic profile may differ from adults such that BSA-adjusted dosing was needed to provide a comparable exposure to entrectinib in adolescents as in adults at the 600 mg orally once daily dosage regimen and support the extrapolation of safety from adults to adolescent patients. Finally, at the time of approval, there is no FDA-approved companion diagnostic test for identification of patients for whom entrectinib is indicated. Although FDA generally requires contemporaneous approval of a companion diagnostic test, the nature of the mutation (gene fusion) increases the likelihood that this can be accurately detected with NGS. Given the restriction of the indication to patients with disease progression on (or who have no) available therapy, the risks of false positives test results are less severe. Furthermore, studies are underway to analytically validate a companion diagnostic assay for this purpose.

The other major issue with this application was the poor quality of the application, which included numerous mis-statements and poor data presentation and required more than 70 requests for clarification of data; the apparent lack of familiarity of the Genentech team with the data included in the application, such that initial responses to information

requests were often inaccurate, requiring duplicative follow-up by FDA to obtain clarification on the information presented in the NDA; and the failure of Genentech to provide timely updates on important safety data (risk of skeletal fractures). Additionally, Genentech's failure to submit complete data for the required financial disclosure information diverted staff time and attention from review of the primary data, that required multiple internal and external meetings, review of additional submissions describing corrective actions as well as new data submissions over the course of several months to adequately address this deficiency. Given these major deficiencies in application content and quality, the review of this application from a clinical standpoint required excessive time and delayed the time to final action on this application.

Given the uncertainties regarding the safe and effective use of entrectinib for this indication, I concur with granting accelerated approval for this application. Specifically, I concur with the requirement for post-marketing studies under 21 CFR 314 Subpart H to further characterize the treatment effect of entrectinib overall and in common adult tumors in adults. I also concur with the requirement for additional post-marketing studies to further characterize the effects of entrectinib on growth and development of pediatric patients; to further characterize the adverse reaction of congestive heart failure; to further characterize the adverse reaction of fractures; and to evaluate the effects of moderate and severe hepatic impairment on the pharmacokinetics of entrectinib. Finally, I concur with agreed-upon commitment to identify at least one analytically validated commercial assay(s) that will accurately identify the presence of *NTRK* gene fusions in tumor specimens to identify patients for whom entrectinib is indicated.

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Patricia Keegan, MD
Director, Division of Oncology Products 2

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of entrectinib (Rozlytrek) *was also assessed by Drs. Martha Donoghue and Leigh Marcus. I concur with their recommendation to approve this drug. My signature below also represents an approval recommendation for the clinical portion of this application under CDER.*

_____

Gideon Blumenthal, MD
Deputy Center Director, Oncology Center for Excellence

19 Appendices

19.1. References

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Package-Insert (for the US) PRESCRIBING INFORMATION for:

olaratumab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761038lbl.pdf

imatinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021588s052lbl.pdf

regorafenib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203085s008lbl.pdf

sunitinib malate:
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sorafenib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021923s018lbl.pdf

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lenvatinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206947s008lbl.pdf

crizotinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202570s023lbl.pdf

alectinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208434s004lbl.pdf

ceritinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s010lbl.pdf

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https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=210861

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19.2. Financial Disclosure

During the filing review, the review teams noted that there was a substantial proportion (12%, 32%, and 54%) of missing financial disclosure forms (FDFs) in three of the four studies evaluating safety and efficacy.

Relevant dates for applications:

- Genentech-Ignyta merger: effective February 8, 2018
- Transfer of INDs to Genentech: June 12, 2018
- Change of Sponsor letters issued on August 10, 2018 under IND 120500 and on December 4, 2018 under IND 135124

Genentech's "Note to File" in the original NDA documented the following reasons that FDFs were not collected:

- Investigator did not respond to contacts
- Genentech was not required to obtain FDFs for investigators who discontinued study participation more than one year prior to Genentech's acquisition of Ignyta.

The Division chose to file the NDAs despite the missing FDFs. Multiple requests (January 3, 2019 information request [IR]; February 8, 2019 IR, March 1, 2019 March 1, 2019 Filing letters; and March 14, 2019 teleconference) were made by the Division to obtain additional information on the missing FDFs, including evidence of due diligence

and Genentech's ability to obtain the missing FDFs. DOP2 also requested that Genentech provide justification as to why the absence of the required financial disclosure forms for a substantial proportion of clinical investigators does not impact the reliability of the clinical information submitted to the NDA due to potential bias due to undisclosed relationships.

On February 1, 2019, in response to FDA's request for additional information, Genentech provided a 300+ page PDF document that included line listings of investigators for each trial indicating the FDF status for Ignyta (no disclosable interests, disclosable interests, or missing/unable to obtain). These line listings were of little utility. FDA concluded that the response was inadequate.

On March 15, 2019 and March 29, 2019, Genentech submitted amendments describing

- procedures for collection of Ignyta and Genentech FDFs
- summary-level information regarding the status of FDF documentation.

Genentech acknowledged that Ignyta did not maintain records of their due diligence to obtain missing FDFs.

Genentech stated that, based on the FDA *Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators* which states "If a clinical investigator did not participate in the entire study, information collected should be for the period of time he or she participated in the study and for one year following the end of his or her participation," Genentech prioritized obtaining financial disclosure information for Roche/Genentech for investigators who participated on study within a year of the merger (June 2018).

The tables below summarize the updated financial disclosure information provided by Genentech in the March 15, 2019 and March 29, 2019 amendments.

Table 67: Summary of Financial Disclosure Information NDAs 212725/6
(Updated FDF collection status dated March 15, 2019)

STUDY	Total Number of Investigators to Date	Ignyta		Genentech	
		FDFs collected n	FDFs missing n	FDFs collected n	FDFs missing n
ALKA	38	27	11	26	12
STARTRK1	149	139/140*	1	70	79**
STARTRK2	1996***	1240/1273*	33	1031	965****
STARTRKNG	144	129/129*	0	141	3

*Denominator differs from the total number of investigators to date because additional investigators were added following the Genentech-Ignyta merger.
**Genentech states 64 investigators ended their participation in this study more than a year prior to Roche/Genentech-Ignyta merger; therefore, Genentech considers FDFs to be missing for 15 investigators.
***Genentech assumes only 1357 investigators from this study contributed to the NDA, FDFs were collected for 1017 of these investigators and FDFs were missing for 340.

****Per Genentech 73 of the 1357 investigators who contributed data to the NDA ended their participation in this study more than a year prior to Roche/Genentech-Ignyta merger; therefore, Genentech considers FDFs to be missing for 267 investigators.

A summary of the FDF obtained by Ignyta and Genentech by investigator across the four studies limited to sites that enrolled patients are provided in Table 68 and Table 69, respectively.

Table 68: Summary of Ignyta Financial Disclosure Information by Investigator

	Disclosable Interest	Non Disclosable Interest	Missing Financial Disclosure Information	Total
Total Number of Investigators	4*	1520	57	1581
Number of investigators who enrolled patients with an Objective Response	1	814	22	837
Number of Investigator who enrolled patients with at least one dose	4*	1520	57	1581

* Since performing this analysis we have confirm that 2 of these investigators submitted a positive disclosure in error (see above).

Source: copied from IR response 29 March 2019

Table 69: Summary of Genentech Financial Disclosure Information by Investigator

	Disclosable Interest	Non Disclosable Interest	Missing Financial Disclosure Information	Total
Total Number of Investigators	3	1112	573	1688
Number of investigators who enrolled patients with an Objective Response	1	642	290	933
Number of Investigator who enrolled patients with at least one dose	3	1112	573	1688

Source: copied from IR response 29 March 2019

A summary of the financial disclosure information by patient across the four studies for sites that enrolled patients included in NDAs 212725 and 212726 for Ignyta and Genentech are provided in Table 70 and Table 71, respectively.

Table 70: Summary of Ignyta financial disclosure information by patient

	Disclosable Interest	Missing FDF
Number of patients with objective response (assessed by BICR) enrolled at site with	1	18
Number of patients enrolled into safety population at site with	12	108
Number of patients enrolled into NTRK efficacy evaluable population at site with	4	18

Source: copied from IR response 29 March 2019

Table 71: Summary of Genentech financial disclosure information by patient

	Disclosable Interest	Missing FDF	
		Investigator Left Study One Year Prior to Merger	Other
Number of patients with objective response (assessed by BICR) enrolled at site with	2	52	0
Number of patients enrolled into safety population at site with	8	241	13
Number of patients enrolled into NTRK efficacy evaluable population at site with	2	40	0

Source: copied from IR response 29 March 2019

Genentech asserted that bias related to the assessment of efficacy is mitigated by use of BICR for assessment of the key efficacy endpoints of ORR and duration of response; Genentech noted that ORR by BICR and Investigator assessment for both NDAs was similar.

To assess for bias in safety reporting, Genentech compared adverse event reporting in patients enrolled at sites without missing financial disclosure information and disclosable financial interests and adverse event reporting in patients enrolled by sites with disclosable interests or missing financial disclosure information for Ignyta and Genentech (Table 72, and Table 73). For the purposes of this analysis, the assumption was made that investigators with non-disclosable interests would not have any alterations in reporting behavior and therefore these investigators served as a “control” group. Genentech concluded that the patterns of reporting were consistent over time between the two groups irrespective of reporting status.

Table 72: Adverse Event Reporting Patterns Based on Ignyta Financial Disclosure Status

	Disclosure Status (n=355)	
	Enrolled at Site with NoDisclosable Interests (n=241)	Enrolled at Site with Disclosable Interest or Missing Financial Disclosure Information (n=114)
Patients with an AE reported while on treatment for < 3 months	240 (99.6%)	113 (99.1%)
Patients with an AE reported while on treatment ≥ 3 month and <6 months	146 (60.6%)	58 (50.9%)
Patients with an AE reported while on treatment ≥ 6 months and < 9 months	107 (44.4%)	41 (36.0%)
Patients with an AE reported while on treatment ≥ 9 months	71 (29.5%)	31 (27.2%)

AE=Adverse Event; Data source: ah_sa1898_t_ae_fdis_ign_SE

Source: copied from IR response 29 March 2019

Table 73: Adverse Event Reporting Patterns Based on Genentech Financial Disclosure Status

	Disclosure Status (N=355)	
	Non-Disclosable Interests* (n=100)	Disclosable Interest or Missing Financial Disclosure Information* (n=242)
Patients with an AE reported while on treatment for < 3 months	99 (99.0%)	242 (100%)
Patients with an AE reported while on treatment ≥ 3 month and <6 months	63 (63.0%)	140 (57.9%)
Patients with an AE reported while on treatment ≥ 6 months and < 9 months	41 (41.0%)	107 (44.2%)
Patients with an AE reported while on treatment ≥ 9 months	28 (28.0%)	74 (30.6%)

AE= Adverse Event; Data source: ah_sa1898_t_ae_fdis_ro_SE
*There are 13 patients in the safety population excluded as they were enrolled at sites where the investigator left one year prior to the acquisition by Roche and therefore not represented in this analysis. (source: t_fin_dis_pat_roche)

Source: copied from IR response 29 March 2019

Based upon these analyses, the clinical reviewers concluded that there did not appear to be a pattern of underreporting of adverse events at sites with disclosable interests for Ignyta or Genentech.

The Office of Regulatory Policy (ORP) and the review teams met on April 18, 2019. ORP clarified that financial disclosure (FD) information should be obtained for all investigators or sub-investigators who were directly involved in the treatment or evaluation of research subjects, or documentation of due diligence should be provided. ORP confirmed that if a clinical

investigator did not participate in the entire study, information collected should be for the period of time he or she participated in the study and for one year following the end of his or her participation. 21CFR 54.4(b) requires investigators to provide information on financial interests and arrangements during the "course of the study and one year after completion of the study." For the purposes of determining the time period for obtaining FD information, FDA considers the completion date for both NDAs to be October 31, 2018, which is the data-cutoff date used for follow-up data for duration of response that was submitted to the NDAs on March 4, 2019. In addition to the relevant time period for Ignyta FD information, Genentech FD information should be obtained for investigators and sub-investigators who were directly involved in the treatment or evaluation of research subjects from the date of the merger (February 8, 2018) through the completion study date (October 31, 2018), and will need to be updated for a year following the completion of the study.

In an information request sent on May 7, 2019, FDA conveyed to Genentech that more than one attempt at contacting an investigator and more than one method of contact should be attempted in order to demonstrate due diligence. Genentech was further advised that all attempts to contact the investigator should be documented (e.g., email, letter, telephone calls, written memos, and certified mail or reliable courier service that provides notice of recipient's receipt), along with the date that these attempts were made (which should be separated by a reasonable interval of time, in order to reach investigators that may be traveling, on leave, etc.). If an investigator is no longer at the institution where the study was conducted, FDA recommended that Genentech make a reasonable attempt to locate the investigator, for example by conducting an Internet search, contacting professional associations, or requesting contact information from the institution. For those investigators that are no longer employed by the enrolling institution, Genentech was advised to indicate whether they were able to obtain current contact information, and if not, how they attempted to obtain this information.

In reviewing the information provided by Genentech on May 22, 2019 (dated May 21, 2019) and June 7, 2019 in response to this request, FDA reviewers focused on clinical study sites with the largest number of patients enrolled and the number of attempts made by Genentech to obtain missing FDFs, the methods of contact (email, phone, mail), and the dates in which the attempts were made. In some cases, an investigator was on maternity or medical leave, had left the hospital/was no longer employed (most investigators in this category had left in 2017), or there was an upcoming site visit (June 2019) in which Genentech would attempt to contact the investigator again. In many cases, Genentech attempted to contact an investigator to obtain a FDF up to 10 times. Overall, the reasons cited for failing to obtain FDFs seemed reasonable and the FDA reviewers concluded that Genentech demonstrated due diligence in attempting to obtain the missing FDFs.

Clinical Reviewer Comment: *Based on the review of Genentech's responses to the multiple requests for information from FDA, Genentech demonstrated due diligence in attempting to contact investigators for whom FDFs were missing. Relevant tables from this submission are provided below.*

Table 74: Summary of Financial Disclosure Information

Description	Sub-Total (if applicable)	Total
Grand Total Number of All Investigators/ Sub-Investigators		Ignyta: 1604[1] Roche/Genentech: 1682[1]
Total Number of Investigators/ Sub-Investigators Certified Regarding the Absence of Financial Interests and/or Arrangements for Ignyta		1597
Total Number of Investigators/ Sub-Investigators Certified Regarding the Absence of Financial Interests and/or Arrangements for Genentech/Roche		1381
Total Number of Investigators/ Sub-Investigators Not Certified for Ignyta		5
Total Number of Investigators/ Sub-Investigators Not Certified for Roche/Genentech		296
Total Number of Investigators/ Sub-Investigators Who Hold Financial Interests and/or Arrangements with Ignyta Requiring Disclosure	• Significant Payments of Other Sorts n= 1 • Unknown n=1	2
Total Number of Investigators/ Sub-Investigators Who Hold Financial Interests and/or Arrangements with Genentech/Roche Requiring Disclosure	• Compensation n= 3 • Equity Interest n= 1 • Significant Payments of Other Sorts n= 1	5

Source: IR 42 submitted 7 June 2019

This tabular summary includes investigators at sites that enrolled ≥1 patient into the NDA dataset and sites that enrolled ≥1 patient included in the Second Update Report for Study STARTRK-NG (data cut 31 March 2019). A table of all clinical investigators/sub-investigators not certified for Ignyta and Genentech, and the due diligence attempts made to obtain the missing information for Ignyta and Genentech were submitted with Genentech's June 7, 2019 response to FDA's IR-42 which was adequate and demonstrated due diligence in attempting to collect missing financial disclosure forms.

Reviewer: Leigh Marcus, MD

Date of Review: 5 August 2019

Covered Clinical Study (Name and/or Number): ALKA

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 38		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2*		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

There were no disclosable financial interests for this trial and Genentech demonstrated adequate due diligence in collecting financial disclosure forms.

Covered Clinical Study (Name and/or Number): STARTRK1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 149		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6*		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

The clinical reviewers determined that the disclosed financial interest was unlikely to have a material impact on the integrity of the data provided from this trial and that Genentech demonstrated due diligence in collecting financial disclosure forms.

Covered Clinical Study (Name and/or Number): STARTRK2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1996		
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): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Unknown: 1* Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4 forms missing for Ignyta and 308 forms missing for Genentech; FDA reviewers determined that due diligence was exerted to collect these missing FDFs.**		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Per Genentech, this investigator marked both the "yes" and "no" box on the financial disclosure form but did not provide details on the disclosure. This investigator is no longer at the site and attempts to contact the investigator for clarification were unsuccessful.*
***Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

The clinical reviewers determined that the disclosed financial interests/arrangements were unlikely to impact the integrity of the data from this trial and that Genentech exerted due diligence in their attempts to collect the missing financial disclosure forms.

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

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 144		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 for Ignyta and 1 for Genentech Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 financial disclosure forms were missing for Ignyta and 26 were missing for Genentech. FDA reviewers determined that due diligence was exerted to collect these missing FDFs.*		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

**Based on updated information submitted by Genentech on May 22, 2019 (dated May 21, 2019) in response to FDA's May 7, 2019 request for information.*

The clinical reviewers determined that the disclosed financial interests/arrangements were unlikely to impact the integrity of the data from this trial and that Genentech exerted due diligence in their attempts to collect the missing financial disclosure forms.

19.3. Nonclinical Pharmacology/Toxicology

No additional information.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical

A bioanalytical assay method based on liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) was developed to simultaneously measure entrectinib and its active metabolite M5 in human plasma and urine. The method was modified and transferred between three bioanalytical laboratories ([redacted] (b) (4) and Ignyta). In the cross-validation, the [redacted] (b) (4) inter-lab incurred sample results did not meet the pre-defined acceptance criteria, therefore the concentration data generated from [redacted] (b) (4) for Study ALKA-372-001 were not included in the pooled analysis for the PopPK model development nor in the exposure-response (E-R) analyses.

For the Ignyta method, entrectinib and M5 concentrations in human plasma and urine were determined using a protein precipitation extraction procedure. The extraction is performed in an ice-water bath. Aliquots of 50 µL human plasma (sodium heparin) samples or urine samples (treated with 0.5% Tween 20) were spiked with 300 µL of D8-entrectinib and D8-M5 in acetonitrile. 50.0 µL aliquots of the protein precipitation supernatant were then transferred to a plate containing 250 µL of reconstitution solution. The extract was chromatographed under reverse phase conditions on a Kinetex C18 HPLC column using a gradient system with 10 mM ammonium formate, 0.05% formic acid in water and 0.1% formic acid in acetonitrile. MS detection uses an [redacted] (b) (4) SCIEX API 5000 with TurboIonSpray interface and MRM operated in positive ion mode.

Entrectinib and M5 were found to be stable in human plasma for up to 483 days at -80°C. When stored at -20°C, the compounds were stable for up to 380 days.

The bioanalytical methods, validation parameters, and method performance are summarized in **Table 75**.

Table 75: Summary of Bioanalytical Methods Used in Entrectinib Clinical Program

Matrix	Analyte	Validation Study Number (Roche Report No.)	Bioanalytical Laboratory	Calibration Range (ng/mL)	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
Plasma	Entrectinib	8432.121814.1 (1087331)	(b) (4)	2-2000	2	-9.83 to -2.00 (intra-assay) -4.67 to -2.67 (inter-assay)	3.03 to 8.15 (intra-assay) 3.61 to 6.92 (inter-assay)
		SR-15-026-AM-01 (1087327)	Ignyta	2-2000	2	-6.1 to 8.0 (intra-assay) -3.4 to 7.5 (inter-assay)	2.4 to 10.4 (intra-assay) 3.4 to 6.6 (inter-assay)
	M5	8432.121814.1 (1087331)	(b) (4)	2-2000	2	-8.67 to 0.00 (intra-assay) -6.00 to -2.00 (inter-assay)	1.69 to 8.14 (intra-assay) 3.01 to 6.58 (inter-assay)
		SR-15-026-AM-01 (1087327)	Ignyta	2-2000	2	-6.4 to 8.0 (intra-assay) -2.5 to 5.0 (inter-assay)	3.0 to 11.0 (intra-assay) 3.9 to 7.2 (inter-assay)
Urine	Entrectin b	SR-16-006 (1087328)	Ignyta	50-10000	50	-10.8 to 6.2 (intra-assay) -4.9 to -2.9 (inter-assay)	0.6 to 4.5 (intra-assay) 4.1 to 8.0 (inter-assay)
	M5	SR-16-006 (1087328)	Ignyta	50-10000	50	-4.6 to 6.6 (intra-assay) -1.4 to 3.0 (inter-assay)	0.6 to 5.8 (intra-assay) 2.9 to 5.5 (inter-assay)

Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods (M2.7.1), Table 5.

Table 76: Summary of Bioanalytical Method Performance for Analysis of Clinical Study Samples

Study	Bioanalytical Laboratory	Bioanalytical Method	Analyte	Biological Matrix	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
RXDX-101-01	(b) (4) (1st Part)	8432.121814	Entrectinib	Plasma	2	-6.10 to 1.83	5.10 to 9.00
	(b) (4) (1st Part)	8432.121814	M5	Plasma	2	-3.50 to 0.667	4.74 to 12.3
	Ignyta (2nd Part)	SR-15-026-AM-01	Entrectinib	Plasma	2	-0.9 to 3.1	4.2 to 16.4
	Ignyta (2nd Part)	SR-15-026-AM-01	M5	Plasma	2	-0.3 to 3.8	4.8 to 6.2
RXDX-101-02	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-0.8 to 2.5	4.3 to 13.0
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-2.0 to 3.1	4.9 to 15.2
RXDX-101-03	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-1.5 to 1.9	4.1 to 12.9
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-2.5 to 2.5	2.5 to 5.8
CA14707	(b) (4)	8432.121814	Entrectinib	Plasma	2	0.00 to 2.00	4.69 to 6.93
		8432.121814	M5	Plasma	2	0.00 to 5.33	4.61 to 8.63

RXDX-101-04	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	0.6 to 8.0	4.2 to 4.4
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	1.3 to 8.6	3.2 to 4.1
RXDX-101-05	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-11.8 to -4.4	1.5 to 2.6
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-1.9 to -8.5	2.1 to 4.8
	Ignyta	SR-16-006	Entrectinib	Urine	50	1.0 to 4.3	1.6 to 6.2
	Ignyta	SR-16-006	M5	Urine	50	-0.6 to 6.1	2.2 to 4.5
RXDX-101-06	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-11.5 to -1.3	3.0 to 7.4
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-5.2 to 0.0	3.5 to 4.8
RXDX-101-07	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-5.6 to -3.1	2.1 to 5.6
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-3.8 to -0.6	2.1 to 5.4
RXDX-101-08	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-3.3 to 0.0	1.6 to 2.9
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-5.0 to 0.6	2.3 to 3.4
RXDX-101-09	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-2.0 to -0.6	3.1 to 7.6
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-3.7 to 0.0	4.2 to 5.5
RXDX-101-12	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-3.8 to -1.3	1.5 to 3.7
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-4.7 to 0.0	2.1 to 3.1
RXDX-101-13	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-4.7 to 3.1	1.0 to 5.8
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-7.3 to 3.8	1.7 to 5.7
RXDX-101-14	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-4.5 to 4.4	2.2 to 5.0
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-3.3 to 3.1	2.7 to 5.6
RXDX-101-15	Ignyta	SR-15-026-AM-01	Entrectinib	Plasma	2	-3.0 to 5.0	2.4 to 6.0
	Ignyta	SR-15-026-AM-01	M5	Plasma	2	-3.5 to 1.9	2.4 to 4.1

The performance of the bioanalytical methods during the analysis of PK samples for individual clinical studies is summarized in **Table 76**.

19.4.2. Pharmacometrics

1. Population Pharmacokinetic Analyses

1) Methods and Data

The goal of population PK analysis (popPK) was to develop a population PK model to assess sources of variability (intrinsic and extrinsic covariates) of entrectinib and its active metabolite M5 in patients with advanced/metastatic solid tumors. The final popPK model was then used to predict a pediatric dose that matches the entrectinib exposure in adult patients. The population PK model included pooled data from 3 clinical trials, comprising 276 patients with advanced solid tumors. The key covariate information in 276 patients is summarized in **Table 77**.

Table 77: Summary of Covariate Data in the PopPK Analysis

Covariate	Data
Weight (Kg): Median (Range)	68.2 (13.3, 130.2)
Age (Yrs.): Median (Range)	55 (4, 86)
BSA (m^2): Median (Range)	1.78 (0.59, 2.58)
Hepatic Function	
Normal	N=234
Mild Impairment	N=41
Moderate Impairment	N=0
Severe Impairment	N=1
Renal Function	
CrcL>90	N=156
60<CrcL<90	N=93
30<CrcL<60	N=26
Race	
Asian	N=78
Black or African American	N=14
White	N=166
Others	N=2
Missing	N=16
Ethnicity	
Hispanic or Latino	N=9
Not Hispanic or Latino	N=245
Missing	N=22
Formulation	
F1	N=68
F2A or F2B	N=207
F1 and F2A	N=1
Pediatric Patients	
12 <= Age<18	N=7
6 <=Age<12	N=9
Age<6	N=1
Study	
RXDX-101-01	N=57
RXDX-101-02	N=203
RXDX-101-03	N=16

Source: Reviewer's Analysis based on "poppk.xpt"

The popPK analysis was conducted by the applicant and evaluated by the reviewer. The PK of entrectinib was characterized by a one-compartment model with first-order elimination and with a sequential zero- and first-order absorption without lag-time. The residual variability was

modeled as a combination of an additive and a multiplicative error model. In the applicant's analysis, apparent clearance and apparent volume of distribution were allometrically scaled by weight with power coefficient fixed to 0.75 and 1, respectively. The bioavailability of F1 compared to F2A in adults were assumed to be 1, while the bioavailability of F1 compared to F2A in pediatric patients in study RXDX-101-03 were estimated to be 68.9%. In reviewer's evaluation, the estimated power coefficient of weight on CL were 0.348, which is significantly different from the assumed power coefficient of 0.75 based on allometric scaling. The relative BA of F1 compared to F2A in pediatric patients in study RXDX-101-03 also changed from 68.9% to 91.2% when the effect of weight on CL is relaxed. Although the point estimate of weight effect on CL may not be very robust because of the small sample size of pediatric patients, the allometric scaling assumption was also not supported by the observed entrectinib PK data in adult and pediatric patients. In addition, the assumption of lower bioequivalence of F1 formulation compared to F2A/F06 is not well supported as F1 formulation has been shown to be bioequivalent (the GMR (90% CI) for AUCINF were 0.98 (0.89, 1.08)) to F06 formulation in adult subjects.

2) Effect of intrinsic/extrinsic factors on drug exposure

A full covariate modeling approach was implemented for this popPK analysis to investigate the effects of covariate on entrectinib by the reviewer. Parameter estimates of full covariate model based on reviewer's evaluation were provided in **Table 78**. No signs of model misspecification were identified in the goodness-of-fit plots (**Figure 30**). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of entrectinib in both adult and pediatric population with F1 or F2A formulation (**Figure 31).** Bootstrap analyses demonstrated consistency in parameter estimates and indicated the robustness of the model.

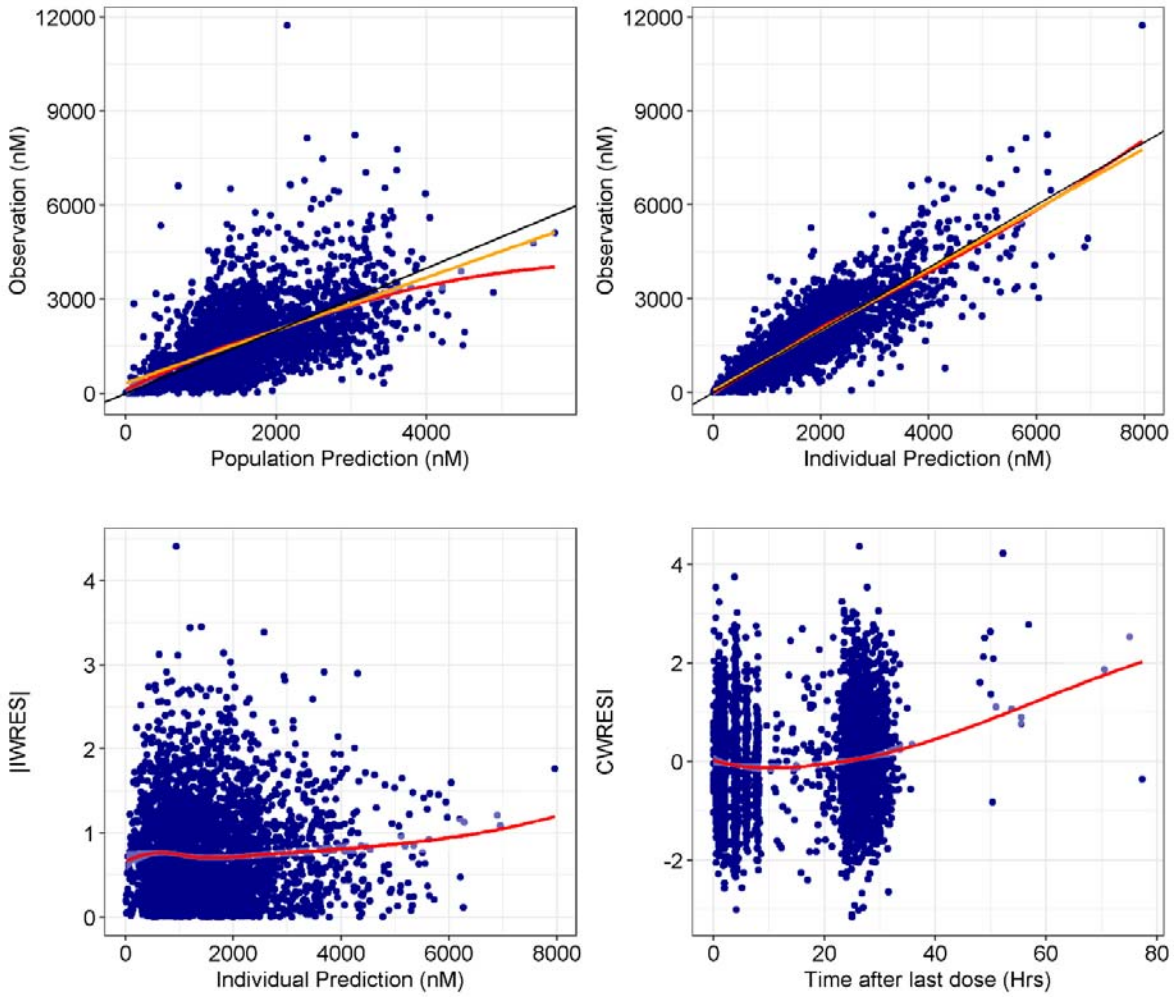
Table 78: Parameter Estimates of the Full Covariate PopPK Model

Parameter	*Estimate*	*Bootstrap Median*	*Bootstrap CV*	*Bootstrap CI*
CL (L/h)	20.5	20.4	5.3	(18.4, 22.2)
V (L)	549	549	3.6	(519, 583)
KA	1.08	1.2	18.2	(0.917, 1.65)
F1	1*			
D1	1.83	2.05	11.6	(1.69, 2.45)
ADD	167	169	10.0	(145, 201)
PROP	0.268	0.264	4.5	(0.244, 0.283)
F1 formulation on F1 in pediatrics	0.912	0.912	4.7	(0.844, 0.983)
Covariate Effects				
M his	0.348	0.349	32.0	(0.167, 0.538)
CLHEMO	0.162	0.186	87.6	(-0.0642, 0.471)

CLAGE	-0.0867	-0.0885	-72.9	(-0.195, 0.0165)
CLHEP1	0.0181	0.0221	308.4	(-0.0921, 0.146)
CLHEP2	0.61	0.61	14.0	(0.483, 0.785)
CLREN1	-0.0255	-0.026	-201.7	(-0.114, 0.0634)
CLSEX	-0.0917	-0.0815	-61.2	(-0.164, 0.00122)
CLINHIBIT	-0.168	-0.167	-41.7	(-0.248, -0.0431)
CLPH	-0.0365	-0.0352	-111.6	(-0.101, 0.0275)
CLASIA	0.0206	0.0155	341.8	(-0.0698, 0.0991)
CLBLACK	-0.323	-0.329	-38.6	(-0.544, -0.105)
CLHISPANIC	0.177	0.186	96.9	(-0.0866, 0.454)
CLREN2	0.0329	0.0277	297.6	(-0.114, 0.175)
VWEIGHT	0.714	0.721	12.4	(0.56, 0.859)
Random Effects				
IIV CL	0.0492	0.0434	26.7	(0.0245, 0.062)
IIV V	0.0686	0.0698	28.7	(0.0393, 0.105)
IIV KA	0.494	0.531	30.5	(0.298, 0.815)
IIV F1	0.0938	0.0903	15.5	(0.0705, 0.115)
IIV D1	0.551	0.504	23.4	(0.346, 0.748)
IIV RV additive	0.687	0.687	17.1	(0.517, 0.913)

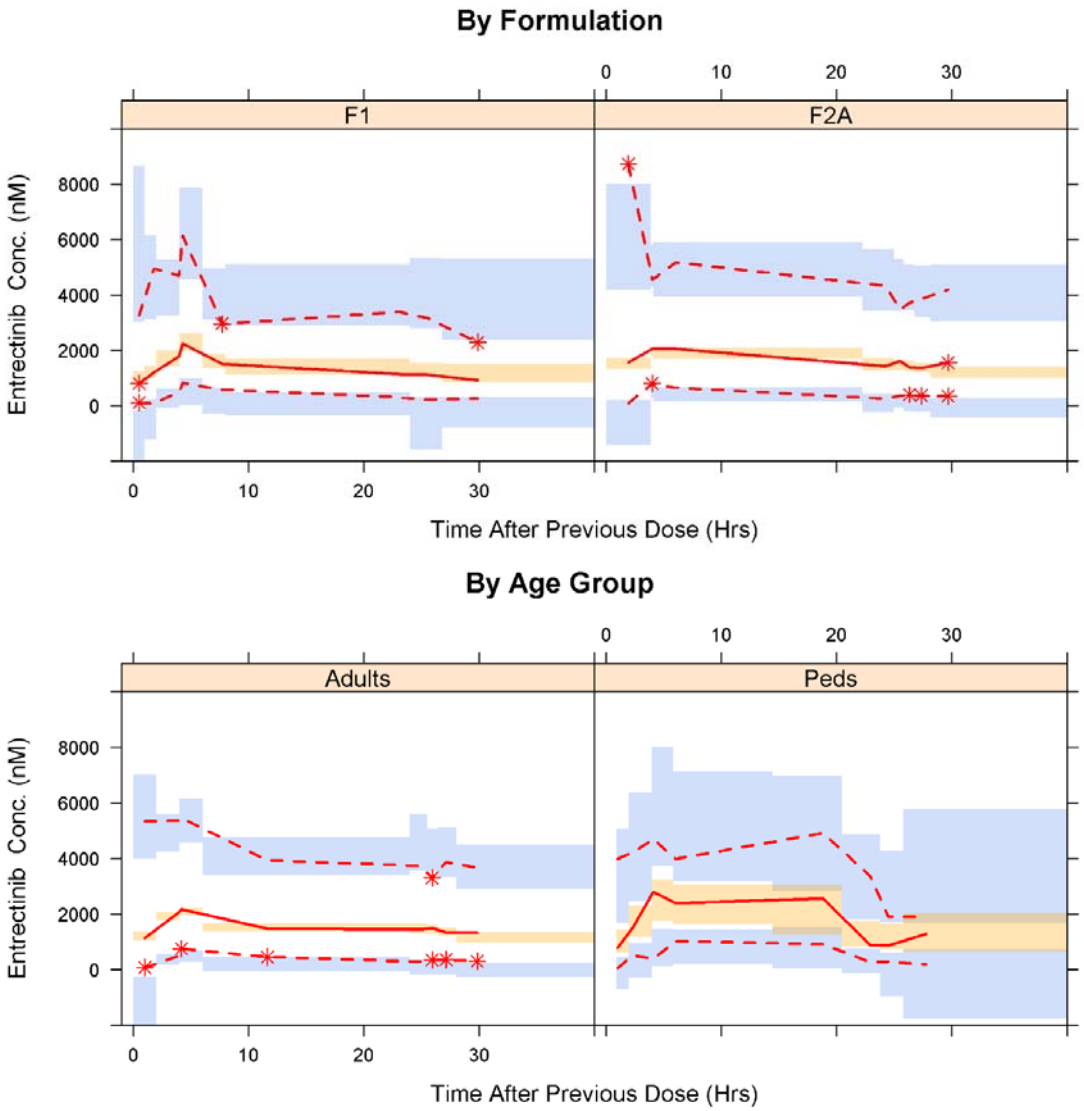
Source: Reviewer's Analysis based on "poppk.xpt"

Figure 30: Goodness of Fit Plots of the Final Model for Parent Drug



Source: Reviewer's Analysis based on "poppk.xpt"

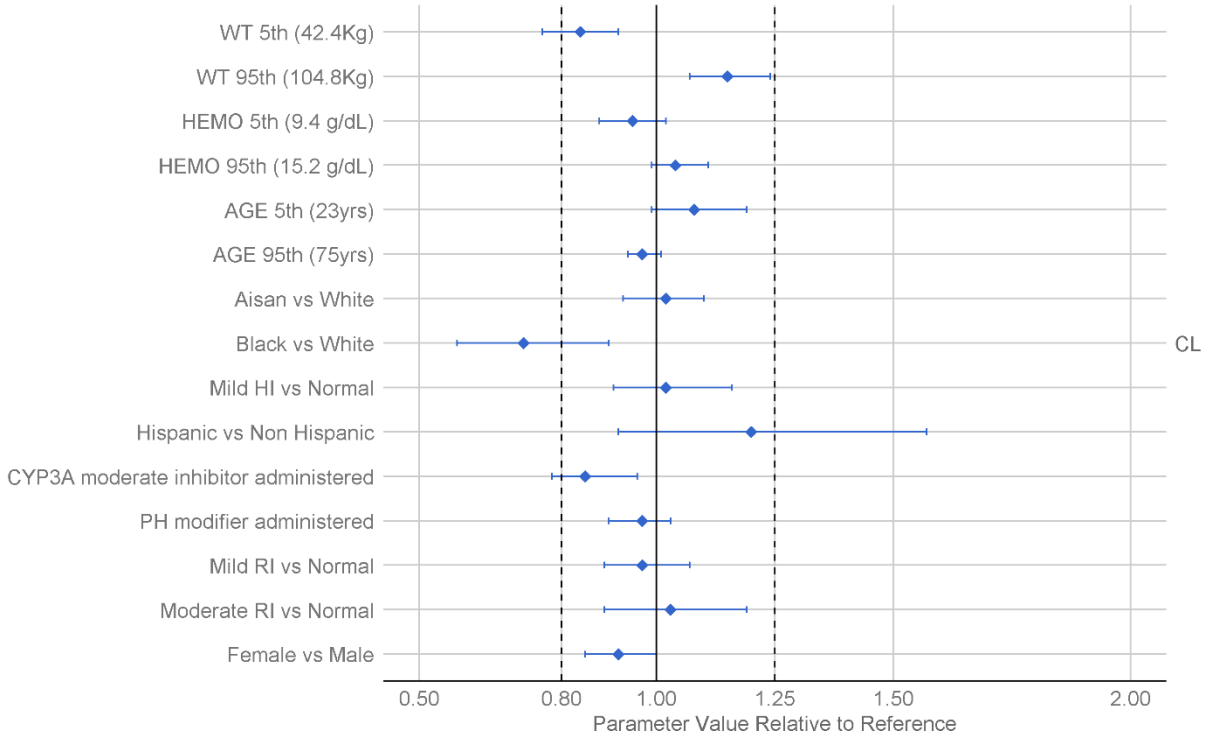
Figure 31: Visual Predictive Checks of Entrectinib Concentration-Time Data stratified by Formulation or Age



Source: Reviewer's Analysis based on "poppk.xpt"

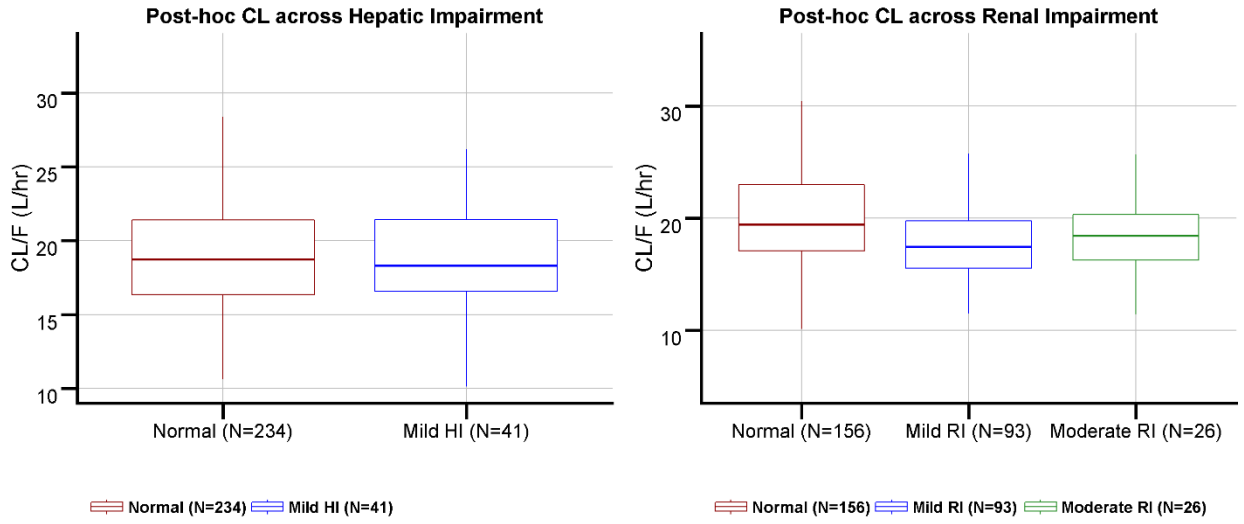
The full model included effects of weight, age, race, hemoglobin, gender, CYP3A moderate inhibitor, pH modifiers, renal and hepatic impairment on CL/F as well as an effect of weight on volume of distribution. The effects of all evaluated covariates on the entrectinib clearance were illustrated in the forest plot based on 500 bootstrap results of full covariate model (**Figure 32**). No intrinsic or extrinsic factors appear to have clinically relevant effects on entrectinib clearance. The clearance in black patients appear to be approximately 28% (90% CI: 10%, 42%) lower than the white patients. Hepatic or renal function with the available data also does not appear to have significant effect on post-hoc entrectinib clearance (**Figure 33**).

Figure 32: Covariate Effects on entrectinib Pharmacokinetic Parameters



Source: Reviewer's Analysis based on "poppk.xpt"

Figure 33: Comparison of Post-hoc CL across Renal or Hepatic Function

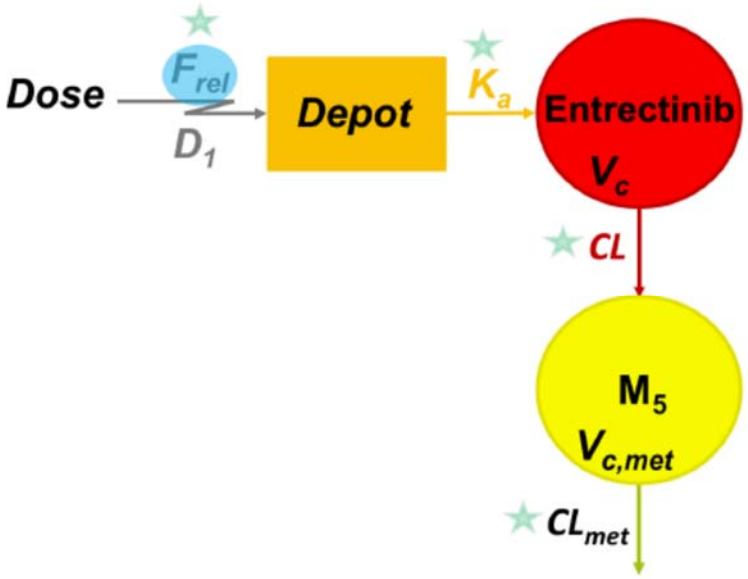


Source: Reviewer's Analysis based on "poppk.xpt"

3) Poppk model for active metabolite M5

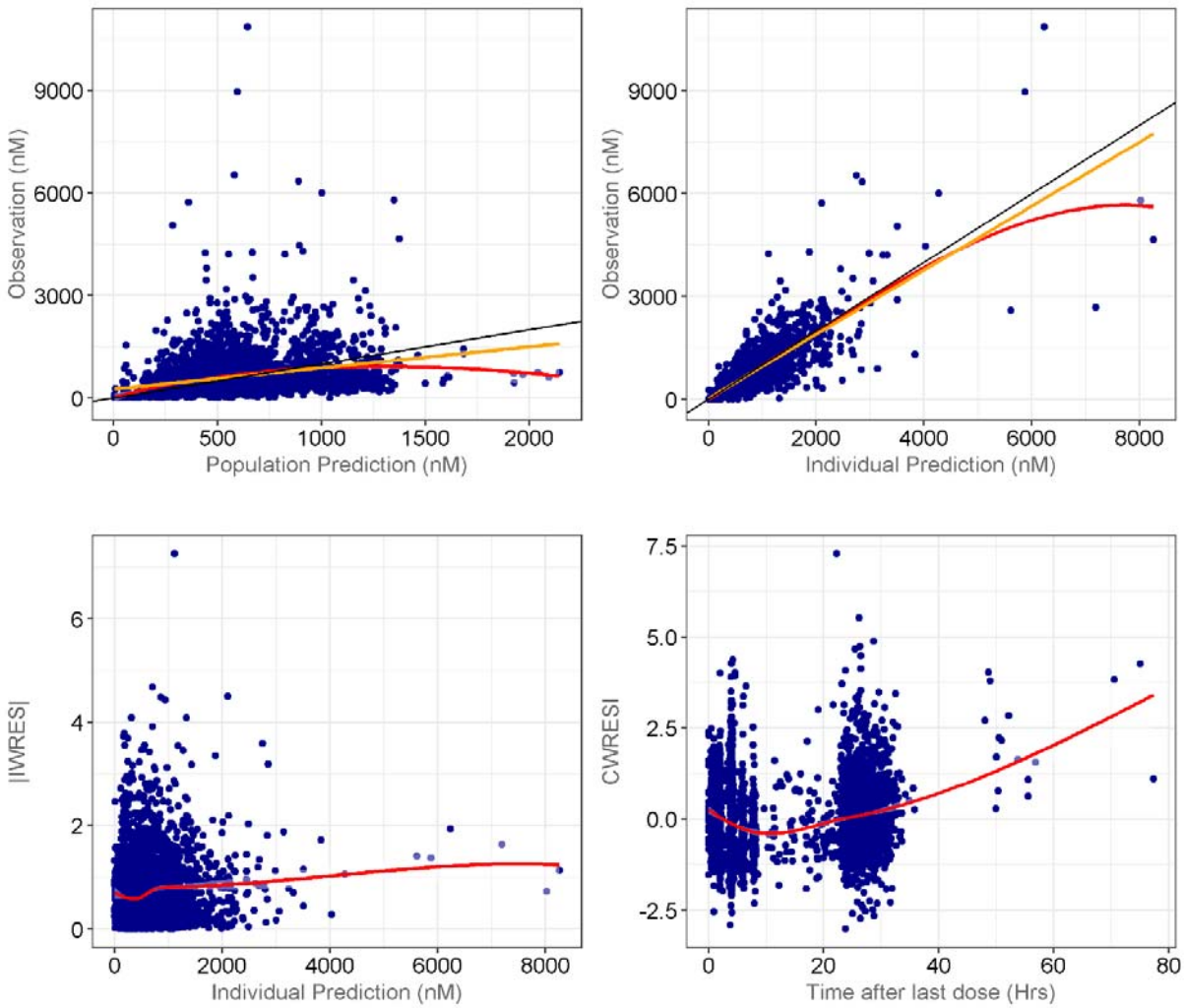
As metabolite M5 is an active metabolite with equal potency as the parent drug, a popPK model was also developed to simultaneously characterize the PK of entrectinib and M5. A schematic representation of the best model was provided in **Figure 34**. To avoid parameter identifiability issues, it was assumed that all entrectinib was metabolized into M5. No signs of model misspecification were identified in the goodness-of-fit plots for M5 (**Figure 35**). However, the estimate of CL for M5 may be affected by the assumption that all entrectinib was metabolized into M5.

Figure 34: Schematic representation of the best model to simultaneously characterize the PK of entrectinib and M5



Source: Applicant's popPK report, Figure 13, Page 60

Figure 35: Goodness of Fit Plots of the Final Model for Metabolite M5



Source: Reviewer's Analysis based on "poppk.xpt"

2. Simulation of exposure with proposed pediatric dosing regimen

(b) (4) (b) (4). An independent simulation exercise was conducted by the reviewer to evaluate the proposed pediatric dose in patients 4 years and older. Poppk simulation was not deemed appropriate to derive an untested dose in pediatric patients younger than 4 years old. Fifty replicates of simulations were conducted in 1200 virtual pediatric patients stratified by ages (300 patients per age group). Body weight, age and BSA in these pediatric patients were sampled without replacement from CDC NHANES 2015-2016 demographic database. Summary of demographics in these 1200 virtual patients was provided in **Table 79**. The actual dose administered by the virtual patients were rounded to the nearest 100 mg because of the strength limitation of

entrectinib F06 formulation. Because there is uncertainty on the effect of weight on clearance, entrectinib exposure was simulated based on 2 different Poppk models. (b) (4) (b) (4) (b) (4) Because of the uncertainty in model assumption and estimates, an appropriate pediatric dosing regimen in patients younger than 12 years old cannot be derived based on simulation alone. Additional PK data in pediatric patients with F06 formulation is needed to confirm the model prediction.

Table 79: Summary of Demographics in 1200 Virtual Pediatric Patients in Poppk Simulation

Age	N	BSA: Median (Range)	Weight: Median (Range)
>=4-<6	300	0.77 (0.56,1.11)	19.4 (12.2,35.2)
>=6-<12	300	1.07 (0.73,2.3)	30.95 (16.6,112.5)
>=12-<18	300	1.66 (1.08,2.91)	60.6 (30.1,163.6)
>=18	300	1.9 (1.33,2.94)	78.1 (41.9,173.4)

Source: CDC NHANES 2015-2016 demographic database [https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Demographics&CycleBeginYear=2015]

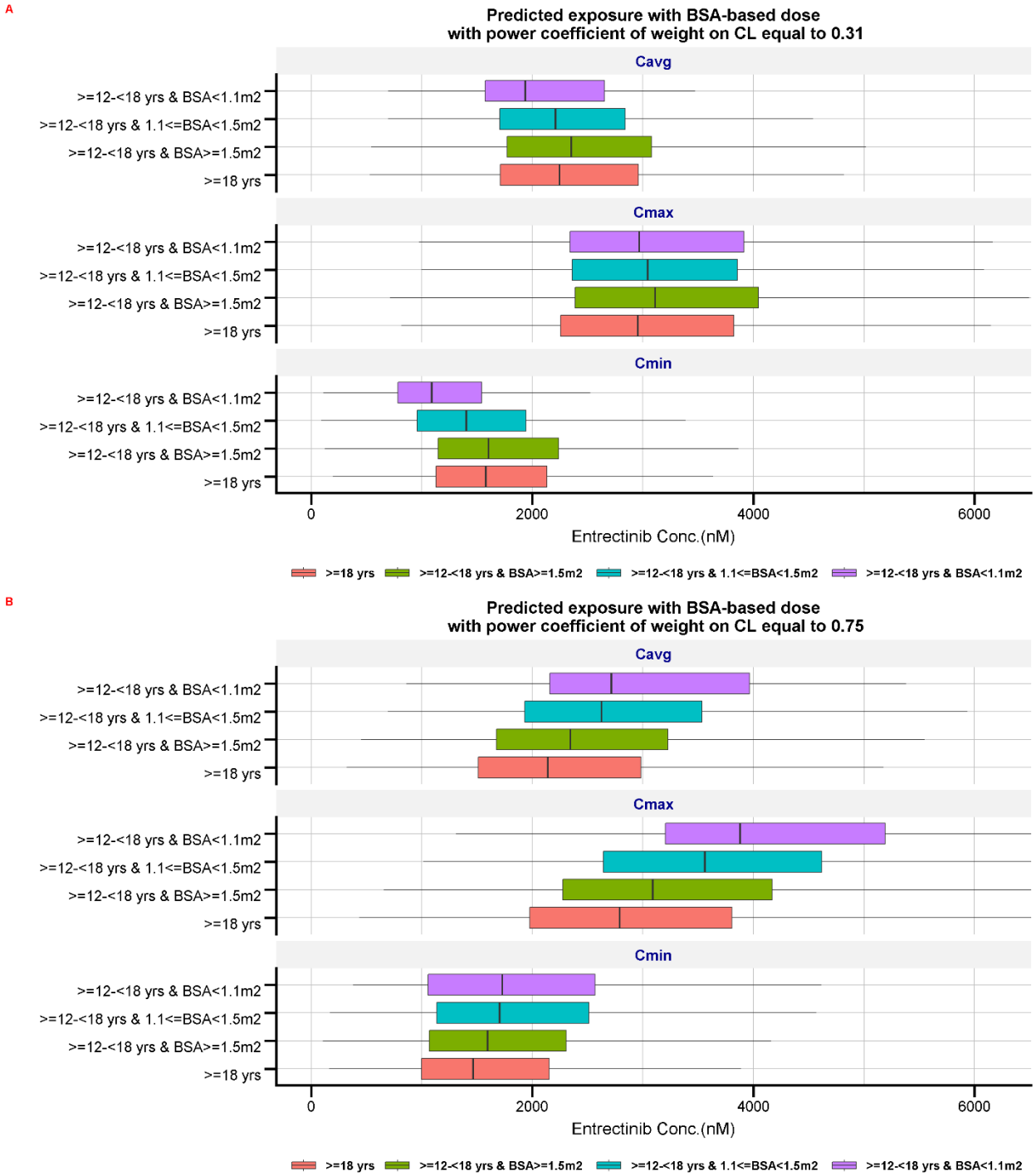
(b) (4)

Source: Reviewer's Analysis based on "poppk.xpt"

A simulation exercise was also conducted by the reviewer to predict the entrectinib exposure with BSA-based dose in adolescent patients. As shown in **Figure 37** and **Table 18**, with the recommended dosing regimen in adolescents, entrectinib exposure in adolescent patients with BSA > 1.5 m^2 is expected to be similar to adult patients. The predicted exposure in adolescents with BSA > 1.5 m^2 is approximately 10% higher than the exposure in adults either based on estimated weight effect on clearance (scenario 1) or based on assumption of allometric scaling (scenario 2). For adolescents with BSA between 1.1 and 1.5 m^2, the predicted exposure is similar compared to adults based on estimated weight effect on clearance (scenario 1), while the predicted average exposure is approximately 20% higher under the assumption of allometric scaling (scenario 2). For adolescents with BSA between 0.9 and 1.1 m^2, the predicted exposure is about 10% lower compared to adults based on estimated weight effect on clearance (scenario 1), while the predicted average exposure is approximately 30% higher under the assumption of allometric scaling (scenario 2) (see **Table 18**). It should be noted while the assumption of allometric scaling is in general reasonable for younger pediatric subjects, it is not supported by the observed PK data of entrectinib in adult patients. Therefore, the estimate of 20-30% higher exposure in adolescents with BSA less than 1.5 m^2 compared to adults based on allometric scaling is likely to be overestimated.

Figure 37: Boxplots of Predicted Entrectinib Exposure with Proposed BSA-based Dosing Regimen in Adolescent Patients 12 Years and Older. (Panel A Is Based on Poppk Model Where

the Power Coefficient of Weight on CL Is Estimated. Panel B Is Based on Poppk Model Where the Power Coefficient of Weight on CL Is Fixed to 0.75)



Source: Reviewer's Analysis based on "poppk.xpt"

3. Exposure-Response Analyses

1) Methods and Data

Exposure-response analyses were conducted by the applicant to explore the relationship between exposure of entrectinib and efficacy and safety in patients who received entrectinib.

Efficacy data was available in 54 patients with *NTRK*+ solid tumor and 53 patients with *ROS1*+ NSCLC. Exposure-ORR relationship were evaluated in those patients with available entrectinib exposure data, which include 48 patients with *NTRK*+ solid tumor and 39 patients with *ROS1*+ NSCLC.

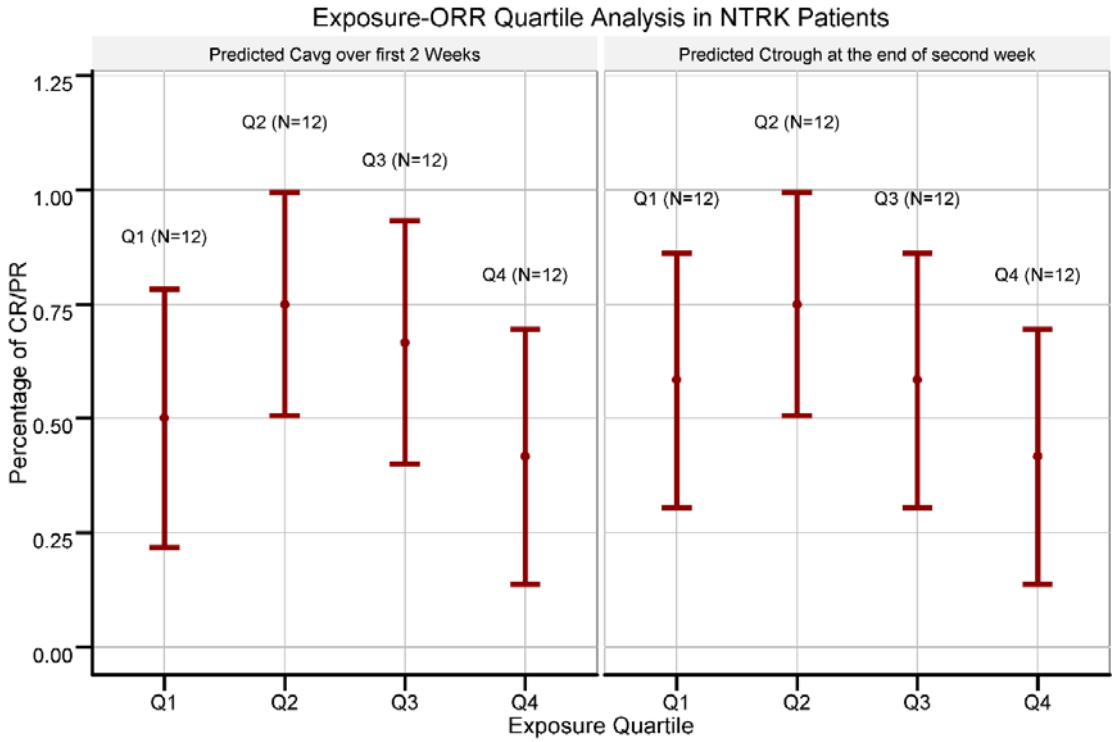
Exposure safety analyses were performed to investigate whether the occurrence of safety events could be attributed to the variability in entrectinib. The markers of lack of tolerability used in the analyses include treatment emergent adverse event (TEAE) CTCAE Grade 3 or above and serious adverse event (SAE). The exposure-safety analyses were conducted in 263 patients pooled from studies RXDX-101-01, RXDX-101-02 and RXDX-101-03.

The primary exposure metrics for both exposure-efficacy and exposure-safety assessment is individual predicted average, trough and maximum concentration for entrectinib or metabolite M5 over the first 2 weeks. Graphical quartile analyses and logistic regressions were used to investigate the exposure-ORR and exposure-AE relationships.

2) Exposure-response Relationships

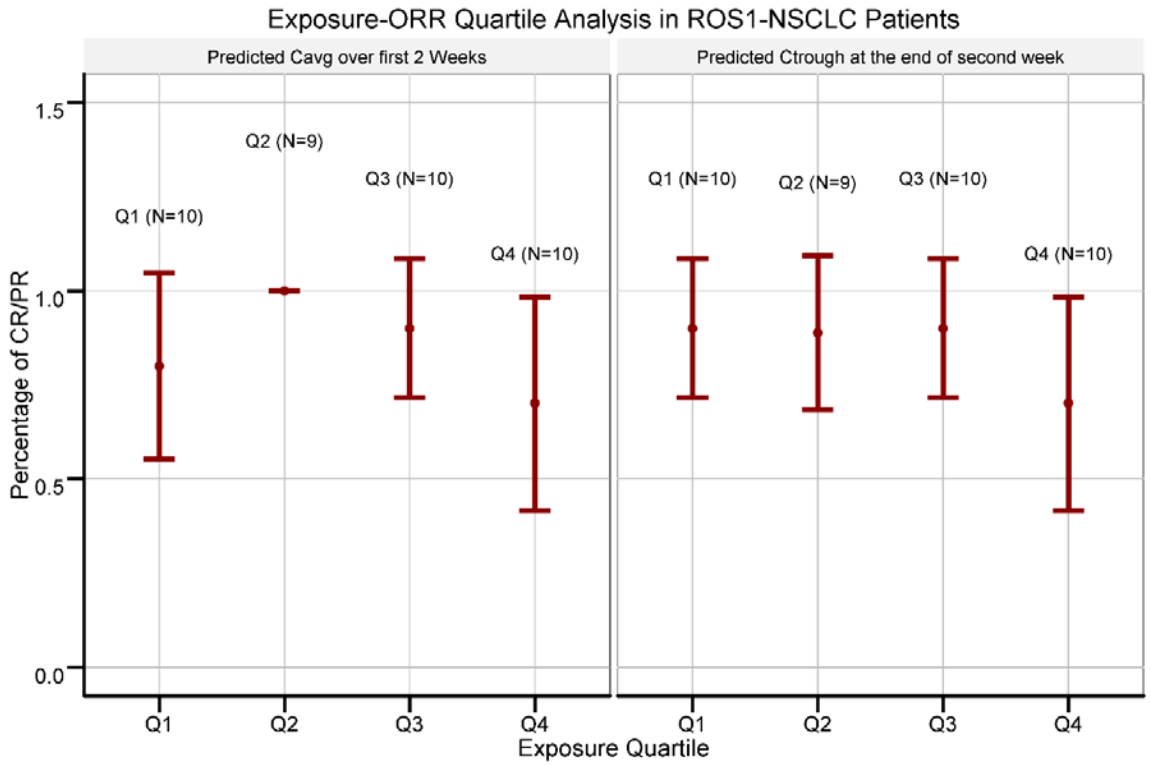
Overall, no trend was observed between entrectinib exposure and ORR in patients with *NTRK*+ solid tumor or *ROS1*+ NSCLC (**Figure 38** and **Figure 39**). The relationship between metabolite M5 and ORR showed similar trends (**Figure 40** and **Figure 41**). However, caution should be taken when interpreting these relationships as they were based on small sample size with one dosing regimen. The baseline covariates across all exposure quartiles in the exposure-ORR analyses were provided in **Table 80**. Imbalances were observed in some baseline factors such as gender across 4 exposure quartiles, but it is likely due to small number of patients in each quartile, and such imbalances were not found to be consistent across exposure-efficacy analyses.

Figure 38: Relationship between Entrectinib Exposure and ORR in Patients with *NTRK*+ Solid Tumors



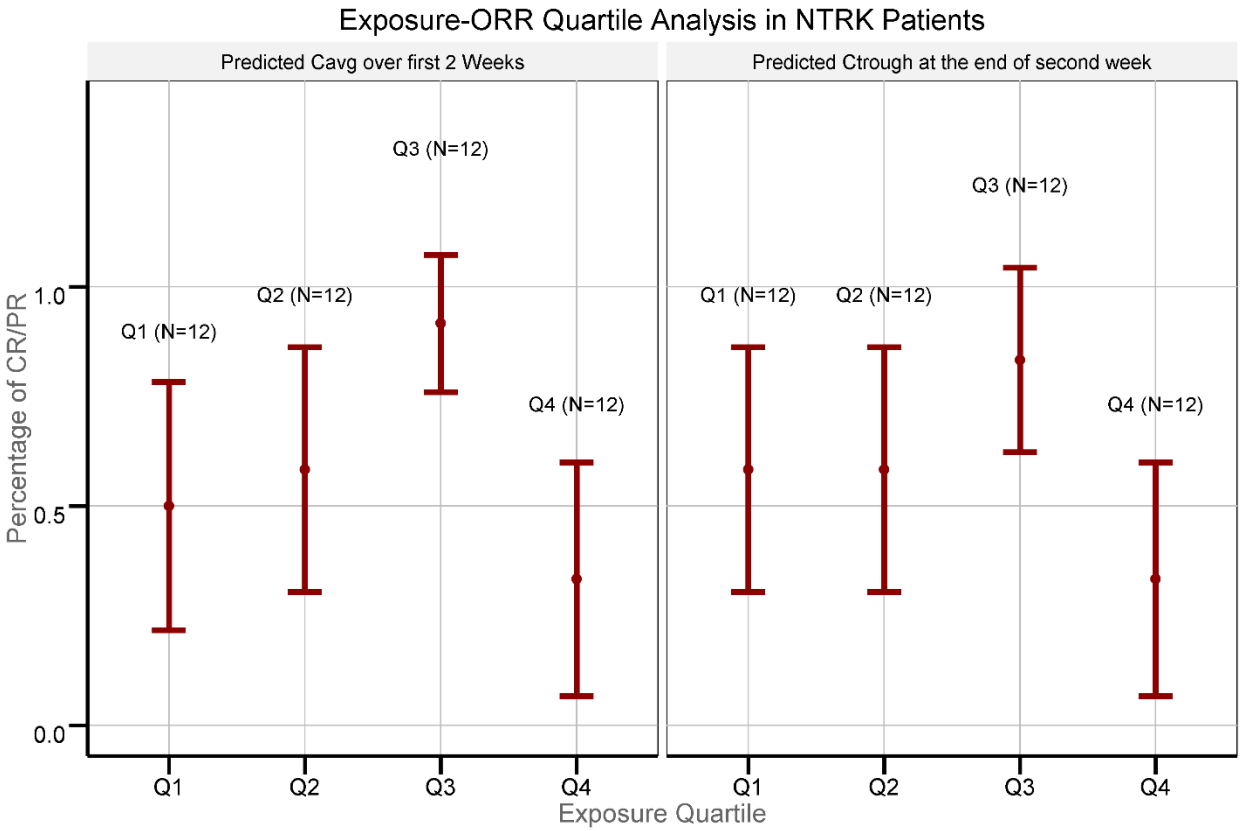
Source: Reviewer's Analysis based on "poppk.xpt" and "ars.xpt"

Figure 39: Relationship between Entrectinib Exposure and ORR in Patients with *ROS1*+ NSCLC



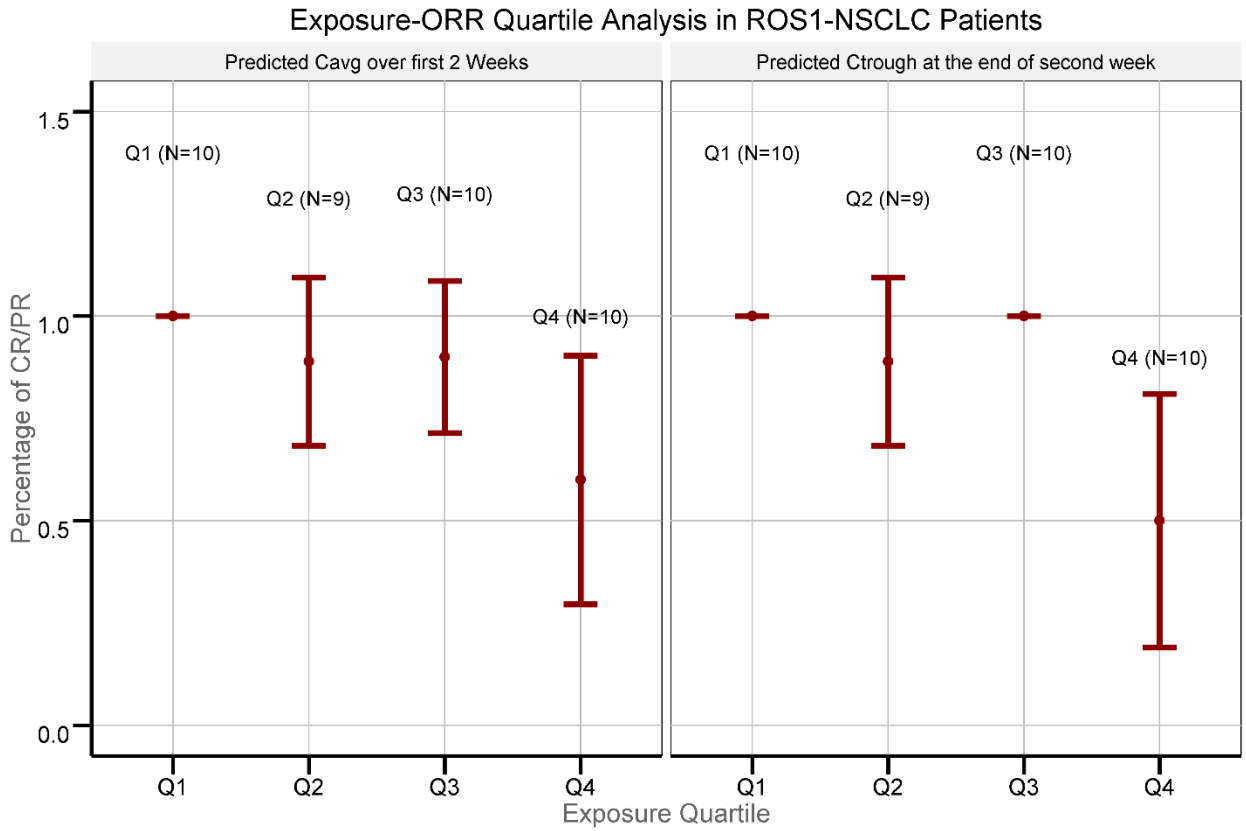
Source: Reviewer's Analysis based on "poppk.xpt" and "ars.xpt"

Figure 40: Relationship between M5 Exposure and ORR in Patients with *NTRK*+ Solid Tumors



Source: Reviewer's Analysis based on "poppk.xpt" and "ars.xpt"

Figure 41: Relationship between M5 Exposure and ORR in Patients with *ROS1*+ NSCLC



Source: Reviewer's Analysis based on "poppk.xpt" and "ars.xpt"

Table 80: Baseline covariates across 4 exposure quartiles in the exposure-ORR Analyses

Covariate	Value	Q1	Q2	Q3	Q4
A1; Number of Subjects		12	12	12	12
Age (yrs.): Median (SD)		53.5 (17.5)	51.5 (13)	55.5 (16.1)	60.5 (9)
Body Weight (kg): Median (SD)		79.8 (16.9)	68.8 (14.3)	74.9 (9.9)	72.2 (24)
Baseline ECOG	0	5 (41.7%)	5 (41.7%)	5 (41.7%)	7 (58.3%)
Baseline ECOG	1+	7 (58.3%)	7 (58.3%)	7 (58.3%)	5 (41.7%)
CNS at Baseline for BICR	N	8 (66.7%)	9 (75%)	10 (83.3%)	10 (83.3%)
CNS at Baseline for BICR	Y	4 (33.3%)	3 (25%)	2 (16.7%)	2 (16.7%)
Stage at Initial Diagnosis	IV	6 (50%)	5 (41.7%)	3 (25%)	2 (16.7%)
Stage at Initial Diagnosis	Not IV	6 (50%)	7 (58.3%)	9 (75%)	10 (83.3%)
Prior Chemotherapy	N	4 (33.3%)	2 (16.7%)	1 (8.3%)	1 (8.3%)
Prior Chemotherapy	Y	8 (66.7%)	10 (83.3%)	11 (91.7%)	11 (91.7%)
Gender	F	2 (16.7%)	8 (66.7%)	9 (75%)	9 (75%)
Gender	M	10 (83.3%)	4 (33.3%)	3 (25%)	3 (25%)
A2; Number of Subjects		10	9	10	10

Age		52.5 (11)	54 (8.5)	59.5 (11)	50.5 (11.9)
Body Weight		71.3 (19.6)	73.1 (18.9)	74.3 (13.2)	64 (10)
Baseline ECOG	0	3 (30%)	5 (55.6%)	5 (50%)	3 (30%)
Baseline ECOG	1+	7 (70%)	4 (44.4%)	5 (50%)	7 (70%)
CNS at Baseline for BICR	N	6 (60%)	6 (66.7%)	6 (60%)	4 (40%)
CNS at Baseline for BICR	Y	4 (40%)	3 (33.3%)	4 (40%)	6 (60%)
Stage at Initial Diagnosis	IV	5 (50%)	5 (55.6%)	8 (80%)	6 (60%)
Stage at Initial Diagnosis	Not IV	5 (50%)	4 (44.4%)	2 (20%)	4 (40%)
Prior Chemotherapy	N	2 (20%)	4 (44.4%)	3 (30%)	1 (10%)
Prior Chemotherapy	Y	8 (80%)	5 (55.6%)	7 (70%)	9 (90%)
Gender	F	7 (70%)	4 (44.4%)	6 (60%)	7 (70%)
Gender	M	3 (30%)	5 (55.6%)	4 (40%)	3 (30%)
A3; Number of Subjects		12	12	12	12
Age		56 (13.4)	51.5 (14.3)	58.5 (11.8)	61 (17.4)
Body Weight		70.1 (15.2)	72.4 (20.8)	75.3 (14.7)	78.7 (19)
Baseline ECOG	0	6 (50%)	9 (75%)	3 (25%)	4 (33.3%)
Baseline ECOG	1+	6 (50%)	3 (25%)	9 (75%)	8 (66.7%)
CNS at Baseline for BICR	N	9 (75%)	10 (83.3%)	9 (75%)	9 (75%)
CNS at Baseline for BICR	Y	3 (25%)	2 (16.7%)	3 (25%)	3 (25%)
Stage at Initial Diagnosis	IV	6 (50%)	4 (33.3%)	3 (25%)	3 (25%)
Stage at Initial Diagnosis	Not IV	6 (50%)	8 (66.7%)	9 (75%)	9 (75%)
Prior Chemotherapy	N	3 (25%)	3 (25%)	2 (16.7%)	.
Prior Chemotherapy	Y	9 (75%)	9 (75%)	10 (83.3%)	12 (100%)
Gender	F	5 (41.7%)	8 (66.7%)	8 (66.7%)	7 (58.3%)
Gender	M	7 (58.3%)	4 (33.3%)	4 (33.3%)	5 (41.7%)
A4; Number of Subjects		10	9	10	10
Age		55.5 (6.4)	47 (10.5)	54 (12.8)	55 (11.7)
Body Weight		83 (18.4)	71.8 (17.3)	72.2 (9.3)	60.6 (14)
Baseline ECOG	0	7 (70%)	4 (44.4%)	3 (30%)	2 (20%)
Baseline ECOG	1+	3 (30%)	5 (55.6%)	7 (70%)	8 (80%)
CNS at Baseline for BICR	N	6 (60%)	6 (66.7%)	5 (50%)	5 (50%)
CNS at Baseline for BICR	Y	4 (40%)	3 (33.3%)	5 (50%)	5 (50%)
Stage at Initial Diagnosis	IV	5 (50%)	6 (66.7%)	9 (90%)	4 (40%)
Stage at Initial Diagnosis	Not IV	5 (50%)	3 (33.3%)	1 (10%)	6 (60%)
Prior Chemotherapy	N	3 (30%)	3 (33.3%)	2 (20%)	2 (20%)
Prior Chemotherapy	Y	7 (70%)	6 (66.7%)	8 (80%)	8 (80%)
Gender	F	5 (50%)	4 (44.4%)	7 (70%)	8 (80%)
Gender	M	5 (50%)	5 (55.6%)	3 (30%)	2 (20%)

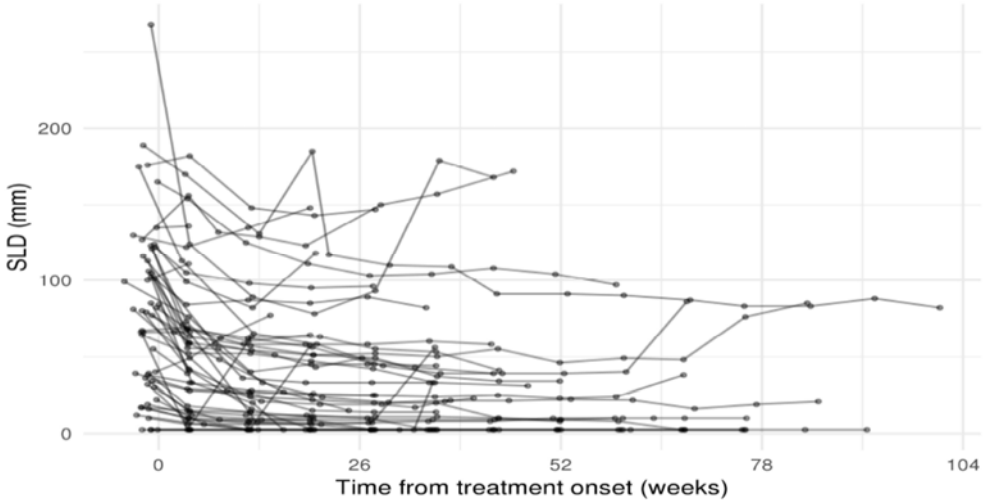
A1: 4 exposure quartiles based on predicted average entrectinib concentration at first 2 weeks in patients with *NTRK*+ solid tumors.

A2: 4 exposure quartiles based on predicted average entrectinib concentration at first 2 weeks in patients with *ROS1*+ NSCLC.
A3: 4 exposure quartiles based on predicted average M5 concentration at first 2 weeks in patients with *NTRK*+ solid tumors.
A4: 4 exposure quartiles based on predicted average M5 concentration at first 2 weeks in patients with *ROS1*+ NSCLC.

Source: Reviewer's Analysis based on "poppk.xpt" and "ars.xpt"

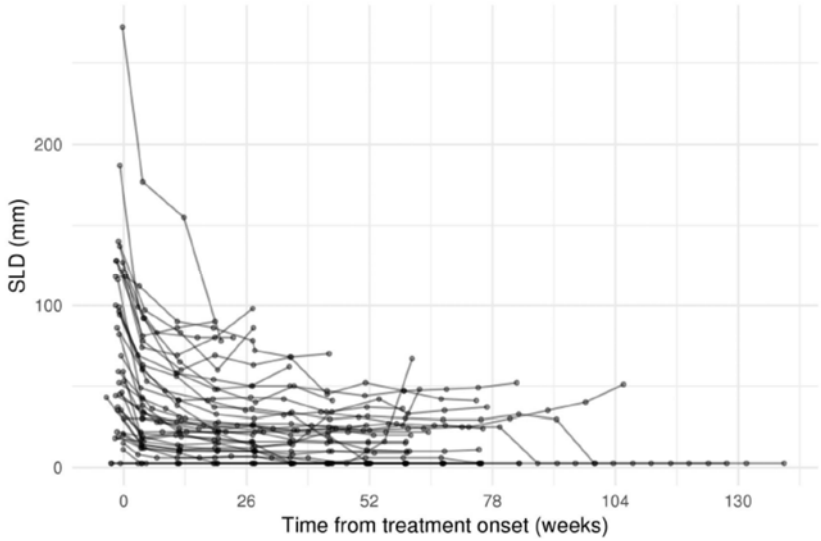
The applicant also conducted exploratory analysis to assess change of sum of longest diameter (SLD) values overtime during the treatment. As shown in **Figure 42**, there was a significant decrease in SLD during the initial treatment and then reached a plateau for majority of the *NTRK* fusion-positive patients treated with entrectinib. A similar trend was also observed in patients with *ROS1*+ NSCLC (**Figure 43**).

Figure 42: Sum of Longest Diameter (SLD) Values Over Time in Patients with Fusion-positive Solid Tumors (N=51)



Source: Summary of Clinical Pharmacology, Figure 27

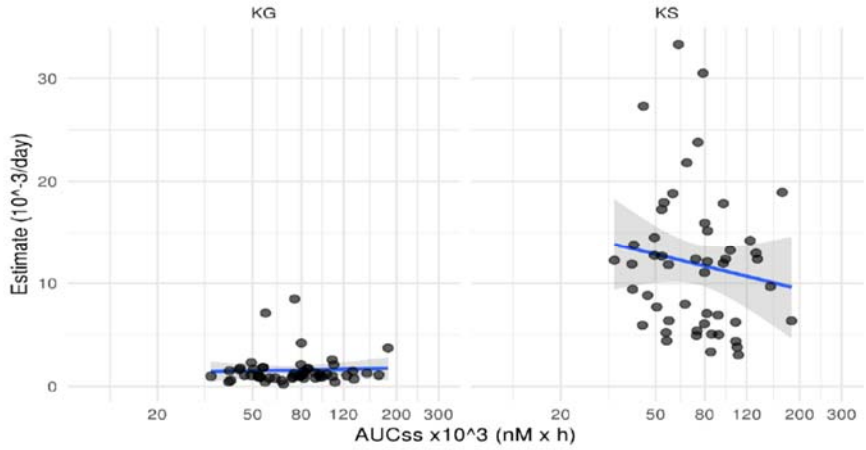
Figure 43: SLD Values Over Time in *ROS1*-positive NSCLC Patients (N=39)



Source: Summary of Clinical Pharmacology, Figure 25

However, as shown in **Figure 44** and **Figure 45,** there is no clear trend between combined entrectinib and M5 exposure and tumor growth rate (KS) and tumor shrinkage rate (KS) in both patient populations. The lack of correlation between PK exposure and the tumor growth and shrinkage parameters may be related to the limited exposure range assessed or the plateau of the pharmacological activity at the recommended therapeutic dose of 600 mg.

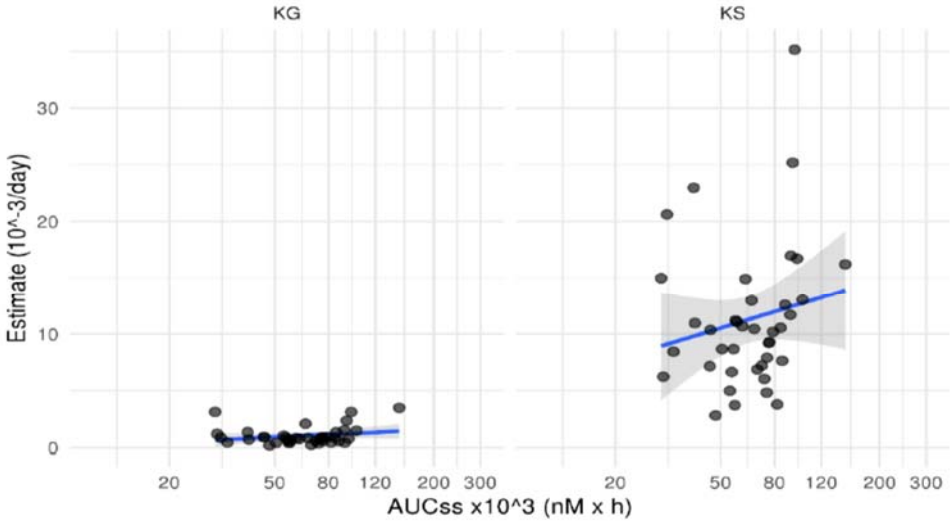
Figure 44: Tumor Shrinkage (KS) and Tumor Growth (KG) Rates as a Function of Exposure (AUCss) in Patients with *NTRK* Fusion-positive Solid Tumors



Note: The blue line and associated grey area represent linear regression models used for illustrative purpose only.

Source: Summary of Clinical Pharmacology, Figure 28

Figure 45: Tumor Growth (KG) and Tumor Shrinkage (KS) Rates as a Function of Exposure (AUCSS) in *ROS1*-positive NSCLC Patients



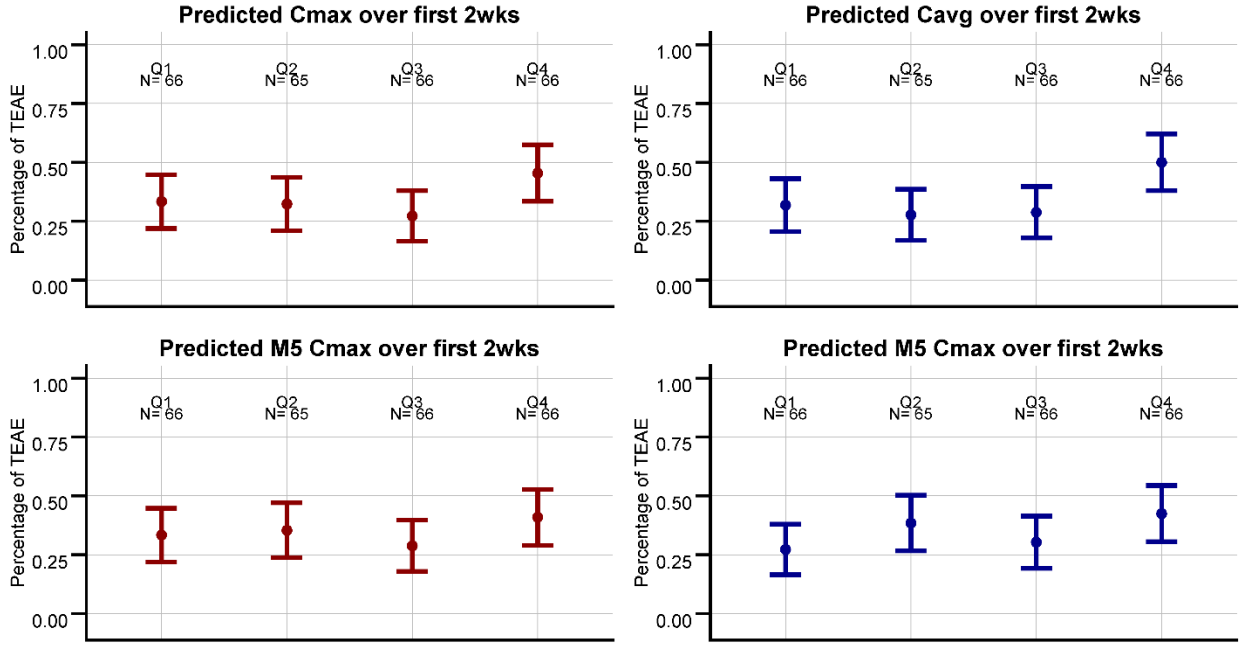
Note: The blue line and associated grey area represent linear regression models used for illustrative purpose only.

Source: Summary of Clinical Pharmacology, Figure 26

3) Exposure-AE Relationships

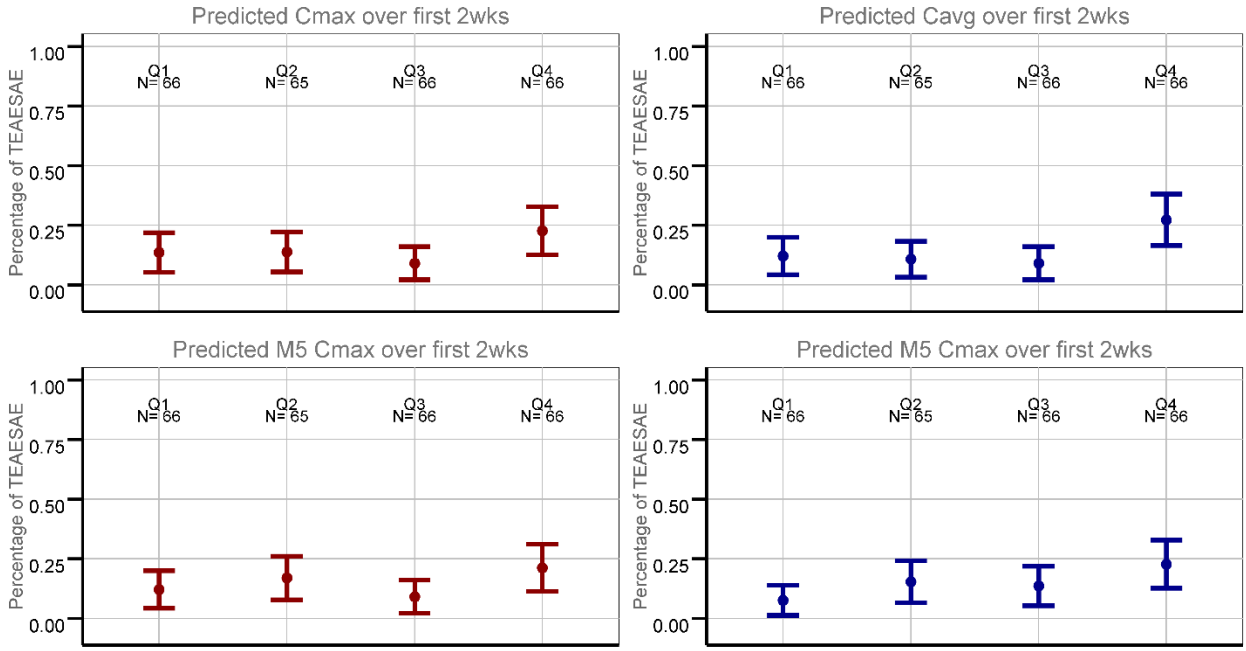
Graphical quartile analyses suggest a higher frequency of SAE or Grade 3+ AE were observed in patients with higher entrectinib exposure (Q4) (**Figure 46**). Similar trends were also observed in patients with higher M5 exposure (**Figure 47**). However, the relationship between entrectinib exposure and Grade 3+ AE or SAE was not statistically significant in the logistic regression analysis after accounting for the effect of gender (**Figure 48** and **Figure 49**). The baseline covariates across all exposure quartiles in the exposure-AE analyses appear to be balanced except for gender (**Table 81**). As the rate of SAE or Grade 3+ AE is numerically higher in female patients (18.8% and 39.6%, respectively) compared to male patients (10.1% and 28.6%, respectively), the higher numerical rate of AE in the 4th exposure quartile may be confounded by the higher percentage of female patients.

Figure 46: Relationship between Entrectinib or M5 Exposure and Grade 3+ AE in Patients Who Received Entrectinib



Source: Reviewer's Analysis based on "aex.xpt"

Figure 47: Relationship between Entrectinib or M5 Exposure and SAE in Patients Who Received Entrectinib



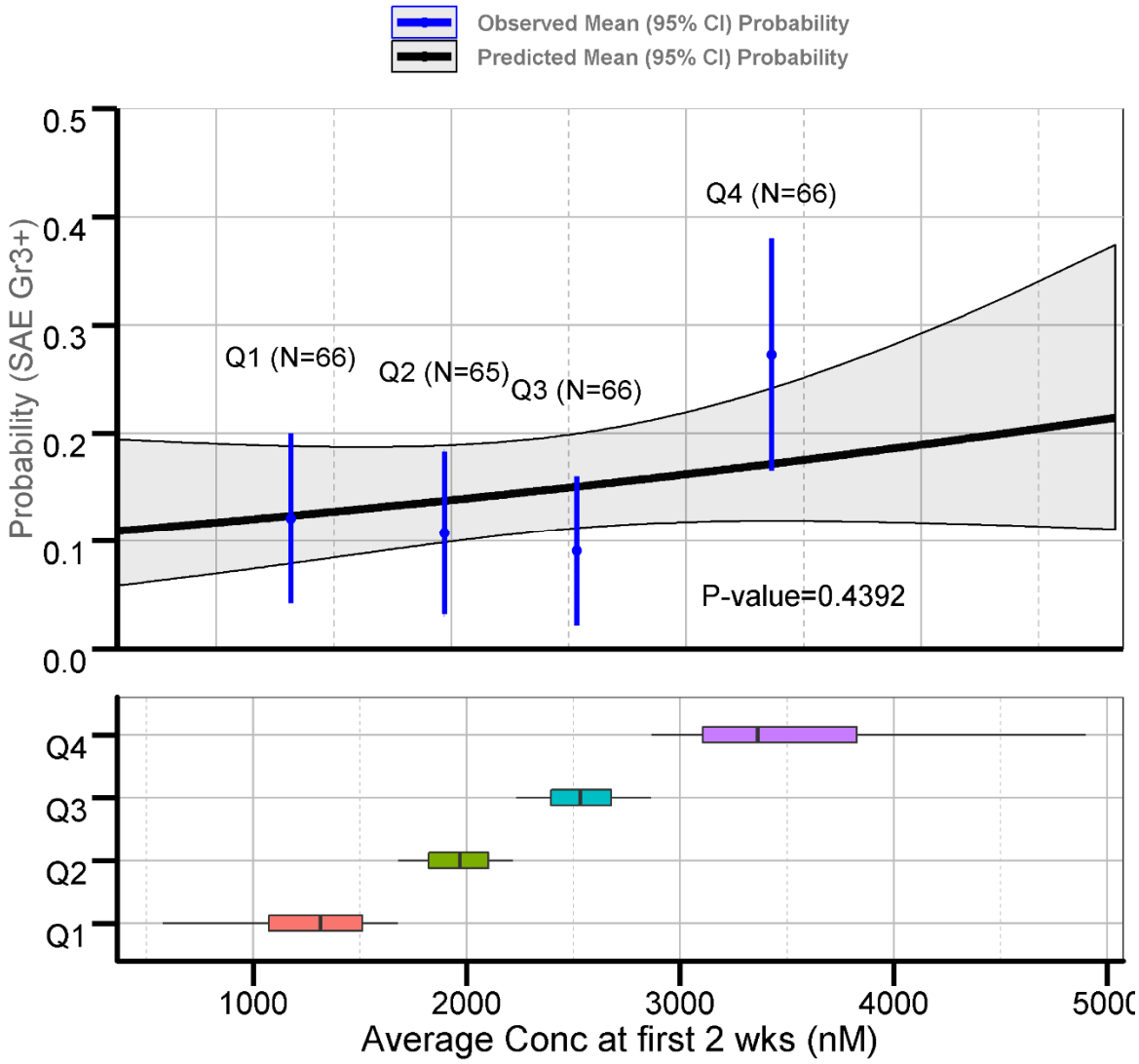
Source: Reviewer's Analysis based on "aex.xpt"

Table 81: Baseline Covariates Across 4 Exposure Quartiles in the Exposure-AE Analyses

Covariate	Value	Q1	Q2	Q3	Q4
A1: Number of Subjects		66	65	66	66
Age		53 (18.3)	53 (17)	53.5 (17.3)	56 (16.3)
Body Weight		74.8 (20.2)	67.3 (19.3)	68 (15.8)	64.2 (20.5)
Baseline ECOG	0	18 (27.3%)	30 (46.2%)	30 (45.5%)	22 (33.3%)
Baseline ECOG	1+	48 (72.7%)	35 (53.8%)	36 (54.5%)	44 (66.7%)
CNS at Baseline for BICR	N	48 (72.7%)	46 (70.8%)	50 (75.8%)	48 (72.7%)
CNS at Baseline for BICR	Y	18 (27.3%)	19 (29.2%)	16 (24.2%)	18 (27.3%)
Stage at Initial Diagnosis	IV	40 (60.6%)	42 (64.6%)	37 (56.1%)	34 (51.5%)
Stage at Initial Diagnosis	Not IV	26 (39.4%)	23 (35.4%)	29 (43.9%)	32 (48.5%)
Prior Chemotherapy	N	17 (25.8%)	21 (32.3%)	13 (19.7%)	13 (19.7%)
Prior Chemotherapy	Y	49 (74.2%)	44 (67.7%)	53 (80.3%)	53 (80.3%)
Gender	F	24 (36.4%)	35 (53.8%)	38 (57.6%)	47 (71.2%)
Gender	M	42 (63.6%)	30 (46.2%)	28 (42.4%)	19 (28.8%)
A2: Number of Subjects		66	65	66	66
Age		52 (16.7)	50 (15.9)	59.5 (17.9)	57 (17.6)
Body Weight		73.8 (19.3)	67.6 (20.2)	70.2 (17.5)	64.5 (19.4)
Baseline ECOG	0	34 (51.5%)	32 (49.2%)	19 (28.8%)	15 (22.7%)
Baseline ECOG	1+	32 (48.5%)	33 (50.8%)	47 (71.2%)	51 (77.3%)
CNS at Baseline for BICR	N	43 (65.2%)	51 (78.5%)	49 (74.2%)	49 (74.2%)
CNS at Baseline for BICR	Y	23 (34.8%)	14 (21.5%)	17 (25.8%)	17 (25.8%)
Stage at Initial Diagnosis	IV	39 (59.1%)	41 (63.1%)	36 (54.5%)	37 (56.1%)
Stage at Initial Diagnosis	Not IV	27 (40.9%)	24 (36.9%)	30 (45.5%)	29 (43.9%)
Prior Chemotherapy	N	23 (34.8%)	15 (23.1%)	12 (18.2%)	14 (21.2%)
Prior Chemotherapy	Y	43 (65.2%)	50 (76.9%)	54 (81.8%)	52 (78.8%)
Gender	F	28 (42.4%)	32 (49.2%)	40 (60.6%)	44 (66.7%)
Gender	M	38 (57.6%)	33 (50.8%)	26 (39.4%)	22 (33.3%)

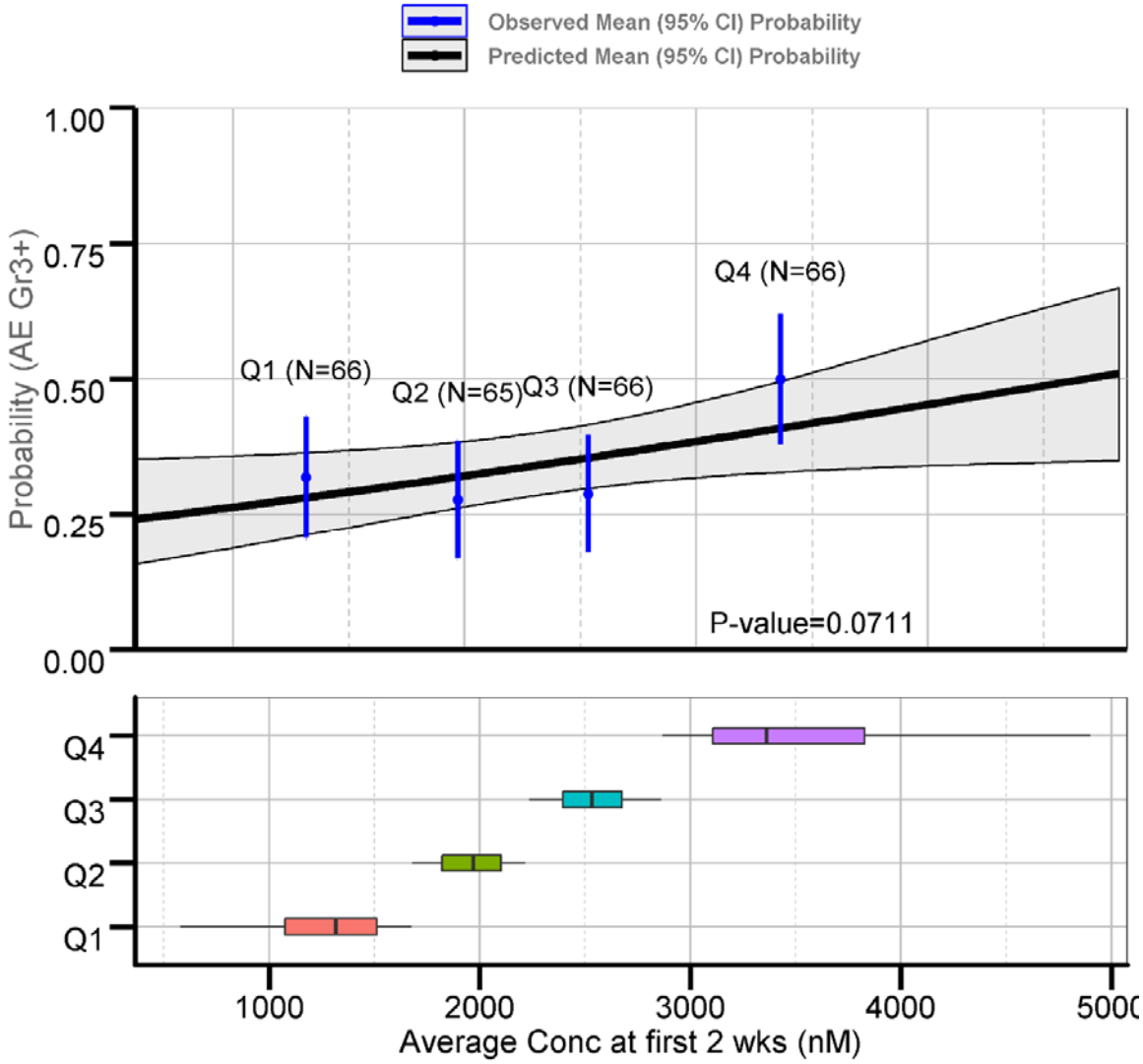
A1: 4 exposure quartiles based on predicted average entrectinib concentration at first 2 weeks
A2: 4 exposure quartiles based on predicted average M5 concentration at first 2 weeks

Figure 48: The Relationship between Entrectinib Exposure and Probability of SAE Fit by a Logistic Regression Model



Source: Reviewer's Analysis based on "aex.xpt"

Figure 49: The Relationship between Entrectinib Exposure and Probability of Grade 3+ AE Fit by a Logistic Regression Model



Source: Reviewer's Analysis based on "aex.xpt"

19.4.3. Physiologically Based Pharmacokinetics (PBPK) Analyses

Executive Summary

The objective of this review is to evaluate the adequacy of Genentech's following physiologically based pharmacokinetic (PBPK) analyses reports and response to the relevant information requests (IRs).

- Report 1091399 dated 23 November 2018: Entrectinib: Physiologically based pharmacokinetic modeling in Simcyp for DDI assessment and Pediatric dose recommendation
- Report 1091111 dated 23 November 2018: Entrectinib: Physiologically based absorption modeling in GastroPlus™
- Response to IR-09 dated March 1, 2019
- Response to IR-15 dated March 29, 2019
- Response to IR-20 dated March 29, 2019
- Response to IR-32 dated May 7, 2019

Specifically, the modeling analyses were used for the following purposes.

1. To assess the effects of a strong (itraconazole) and moderate(erythromycin) CYP3A inhibitor on the PK of entrectinib and its active metabolite M5,
2. To assess the effects of a strong (rifampin) and moderate (efavirenz) CYP3A inducer on the PK of entrectinib and its active metabolite M5,
3. To predict the effect of entrectinib on CYP3A substrates (midazolam and ethinylestradiol), and
4. To predict the entrectinib PK in pediatric populations (4-20 years of age, and less than 4 years of age) following administration of F1, and F2A/F06 formulations.

The Division of Pharmacometrics has reviewed the report, supporting modeling files, and Genentech's responses to our IRs, and concluded that Applicant's PBPK model was adequate to evaluate the effects of a moderate inhibitor or a moderate inducer on the PK of entrectinib. The model predicted a 3.4-fold increase in entrectinib AUCtau at steady state when it was co-administered with erythromycin, and a 56% decrease in entrectinib AUCtau at steady state when it was co-administered with efavirenz.

Background

Entrectinib has low and pH-dependent solubility. The solubility decreases with increasing pH. Entrectinib displayed moderate permeability in in vitro Caco-2 assays. Both entrectinib and its active metabolite, M5, are highly protein bound with f_u (unbound fraction) less than 1%. In an in vitro study, the blood to plasma ratios were 1.3 and 1.0 for entrectinib and M5, respectively. Clearance of entrectinib is largely through metabolism. About less than 1% of administered entrectinib dose is excreted unchanged into the urine. The apparent elimination half-lives of entrectinib and M5 were estimated to be 20 and 40 hours, respectively.

In an in vivo ADME study (bespoke powder-in-capsule formulation), 86% (range: 72% to 91%) of the administered radioactivity was recovered in excreta during the 13-day collection period; only 3% of the dose was recovered in urine, and 83% was recovered in feces. Entrectinib and M5 accounted for 36% and 22% of radiolabeled material in excreta, respectively. Metabolic profiling of plasma samples indicated that entrectinib represented 69% of total radioactivity in the 24 h-period after dosing, while M5 (N-desmethyl metabolite of entrectinib) and M11 (human-specific N-glucuronide conjugate of entrectinib) were identified as major circulating metabolites contributing 12% and 19% of the total radioactivity, respectively.

In vitro, entrectinib is a CYP3A substrate and inhibitor, and a P-gp substrate and inhibitor. The active metabolite, M5, is also a substrate for CYP3A.

Multiple formulations were developed at various stage of this program. Three formulations (F1, F2A and F06) were the most relevant formulations in the review. Refer to the clinical pharmacology review section for the details about the effects of formulation differences on PK.

Genentech conducted PBPK modeling to explore the effects of intrinsic and extrinsic factors using GastroPlus and Simcyp. The GastroPlus modeling focused on the factors affecting entrectinib absorption (such as formulation, food, and gastric pH effects) while the Simcyp modeling was used to evaluate drug-drug interactions (DDIs). Both models were used to predict PK in pediatric populations (0-20 years of age).

<u>Methods</u>

Software

GastroPlus™ Version 9.6 (b) (4) and Simcyp® Version 17.1 (b) (4) were used for PBPK analyses.

Overview of modeling strategy

The modeling strategy in Simcyp

In Simcyp, the entrectinib model was built and verified for F2A and F06 formulations, which were demonstrated to be bioequivalent in adults. The model was then verified with PK, and DDI studies with itraconazole, rifampin, and midazolam. The verified model was applied to predict the effects of a moderate CYP3A inhibitor (erythromycin), and a moderate CYP3A inducer (efavirenz) on the PK of entrectinib and its active metabolite M5, and the effect of entrectinib on the PK of ethinylestradiol (a CYP3A substrate).

The F2A/F06 adult model was modified for the F1 formulation to capture the observed difference between F1 and F2A/F06 formulations by adjusting effective permeability (P_{eff}). To model the fed condition in Simcyp, the default fed physiology was used except the gastric emptying time (GET) was changed from 1 hour to 2 hours. The F1 formulation PBPK model was further applied to pediatric populations. The F1 pediatric PBPK model predictions were compared to the observed PK data in pediatric patients (4-9 years of age) who were administered with F1 formulation. The F2A/F06 PBPK model was applied to the pediatric population to predict the PK pediatric population from birth to 4 years of age.

Reviewer's comments: There is no evidence suggesting that the formulation differences would affect permeability. Adjusting Peff for a different formulation in the same population is an empirical approach to model oral absorption.

The modeling strategy in GastroPlus

The entrectinib adult GastroPlus PBPK model was first built with a 'bottom-up' approach that integrated measured values of solubility vs. pH, biorelevant solubility, permeability and precipitation estimated from in vitro studies. Both full PBPK and compartment models were explored using GastroPlus to describe the distribution and elimination in adults. The adult model was verified with study RXDX-101-07 for F06 under both fasting and fed conditions. The adult model was explored to evaluate the effect of altered stomach pH caused by proton pump inhibitors (PPIs) on entrectinib PK following F06 or F2A under both fasting and fed conditions. sensitivity analyses were conducted for parameters that may affect absorption, such as particle size, permeability, bile salt solubilization ratio (BSSR), precipitation time, and stomach pH.

After verifying the PBPK model for F1 formulation in adults, the model was used to predict F1 PK in pediatric populations. The predicted PK in pediatric population for the F1 formulation was compared to the observed PK (4-20 years of age). The PBPK model was adjusted for BSSR to obtain better prediction of entrectinib PK in 4-20 years of age patients. The model was then used to predict PK in children less than 4 years of age for the F1/F2A/F06 formulations and to derive dose recombination in children based on PK matching to the exposure in adults following 600 mg QD of F2A/F06 formulations.

The active metabolite, M5, was not included in the PBPK modeling in GastroPlus.

PBPK model structures and parameters

The PBPK model structures and input parameters for entrectinib and M5 are summarized in **Table 82**.

The entrectinib model in Simcyp

Absorption: The Advanced Dissolution, Absorption, and Metabolism (ADAM) model was used in Simcyp with the solution formulation without precipitation. The Peff was estimated based on a P_{caco-2} of 3.72×10^{-6} cm/min and calibrated with atenolol $P_{eff,man}$ of 0.19×10^{-6} cm/min.

Distribution: The full PBPK model was used to predict the volume of distribution (V_{ss}). The Rodgers and Rowland method (method 2) was selected to predict tissue to plasma partition coefficients (K_{ps}).

Elimination: The 'Enzyme Kinetic' option and the retrograde model were used to generate the intrinsic clearance values for CYP3A4 and additional hepatic pathway.

Interaction: The CYP3A inhibition and induction parameters of entrectinib were obtained from in vitro studies (**Table 82**).

In the Simcyp entrectinib model, a pair of the values of fraction unbound in gut (f_{ugut}) and fraction metabolized by CYP3A4 ($f_{mcyp3a4\_entrectnib}$) were optimized against the itraconazole DDI

study to best describe the observed PK and DDI results. To do so, the f_{ugut} was varied from 0.5 to 1 and median $f_{mcyp3a4\_entrectnib}$ was varied from 0.74 to 0.83.

Reviewer's comments: In vitro, entrectinib is a P-gp substrate and inhibitor. The entrectinib model did not incorporate P-gp as a substrate nor as an inhibitor.

- ***The entrectinib and digoxin DDI study (RXDX-101-13) showed that digoxin C_{max} and AUC_{inf} were increased by 28% and 18%, respectively, when it was co-administered with entrectinib, suggesting that the effect of entrectinib on the PK of a P-gp substrate is weak. In addition, the model was not intended to simulate the effect of entrectinib on the PK of a P-gp substrate. Therefore, it is acceptable not incorporating P-gp inhibition effect in the model.***
- ***In the response to FDA's IR-20 submitted on March 29, 2019, Genentech provided the following rationales for not including P-gp in the model.***
    - ***In vitro, the entrectinib Papp (A to B) value was not sensitive to a P-gp inhibitor compared to the reference P-gp substrates, digoxin and crizotinib.***
    - ***At steady-state, entrectinib distributed well into the brain in several preclinical in vivo models, suggesting lack of role of P-gp in entrectinib transport.***

  Genentech's rationale for not incorporating P-gp transport in the entrectinib substrate model are acceptable.

The M5 model in Simcyp

Formation: In vitro studies suggested that M5 was formed via the CYP3A4 isoform. 90% of the entrectinib that was metabolized via CYP3A4 ($f_{mcyp3a4}$ = 78%) was converted to M5.

Distribution: A full PBPK model was used to describe the M5 distribution. Method 2 with a Kp scaler of 1 was used to calculate the volume of distribution.

Elimination: In vitro studies suggested that M5 was cleared mainly by CYP3A4. Minor contributions of CYP3A5 and CYP1A1 are expected. M5 total clearance is 2-fold lower than the total clearance of entrectinib based on in vitro data. Sensitivity analysis was conducted for the CYP3A4 fraction of entrectinib assigned to formation of M5 (59%-90%), the metabolic clearance of M5 (2-fold lower to 2-fold higher the metabolic clearance of entrectinib), the fraction of M5 that is metabolized (50%-99%), and the fraction of M5 metabolized via CYP3A4 ($f_{mcyp3a4\_M5}$)(70%-99%).

Reviewer's comments: Genentech indicated that 'M5 is a major circulating metabolite, is pharmacologically active, and is believed to make a meaningful contribution to the clinical efficacy of entrectinib' (Source: Summary of Clinical Pharmacology Studies). However, M5 was not incorporated into PBPK analyses in the original submission. In response to FDA's IR, the sponsor conducted additional PBPK analyses and incorporate a semi-mechanistic M5 model,

in which the formation of M5 and metabolic clearance of M5 were obtained by comparing model predictions with observed PK and DDI data.

The entrectinib model in GastroPlus

Absorption: The Advanced Compartmental and Transit (ACAT) model in GastroPlus was used to mechanistically simulate the impact of formulation, physicochemical properties, and GI physiology on the PK of entrectinib following administration of various formulations.

Distribution: Both a two-compartment and full PBPK models were used to predict Vss in adults. A full PBPK model was used to predict Vss in pediatric population. The Rowland-Lukacova method was selected to predict the Kps for the full PBPK model.

Elimination: The fraction escaping gut metabolism (1-Fg) and renal and hepatic clearance that were verified with clinical data and PBPK modeling in Simcyp were used as in vivo clearance.

Table 82 Summary of model input parameters for entrectinib and M5

Parameter	Entrectinib Gastroplus model	Entrectinib Simcyp model	M5 Simcyp model
Formulation	Immediate-release: capsule	Solution without precipitation	
Model structure			
Absorption	Advanced Compartmental Absorption and Transit (ACAT)	Advanced Dissolution, Absorption and Metabolism (ADAM)	
Distribution	Two-compartment, Vc=1.63 L/kg, V2=1.74 L/kg	Full PBPK, Vss = 3.42 L/kg (method 2, Kp scalar = 0.33)	Full PBPK, Vss = 5.10 L/kg (method 2, Kp scalar = 1)
Elimination	Lumped CL	$f_{m,cyp3a4}$ = 78% $f_{m,addhep}$ = 21.7% CL_{renal} = 0.3%	$f_{m,cyp3a4}$ = 99% $f_{m,addhep}$ = 1%
MW (g/mol)	560.65	560.65	546.6
Fup	0.5%	0.5%	0.5%
pKa	pKa1=2.54; SF 8000, pKa2=5.3; SF 70 (optimized based on solubility vs. pH data)	pKa1 = 2.54 ± 0.09 pKa2 = 7.54 ± 0.01 (measured)	pKa1 = 2.56 ± 0.01 pKa2 = 8.55 ± 0.01 (measured)
B:P	1.3	1.3	1.0
logD	3.96 at pH 7.4	NA	NA
logP		4.336	3.73
Solubility (mg/mL)	pH solubility 1.0 71.40 2.0 1.671 3.0 1.213 4.5 0.215 5.0 0.032 6.0 0.006 6.8-9 0.012		
Biorelevant solubility (mg/mL)	SGF pH 1.2: 42.23 FaSSIF pH 6.5: 0.117 FeSSIF pH 5.0: 3.480		
Pcaco-2 (cm/min)	3.72×10^{-6}	3.72×10^{-6}	
Peff (10^{-4} cm/s)	0.68 (scaled based on Pcaco-2)	1.34	
Fugut	NA	1	

Particle size	30 µm (radius=15µm) (mean D50 of clinical API)	Modeled as solution without precipitation	
Precipitation time (s)	10^6 (high value estimated based on lack of precipitation seen in vitro)		
Fg	66%	66% (estimated by Qgut model)	
Fh	91%		
Clint (µL/min/pmol)		CYP3A4: 5.17 (fmcyp3a=78%)	CYP3A4: 31.0 (fmcyp3a=99%)
CLhep (µL/min/mg-protein) additional clearance in liver		197 (fm_addhep = 21.7%)	0.44 (fm_addhep = 1%)
CLrenal (L/h)	0	0.0375 (renal CL: 0.3%)	0
CL (L/h)	10.2		
CYP3A4 ontogeny	Default GastroPlus ontogeny for 4 year and older, both default Gastroplus model and Upreti et al. for less than 4 years	Default Simcyp ontogeny, and Upreti et al.	
Parameters for entrectinib as a perpetrator			
Ki for CYP3A (µM)		1.02 (Calculated based on measured IC50 in rCYPs; Ki = IC50×0.5)	
Fraction unbound in HLM (fu,mic) for Ki (inhibition)		0.072 for CYP3A4 (0.08 mg/mL)	
Induction slope for CYPs		CYP3A4: 0.61 CYP2C9: 0.25	

Perpetrator models

Default CYP3A inhibitor models itraconazole, and erythromycin, and inducer models, rifampin, and efavirenz were used to simulate the effects of CYP3A modulators on the PK of entrectinib and M5.

Other substrate models

The Simcyp midazolam model was used with refinement. The inter-system extrapolating factor (ISEF) was modified from 1 to 0.75 so that the midazolam model could predict the observed midazolam PK in the entrectinib and midazolam DDI study. The Simcyp default ethinylestradiol was used as a CYP3A substrate.

PBPK model verification

The entrectinib and M5 PBPK model predictions (entrectinib PK, M5 PK, and DDI results) were compared to the observed PK and DDI data obtained from in vivo studies listed in **Table 83**.

Table 83 Summary of human PK data used for entrectinib PBPK model development and verification

Study No.	Formulation	N	Dose (mg)	Description	Model Platform	PBPK model objective
RXDX-101-05	bespoke powder in capsule (b) (4) (b) (4)	6 (fasted)	600	ADME	GastroPlus	Development
RXDX-101-12 Part 1	F06	10 (fasted)	100	DDI: itraconazole	Simcyp (entrectinib and M5) GastroPlus	Development
RXDX-101-12 Part 2	F06	10 (fasted)	600	DDI: rifampin	Simcyp (entrectinib and M5)	Validation
RXDX-101-14	F06	12 (fasted)	600	DDI: entrectinib effects on midazolam in patients	Simcyp	Validation
CA14707	F1 and F2A	48 (fasted) 12 (fed)	800	Food effect, PPI (lansoprazole) effect	GastroPlus	Development
RXDX-101-04	F2A	24	400, 600	Food effect, ethnicity effects	Simcyp	Validation
RXDX-101-07	F2A and F06	48 (fasted) 12 (fed)	600	Food and formulation effects	GastroPlus	Development
RXDX-101-08	F06	24 (fasted)	600	Manufacturing scale effects	GastroPlus	Development
RXDX-101-09	F06	19 (fasted)	600	Relative bioavailability of F06 administered with or without a proton pump inhibitor	GastroPlus	Development
RXDX-101-01/STARTRK-1	F1	8 (fed)	800	Efficacy study in adult patients	Simcyp	Validation
	F1	15 (fed)	600			
	F2A	16 (fed)	600			
RXDX-101-02/ STARTRK-2	F2A	191 (fed)	600	Efficacy study in adult patients	Simcyp (entrectinib and M5)	Validation
RXDX-101-03/ STARTRK-NG	F1	13 (fed)	250-750 mg/m^2	Efficacy study in children, adolescents, and young adults	Simcyp, Gastroplus	Development
	F2B	3				

Source: Table 2 in report 1091399, and Table 2 in report 1091111, N is the number of subjects used for PBPK model development and verification.

The perpetrator models were validated by comparing the predicted to the observed PK after single and multiple dose administrations, and DDI effects on CYP3A substrates. The predicted/observed mean ratios were generally within 0.5-1.5 for Cmax and AUC, respectively, of the perpetrator (source: Simcyp model files). The DDI predictive performance of perpetrator models was summarized in Table 84.

Table 84 Summary of predicted and observed CmaxR and AUCR for perpetrator models regarding the CYP3A pathway

Perpetrator	Substrate	Observed		Predicted		Pred. / Obs.	
		CmaxR	AUCR	CmaxR	AUCR	CmaxR	AUCR
Itraconazole	Midazolam	2.56	5.75	2.48	5.30	0.97	0.92
	Midazolam	3.41	10.77	2.82	11.03	0.83	1.02
	Midazolam	2.91	5.17	3.02	7.97	1.04	1.54
	Zolpidem	1.10	1.34	1.18	1.68	1.07	1.25
Erythromycin	Midazolam	2.70	4.41	2.84	7.84	1.05	1.77
	Triazolam	1.77	3.65	1.93	4.03	1.09	1.10

	Alprazolam	1.18	2.47	1.07	2.62	0.90	1.06
Rifampin	Midazolam	0.06	0.04	0.10	0.07	1.67	1.75
	Midazolam	0.17	0.12	0.16	0.11	0.94	0.92
Efavirenz	Alfentanil, i.v.	NA	0.54	1.0	0.56	NA	1.04
	Alfentanil, p.o.	0.43	0.22	0.40	0.25	0.93	1.14
	Maraviroc	0.44	0.49	0.40	0.35	0.91	0.71

Source: Simcyp model files, CmaxR and AUCR are mean Cmax and AUC ratios when the substrate was given with/without a perpetrator.

PBPK model application

The developed PBPK models were used to simulate the following scenarios.

- The effects of a moderate(erythromycin) CYP3A inhibitor on the PK of entrectinib and its active metabolite M5,
- The effects of a moderate (efavirenz) CYP3A inducer on the PK of entrectinib and its active metabolite M5,
- The effect of entrectinib on a CYP3A substrate (ethinylestradiol), and
- Entrectinib PK in pediatric population (birth to 4 years of age) following administration of F1/F2A/F06 formulations

Results

1. Can the PBPK models provide a reasonable description of the PK of entrectinib and M5 in adults?

Yes. The entrectinib and M5 PBPK models in Simcyp were able to describe the observed PK following single dose and multiple dose administration as shown in **Figure 50**, and **Table 85**. There are a few observations regarding the model predictive performance for entrectinib and M5 PK.

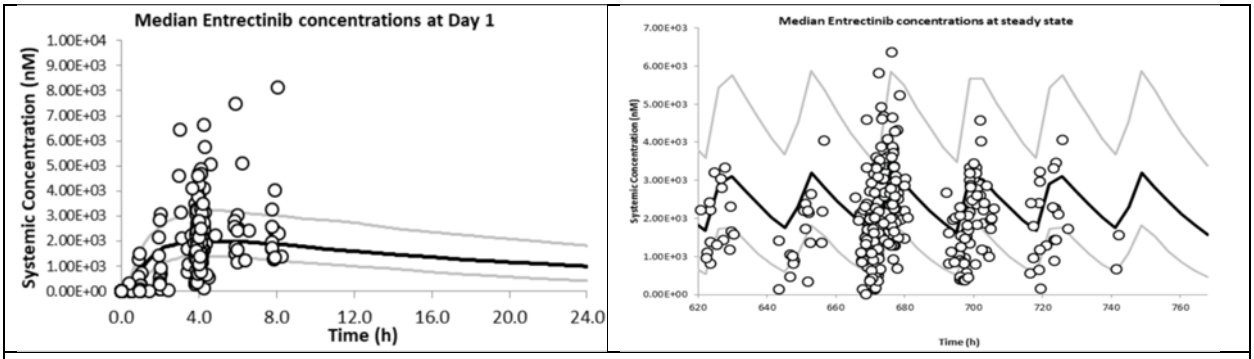
- In general, the predicted vs. observed geometric mean AUC ratios of entrectinib and M5 were within 0.7-1.5 following a single or multiple dose administration of F2A or F06 entrectinib formulation under fasting or fed condition in healthy volunteers and patients (**Table 85**).
- The model under estimated the PK variability on day 1 following multiple dose administration for both entrectinib and M5 (**Figure 50**).
- The predicted geometric mean Cmax values for M5 in patients were generally within 20% of the observed geometric mean values. However, the model over-predicted the geometric mean Cmax for M5 following a single dose administration in healthy volunteers (**Table 85**).

The entrectinib and M5 PBPK models in Simcyp were considered able to describe the observed PK for the following reasons.

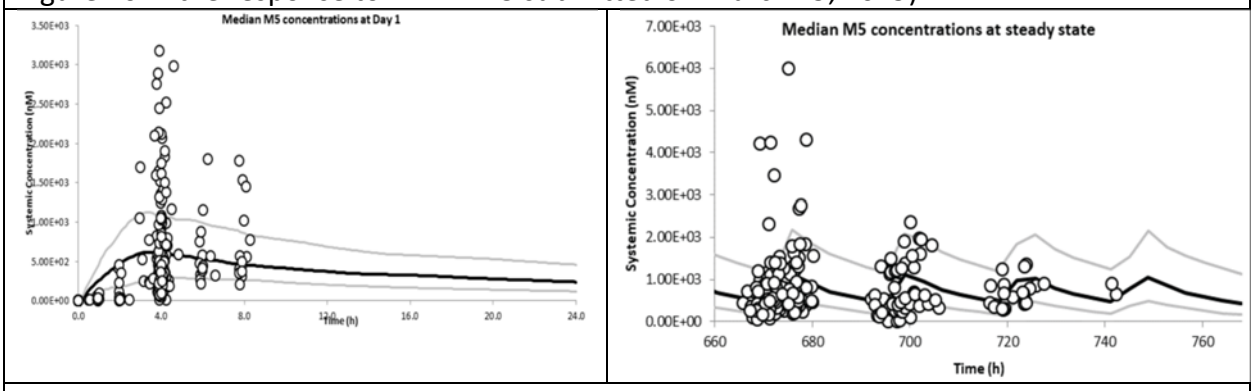
- The geometric mean Cmax of M5 could be captured by the model on day 1 and day 14 in patients which is a more clinically relevant condition compared to the single dose studies in healthy volunteers.

- Cmax is not a metric for dose adjustment consideration.
- The exposure of M5 was about 30-40% of the parent drug and considered as a secondary moiety.

Figure 50 Simulated (in Simcyp) and observed entrectinib and M5 following single or multiple dose administration



Predicted median (and 5th and 95th percentiles) and observed (study RXDX-101-02, 600 mg, F2A adult patients) entrectinib PK profiles on day 1 (left) and at steady state (right) (source: Figure 10 in the response to FDA IR-15 submitted on March 29, 2019)



Predicted median (and 5th and 95th percentiles) and observed (study RXDX-101-02, 600 mg, F2A adult patients) M5 PK profiles on day 1 (left) and at steady state (right) (source: Figure 11 in the response to FDA IR-15 submitted on March 29, 2019)

Table 85 Summary of simulated and observed geometric mean entrectinib and M5 PK following single or multiple dose administration

Study	Dose (mg)	formulation	N	Fasted /fed	Moiety	Observed		Predicted		Pred./obs.	
						Cmax (nM)	AUC (nM·h)	Cmax (nM)	AUC (nM·h)	Cmax (nM)	AUC (nM·h)
RXDX-101-04, Caucasian	400, SD	F2A	11	fasted	Entrectinib	1520	32100	1210	31000	0.80	0.97
					M5[$]	260	8450	625	10058	2.40	1.19
RXDX-101-04, Japanese	400, SD	F2A	12	fasted	Entrectinib	1740	32200	1210	31000	0.70	0.96
					M5[$]	364	11100	625	10058	1.72	0.91
RXDX-101-04, Caucasian	600, SD	F2A	12	fasted	Entrectinib	1920	41500	1770	45600	0.92	1.10
					M5	352	10800	1010	15971	2.87	1.48

RXDX-101-04, Japanese	600, SD	F2A	12	fasted	Entrectinib	2170	40800	1770	45600	0.82	1.12
					M5	430	12600	1010	15971	2.35	1.27
RXDX-101-07	600, SD	F2A	48	fasted	Entrectinib	2240	54500	1770	45600	0.79	0.84
					M5	463	14200	1010	15971	2.18	1.12
RXDX-101-07	600, SD	F06	48	fasted	Entrectinib	2120	51800	1770	45600	0.83	0.88
					M5	416	13300	1010	15971	2.43	1.20
RXDX-101-15	600, SD	F2A	48	fasted	Entrectinib	2330	52800	1770	45600	0.76	0.86
					M5	465	14400	1010	15971	2.17	1.11
RXDX-101-08, Lot A	600, SD	F06	24	fasted	Entrectinib	2360	53000	1770	45600	0.75	0.86
					M5	586	16400	1010	15971	1.72	0.97
RXDX-101-08, Lot B	600, SD	F06	24	fasted	Entrectinib	2310	53000	1770	45600	0.77	0.86
					M5	553	15600	1010	15971	1.83	1.02
RXDX-101-09	600, SD	F06	19	fasted	Entrectinib	2300	55000	1770	45600	0.77	0.83
					M5	451	14700	1010	15971	2.24	1.09
RXDX-101-12, Cohort 2	600, SD	F06	10	fasted	Entrectinib	1810	36300	1770	45600	0.98	1.26
					M5	383	11000	1010	15971	2.64	1.45
RXDX-101-15, Part 1	600, SD	F06	48	fasted	Entrectinib	2180	48300	1770	45600	0.81	0.94
					M5	451	13900	1010	15971	2.24	1.15
RXDX-101-15, Part 2	600, SD	F06	47	fasted	Entrectinib	2250	51200	1770	45600	0.79	0.89
					M5	442	14000	1010	15971	2.29	1.14
RXDX-101-04, Caucasian	600, SD	F2A	11	fed	Entrectinib	1950	49800	2030	53300	1.04	1.07
					M5	305	13200	706	15126	2.31	1.15
RXDX-101-04, Japanese	600, SD	F2A	12	fed	Entrectinib	2200	47800	2030	53300	0.92	1.12
					M5	385	14300	706	15126	1.83	1.06
RXDX-101-07	600, SD	F2A	12	fed	Entrectinib	2290	60900	2030	53300	0.89	0.88
					M5	392	16000	706	15126	1.80	0.95
RXDX-101-07	600, SD	F06	12	fed	Entrectinib	2570	72100	2030	53300	0.79	0.74
					M5	387	17300	706	15126	1.82	0.87
RXDX-101-15	600, SD	F06	46	fed	Entrectinib	2380	57900	2030	53300	0.85	0.92
					M5	403	15700	706	15126	1.75	0.96
RXDX-101-01, day 1	600, QD	F2A	18	fed	Entrectinib	2250	31800 [a,d]	1899	31855	0.84	1.00
					M5	622	10200 [a,d]	623	9050	1.00	0.89
RXDX-101-01, day14	600, QD	F2A	12	fed	Entrectinib	3130	48000 [b,d]	3260	57300	1.04	1.19
					M5	1250	24000 [b,d]	1120	17500	0.90	0.73
RXDX-101-02, day 1[c]	600, QD	F2A	203	fed	Entrectinib	1590	27700 [d]	1899	31855	1.19	1.15
					M5	545	9590 [d]	623	9050	1.14	0.94
RXDX-101-02, day 14 [c]	600, QD	F2A	203	fed	Entrectinib	2860	51700 [d]	3260	57300	1.14	1.11
					M5	995	19000 [d]	1120	17500	1.13	0.92

Source: Tables 7-10, and 15-17 in the Summary of Clinical Pharmacology Studies, Tables 14-17 in PBPK modeling report 1091399, Table 1, 11 in the response to FDA IR-09 submitted on March 1, 2019, Tables 5-6 in CSR RXDX-101-04, and reviewer's analysis using the submitted workspace files. SD: single dose, QD: once daily, N: number of subjects, SS: steady state, [$]presented as mean plasma PK [a] N =16, [b] N =9, [c] PK parameters were predicted using popPK model due to the sparse sampling in study STARTRK-2 (RXDX-101-02), [d] AUC_{0-24} for day 1 or AUC_{tau} for SS. The predicted Cmax and AUC values presented in the PBPK report 1091399 and follow-up analyses were rounded off to three digits.

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

Yes. The PBPK DDI model was developed based on the entrectinib and itraconazole DDI study and validated with the entrectinib and rifampin DDI study. As shown in **Table 86**, the PBPK model was able to capture the geometric mean Cmax and AUC of entrectinib when it was given alone or with itraconazole, or rifampin. The predicted to observed ratios for entrectinib geometric mean PK parameters were between 0.8-1.4 (**Table 86**). The model

over-predicted observed geometric mean PK values of M5 when entrectinib was given alone or with rifampin. Assuming that entrectinib and M5 have equal potency, the model generally could capture the exposure adding both moieties together (entrectinib + M5) with predicted to observed ratios within 0.8-1.5 (**Table 86**) when entrectinib was given alone or with a perpetrator. Considering that the model was able to capture the change in entrectinib exposure and the additive exposure of entrectinib and M5, the substrate model was considered adequate to evaluate the effect moderate CYP3A perpetrators on entrectinib PK.

Table 86 Summary of predicted and observed effects of itraconazole and rifampin on the PK (presented as geometric mean values) of entrectinib and M5 when entrectinib was given as a single dose

		Entrectinib alone		**Entrectinib with perpetrator**		**With/without perpetrator**	
Study/Simulation		Cmax (nM)	AUC (nM·h)	Cmaxinh (nM)	AUCinh (nM·h)	CmaxR	AUCR
Study RXDX-101-12, Cohort 1 (itraconazole), N=10	Entrectinib	358	6010	615	30500	1.72	5.07
	M5	52.3	1430	31.5	2780	0.60	1.94
	Entrectinib + M5	--	7440	--	33280	--	4.47
Simulation: itraconazole 200 mg QD for 10 days, entrectinib 100 mg SD on day 5, fasting	Entrectinib	326	8430	643	38600	1.97	4.58
	M5	112	2000	22.8	2620	0.20	1.31
	Entrectinib + M5	--	10430	--	41220	--	3.95
Pred. / Obs. (itraconazole DDI)	Entrectinib	0.91	1.40	1.05	1.27	1.14	0.87
	M5	2.14	1.40	0.72	0.94	0.33	0.52
	Entrectinib + M5	--	1.40	--	1.24	--	0.88
Study: RXDX-101-12, Cohort 2 (rifampin), N=10	Entrectinib	1810	35900	807	8300	0.44	0.23
	M5	383	10000	108	1270	0.28	0.13
	Entrectinib + M5	--	45900	--	9570	--	0.21
Simulation: rifampin 600 mg QD for 16 days, entrectinib 600 mg SD on day 12, fasting	Entrectinib	1830	47000	662	9380	0.36	0.20
	M5	1189	17136	534	4515	0.45	0.26
	Entrectinib + M5	--	64136	--	13895	--	0.22
Pred. / Obs. (rifampin DDI)	Entrectinib	1.01	1.31	0.82	1.13	0.82	0.87
	M5	3.10	1.71	4.95	3.56	1.59	2.07
	Entrectinib + M5	--	1.40	--	1.45	--	1.04

Source: Tables 4-7, 18 in the PBPK analyses report 1091399, Table 13 in CSR RXDX-101-12, Table 13 in the response to FDA's IR-15 submitted on March 29, 2019, and reviewer's analysis using submitted workspace files; AUC is AUC_{last} for SD (t_{last} = 144 hours for itraconazole DDI, and 120 hours for rifampin DDI), and AUC_{tau} for multiple dose; subscript 'inh' indicating PK parameters with a perpetrator; entrectinib and M5 are assumed equal potency

In general, the perpetrator models were able to capture the observed DDI effects (**Table 84**) except that the erythromycin model over predicted one set of observed effect on midazolam (predicted AUCR of 7.84 vs. observed AUCR of 4.41). The erythromycin model was able to capture its effect on triazolam ($f_{mcyp3a4}$ = 98% based on model estimation) and alprazolam ($f_{mcyp3a4}$ = 74% based on model estimation).

The predicted effects of itraconazole, erythromycin, and efavirenz on the PK of entrectinib and M5 at steady state are summarized in **Table 87**. Itraconazole 200 mg QD was predicted to increase the exposure of entrectinib and entrectinib + M5 by 5.1-fold, and 4.4-fold, respectively. Erythromycin 500 mg TID was predicted to increase the exposure of entrectinib and entrectinib + M5 by 3.4-fold, and 3.1-fold, respectively. When entrectinib 100 mg QD or 200 mg QD co-administered with itraconazole or erythromycin, respectively, the predicted AUCtau were within the range of observed AUCtau at steady state with respect to entrectinib **(Table 85)**.

The reviewer conducted additional simulations to evaluate the effects of fluconazole (a moderate CYP3A4 and CYP2C9 inhibitor) on the PK of entrectinib and M5 following multiple- dose administration of entrectinib. The results showed that fluconazole increased the exposure of entrectinib and entrectinib + M5 by 3.7-fold and 3.3-fold, respectively. The fluconazole-entrectinib simulations added additional level of confidence in predicting the effects of a moderate CYP3A inhibitor on the PK of entrectinib.

Table 87 Summary of predicted effects of itraconazole, erythromycin, and efavirenz on the PK (presented as geometric mean values) of entrectinib and M5 at steady state

		Entrectinib alone		**Entrectinib with perpetrator**		**With/without perpetrator**	
Dosing regimen		Cmax (nM)	AUC (nM·h)	Cmaxinh (nM)	AUCinh (nM·h)	CmaxR	AUCR
Itraconazole 200 mg QD for 25 days, entrectinib 100 mg QD for 20 days starting from day 5	Entrectinib	473	7870	1950	40200	4.13	5.10
	M5	178	2150	174	3910	0.98	1.82
	Entrectinib + M5	--	10020	--	44110	--	4.40
Erythromycin 500 mg TID for 25 days, entrectinib 200 mg QD for 15 days starting from day 11	Entrectinib	992	16200	2870	55000	2.89	3.40
	M5	469	5230	568	10900	1.21	2.08
	Entrectinib + M5	--	21430	--	65900	--	3.08
Fluconazole 400 mg QD for 42 days, entrectinib 200 mg QD for 33 days starting from day 10	Entrectinib	923	15418	2857	57066	3.09	3.70
	M5	415	4865	521	10337	2.12	1.26
	Entrectinib + M5	--	20283	--	67403	--	3.32
Efavirenz 600 mg QD for 30 days, entrectinib 600 mg QD for 18 days starting from day 12	Entrectinib	2670	44000	1530	19500	0.57	0.44
	M5	1740	18800	1250	10000	0.72	0.53
	Entrectinib + M5	--	62800	--	29500	--	0.47

Source: Tables 4-8 in the response to FDA's IR-09 submitted on March 1, 2019, Tables 1-8 in the response to FDA's IR-15 submitted on March 29, 2019, and reviewer's analysis using submitted workspace files; AUC is AUC_{tau} of the last dose interval; subscript 'inh' indicating PK parameters with a perpetrator.

3. Are the PBPK models adequate to predict the effects of entrectinib on ethinylestradiol (a CYP3A substrate) exposure?

Yes, the PBPK model could be used to estimate the effect of entrectinib on the change in ethinylestradiol AUC but not Cmax. The applicant verified the effects of entrectinib on midazolam (MDZ) PK against the entrectinib-midazolam DDI study (RXDX-101-14). The default MDZ model in Simcyp over-predicted the observed MDZ exposure when it was given alone in study RXDX-101-14. Genentech modified the model by reducing the ISEF from 1 to 0.75. The reviewer compared the impact of modified ISEF on the predicted effects of

entrectinib on MDZ PK. As shown in **Table 88**, in general, the model could predict the MDZ AUC change when it was co-administered multiple doses of entrectinib using both Genentech's or the default MDZ model with predicted / observed AUCR of 1.10 and 1.22, respectively. Higher ISEF (used in the default model compared to the value used in Genentech's model) predicted about 10% higher CmaxR and AUCR.

The model over-predicted observed CmaxR. The model predicted increased MDZ Cmax while a decrease in MDZ Cmax was observed when it was co-administered with entrectinib (**Table 88**). Genentech's hypothesis was that midazolam is highly permeable and appears to be partially absorbed in the stomach. The reviewer observed that in the studies evaluating the effects of entrectinib on the PK of MDZ, and digoxin (RXDX-101-13), the Tmax of both substrates (MDZ and digoxin) was prolonged by approximately 1 hour. It was suspected that entrectinib may have an effect on the gastric emptying time, and therefore affect the substrate absorption parameters such as Tmax and Cmax. However, in the response to FDA's IR-32 submitted on May 7, 2019, Genentech indicated that 'the tyrosine kinase pharmacological targets are not associated with the gastrointestinal system, and within the entrectinib preclinical and clinical programs there are no data to suggest that entrectinib treatment alters gastric motility'. Nevertheless, as the model could not capture the change in MDZ Cmax, the model was not adequate the evaluate the effect of entrectinib on the change in Cmax of a CYP3A substrate.

The verified model was used to predict the effects of entrectinib on the AUC of ethinylestradiol (a CYP3A substrate). The reviewer conducted a DDI query between ethinylestradiol and CYP3A strong inhibitors such as ketoconazole and voriconazole using University of Washington DDI database (UWDIDB) (https://www.druginteractioninfo.org/). The survey of the UWDIDB showed an approximately 50% increase in ethinylestradiol AUC when it was co-administered with ketoconazole or voriconazole. Thus, ethinylestradiol is not a sensitive CYP3A substrate. It is expected that the effects of entrectinib on ethinylestradiol should be less than midazolam.

Table 88 Predicted effects of entrectinib on the PK of MDZ using Genentech's model or the default model in Simcyp

Dosing regimen	MDZ model	Predicted		Observed		Pred./obs.	
		$C_{max}R$	$AUC_{inf}R$	$C_{max}R$	$AUC_{inf}R$	$C_{max}R$	$AUC_{inf}R$
Entrectinib (F2A) 600 mg QD (fed) day 8-23, MDZ (fasted) 2 mg on day 8	Applicant	1.53	1.60	0.66	1.00	2.32	1.60
	V17	1.69	1.77			2.56	1.77
Entrectinib (F2A) 600 mg QD (fed) day 8-23, MDZ (fasted) 2 mg on day 21	Applicant	1.55	1.65	0.79	1.50	1.96	1.10
	V17	1.71	1.83			2.16	1.22

Source: Tables 8, 9, 11, and 12 in the PBPK analyses report 1091399, Tables 27 and 28 in the Summary of Clinical Pharmacology Studies; CmaxR and AUCR are geometric mean Cmax and AUC ratios of MDZ when it was given with/without entrectinib.

4. Can the PBPK models be used to predict the PK of entrectinib in pediatrics (less than 4 years of age)?

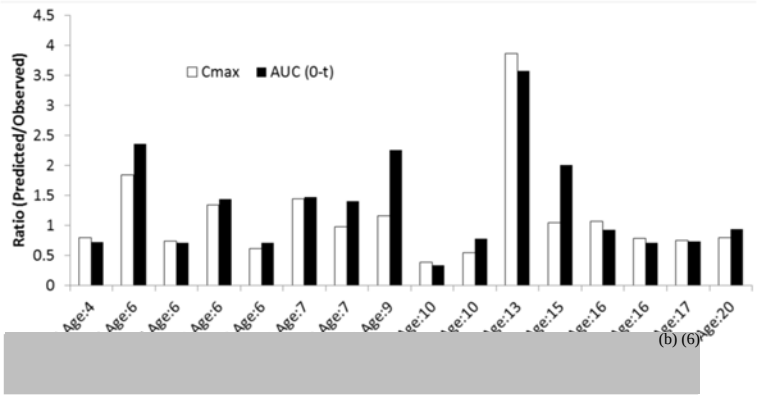
No. Both PBPK models in Simcyp and GastroPlus were used to estimate the PK of entrectinib in pediatric populations (0-20 years of age). Physiological factors that may affect entrectinib PK and were explored in the submission include GI physiology, and CYP3A4 ontogeny.

Three CYP3A4 ontogeny profiles were considered, namely the Simcyp default, the GastroPlus default, and the Upreti et al. (J Clin Pharmacol. 2016 Mar; 56(3):266-83). The Simcyp default and the GastroPlus default profiles are similar while the Upreti profile showed about two-fold higher activity for 1-2 years of age, and 50% higher for 2-4 years of age compared to the software default models (Figure 1 of report 1091111). Therefore, it is expected that the Upreti profile will give lower exposure prediction compared to the software default ontogenies for a CYP3A4 substrate.

The absorption was not modelled mechanistically in the Simcyp entrectinib PBPK model as discussed in the 'overview of modeling strategy' section. The applicant selected the Upreti CYP3A4 ontogeny in the Simcyp model as it provided closer prediction to the observed PK on day 1 in 4-9 years of age population compared to the Simcyp default CYP3A4 ontogeny. The Simcyp entrectinib pediatric PBPK model predictive performance was not further verified by comparing model prediction to the observed PK in children less than 4 years of age. Because both the CYP3A4 ontogeny and GI physiology could affect the PK prediction, missing the mechanistic absorption model could have missed the impact of GI physiology change on PK in pediatric subjects 4 years of age and younger.

The entrectinib PBPK model in GastroPlus adapted a mechanistic absorption model Assuming the same bile salt concentrations in pediatric populations as the bile salt concentrations in adults under fed condition overestimated the observed PK in pediatric patients; therefore,. Genentech lowered the BSSR value to mimic the lower bile salt concentration in pediatric populations. The GastroPlus default CYP3A4 ontogeny was applied. Gastric pH values were adjusted to account for formulation, food, and PPI effects. The model was able to describe the observed entrectinib PK on day 1 in pediatric population 4 years and older as shown in **Figure 51**. Among the 16 subjects, 11 subjects had the ratio of predicted to observed AUC with 0.5-1.5, 1 subject had the ratio of predicted to observed AUC less than 0.5, and 4 subjects had the ratio of predicted to observed AUC larger than 2. Genentech further compared the predicted to the observed entrectinib PK on day 29 in the same subjects and additional 4 subjects in the same age range (4-20 years of age) (response to FDA's IR-20 dated March 29, 2019). The model was able to describe the entrectinib PK on day 29 for majority of the subjects.

Figure 51 Ratio of predicted to observed PK parameters (day 1) in children 4 years and older (GastroPlus model, lower BSSR)



Source: Figure 25 of PBPK report 1091111

The validated GastroPlus model was used to predict the PK in children less than 4 years old. The prediction was compared to the observed PK data in 5 children less than 4 years old which were available after the original submission (response to FDA's IR-20 dated March 29, 2019). Genentech concluded that the model showed a tendency of overestimation of the observed exposure. Even applying the Upreti ontogeny, Cmax was over-predicted by more than 2-fold in two of the three non-obese subjects.

Conclusions

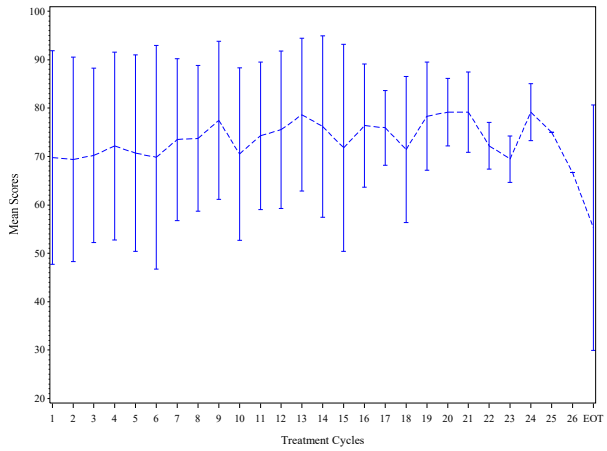
Genentech's PBPK model was adequate to evaluate the effect of a moderate inhibitor or a moderate inducer on the PK of entrectinib. The model predicted a 3.4-fold increase in entrectinib AUCtau at steady state when it was co-administered with erythromycin, and a 56% decrease in entrectinib AUCtau at steady state when it was co-administered with efavirenz.

19.5. Additional Clinical Outcome Assessment Analyses

The outcome of the quality of life as assessed by the QLQ-C30 for the global health status, and the five functional scales: physical, role, cognitive, emotional, and social are summarized in the following figures. The mean score and the mean change from baseline at each assessment time point are represented by the center lines, and the vertical bars represent one standard deviation from the mean score.

Figure 52: EORTC QLQ-C30 Global Health Status

Mean Score over Time



Mean Change from Baseline Over Time

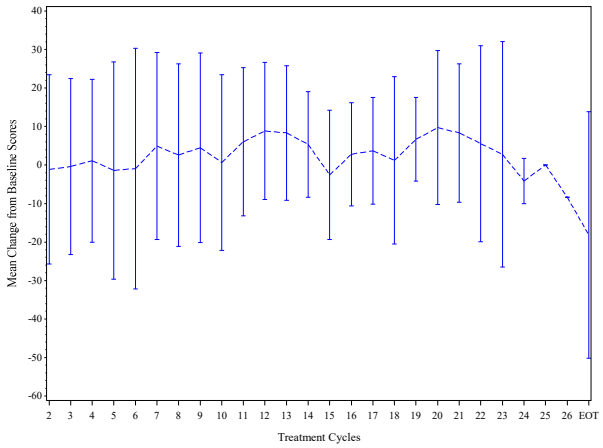
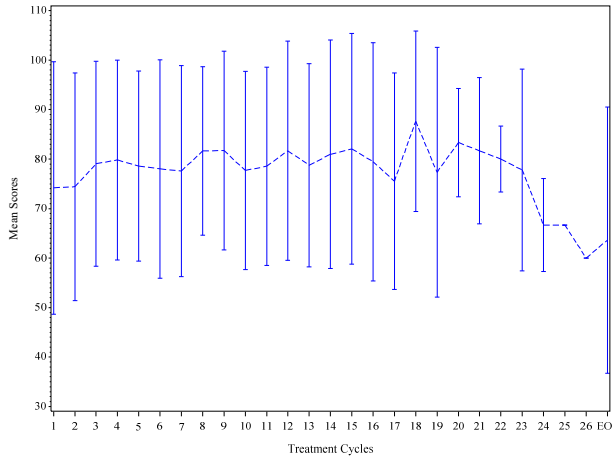


Figure 53: EORTC QLQ-C30 Physical Functioning

Mean Score over Time



Mean Change from Baseline Over Time

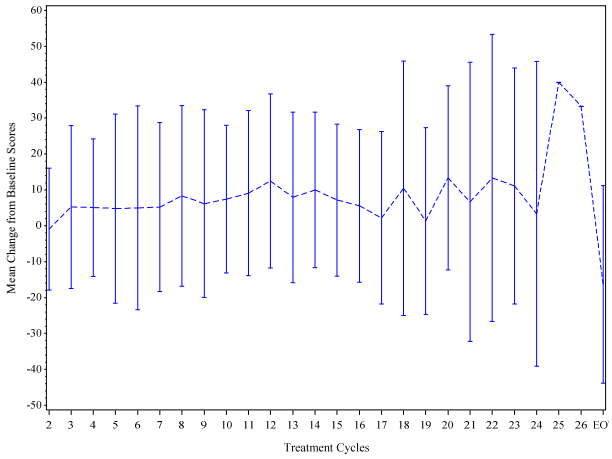
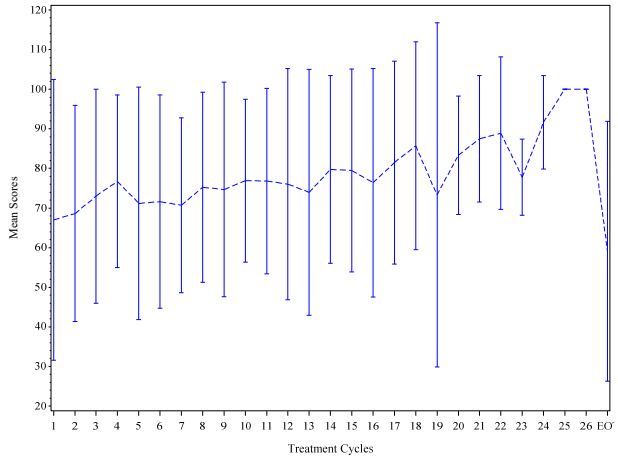


Figure 54: EORTC QLQ-C30 Role Functioning

Mean Score over Time



Mean Change from Baseline Over Time

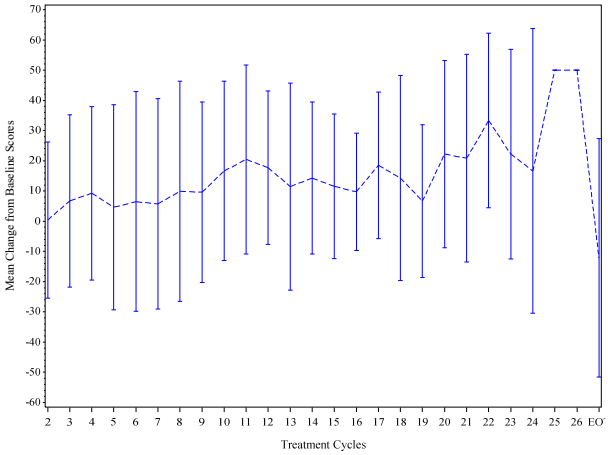
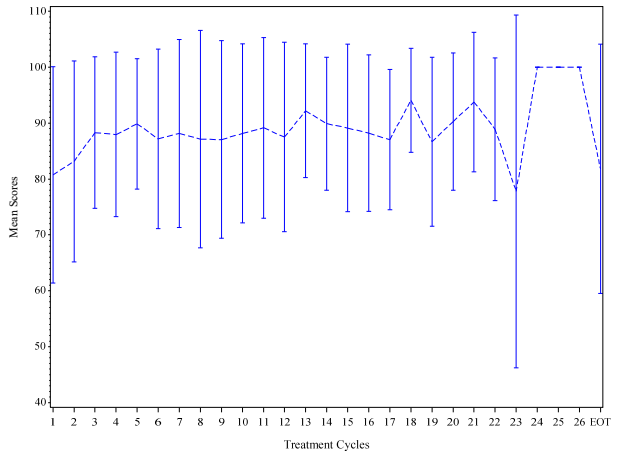


Figure 55: EORTC QLQ-C30 Emotional Functioning

Mean Score over Time



Mean Change from Baseline Over Time

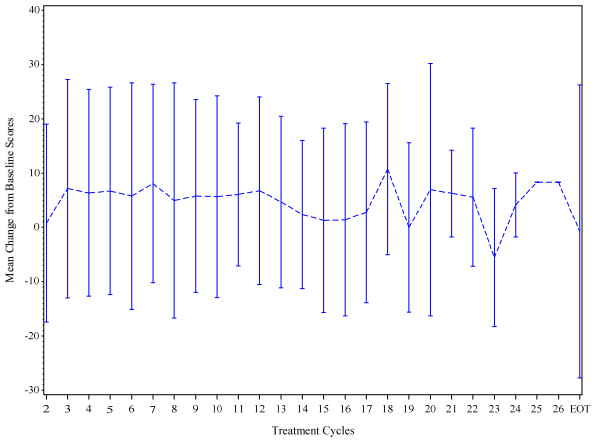
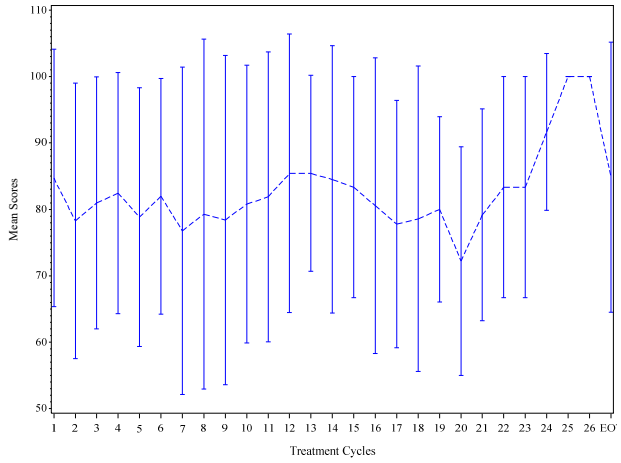


Figure 56: EORTC QLQ-C30 Cognitive Functioning

Mean Score over Time



Mean Change from Baseline Over Time

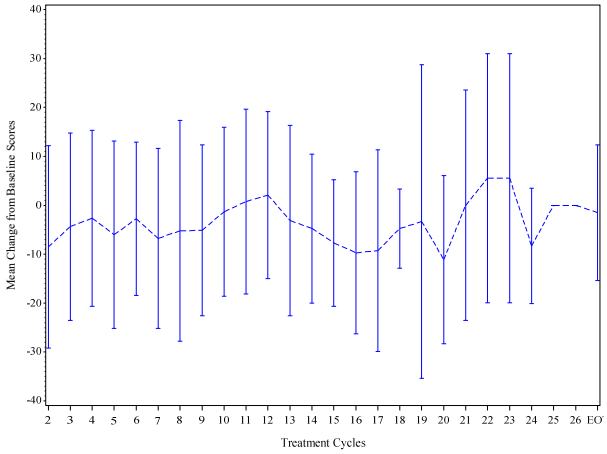
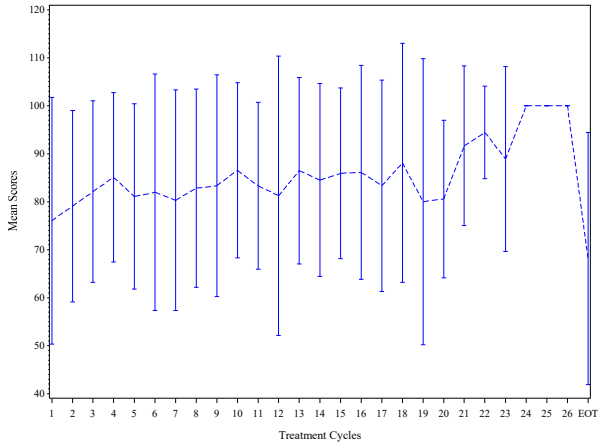
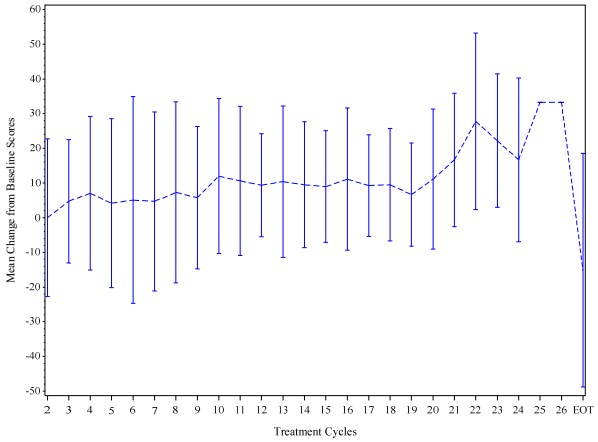


Figure 57: EORTC QLQ-C30 Social Functioning

Mean Score over Time



Mean Change from Baseline Over Time



19.6. Description of Relevant Individual Trials Supporting the NDA

19.6.1. ALKA-372-001Trial Design

Study ALKA-372-001 (GO40783), entitled, "A Phase 1, Dose Escalation Study of Entrectinib (RXDX-101) In Adult Patients With Advanced/ Metastatic Solid Tumors" was the first-in-human, open-label, single arm, nonrandomized, multicenter, dose escalation study in sequential cohorts of adult patients with advanced or metastatic solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK*-positive genetic alterations, including any type of molecular alteration, inclusive of fusions.

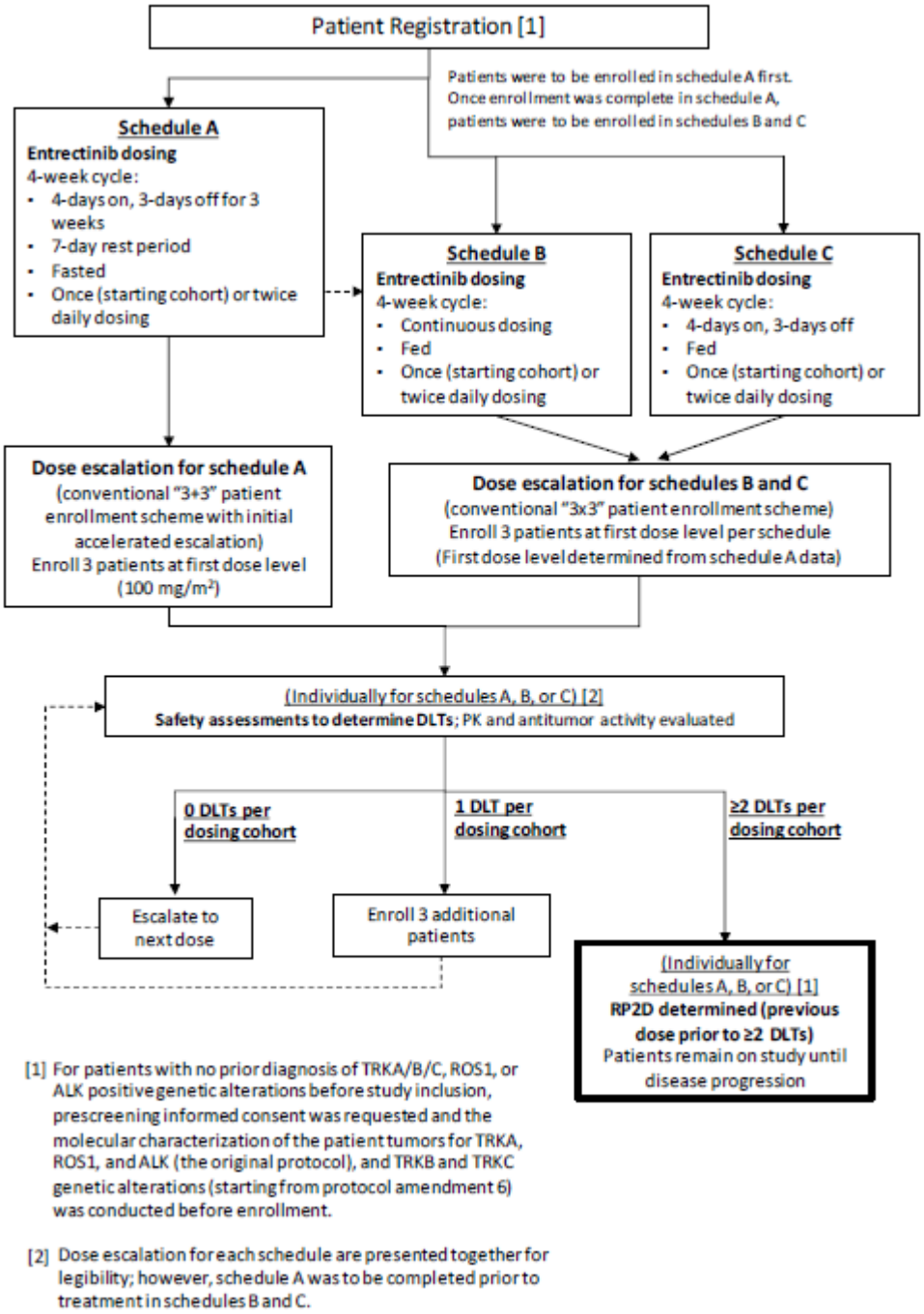
Please see Appendix X for detailed information regarding the design of this trial, including a summary of protocol amendments. including The following dose schedules were investigated in this study:

Schedule A: 100, 200, 400, 800, 1200, or 1600 mg/m^2 once daily (fasted) 4-days on, 3-days off schedule x 3 weeks followed by 7-day rest in a 4-week cycle
Schedule B: 200, 400 mg/m^2 or 600 mg continuous once daily (fed) in a 4-week cycle
Schedule C: 400 or 800 mg/m^2 once daily (fed) in a continuous 4-days on, 3-days off schedule in a 4-week cycle

The dose level and dose schedule for each patient was assigned by the sponsor at the time of patient registration. All patients had to be observed for 1 cycle before subsequent patients were enrolled at the next higher dose level. The study had an initial 100% accelerated escalation phase until a predetermined level of toxicity was encountered. At that point, escalation was to follow a modified Fibonacci scheme.

The design of the study was dose escalation and a standard “3+3” scheme was used to evaluate all the dose schedules and determine the RP2D. Figure 58 presents the dose escalation schema used in this study.

Figure 58: Dose Escalation Schema for ALKA-372-001



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Key Eligibility Criteria

Consenting adult (age ≥ 18) patients with histologically or cytologically confirmed diagnosis of advanced/metastatic solid tumors with *ALK*-positive alterations (per original protocol) or *ALK*-negative patients with TRKA, TRKB, TRKC, or *ROS1* genetic alterations (*ALK*-negative patients

with TRKA or *ROS1* genetic alterations only up to protocol amendment 5) in patients for whom no alternative effective standard therapy was available, standard therapy was considered unsuitable, or had been refused (per protocol amendment 8), were eligible for the study.

Other main selection criteria included:

- ECOG performance status ≤2
- Life expectancy of at least 3 months
- Baseline laboratory data indicating acceptable hematologic status, liver and renal function, and resolution of any acute toxic effects (excluding alopecia) of any prior anticancer therapy (NCI CTCAE [version 4.03] grade ≤ 1 or to the baseline laboratory values)
- Patients with controlled asymptomatic CNS involvement, in absence of therapy with anticonvulsant (up to protocol amendment 7) or in presence of therapy with non-enzyme-inducing anti-epileptic drugs (per protocol amendment 8) or requiring steroids at stable dose (≤ 4 mg/day dexamethasone or equivalent) for at least 2 weeks were also eligible.

Study Endpoints

The primary objective of this study was to determine the first cycle dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD) of entrectinib administered orally in three different dosing regimens: schedule A (4-days on treatment, 3 days off schedule for 3 weeks, followed by a 7-day rest period in a 4-week cycle; fasted condition; once daily dosing); schedule B (continuous daily dosing in a 4-week cycle; fed condition; once daily dosing); or schedule C (4 days on treatment, 3-days off schedule in a 4-week cycle; fed condition; once daily dosing) in adult patients with advanced/metastatic solid tumors with tropomyosin receptor kinases (TRK)A, TRKB, TRKC, tyrosine kinase ROS Proto-Oncogene 1 (*ROS1*), or anaplastic lymphoma kinase (*ALK*) positive genetic alterations.

The secondary objectives were to define the safety profile of entrectenib, to evaluate the pharmacokinetics of entrectinib in plasma, and to document any antitumor activity of entrectenib.

Dose Modification and Management Algorithms

A dose level –1, corresponding to 60 mg/m^2/day, dose de-escalation was required in patients receiving the starting dose level of 100 mg/m^2/day. No more than one intra-patient dose de-escalation was allowed. Doses reduced for drug-related toxicity were not be re-escalated, even if there was minimal or no toxicity with the reduced dose according to Table 89.

Table 89: Dose Modification for Entrectinib Based on the Worst Grade (as per NCI CTCAE Criteria, Version 4.03) Observed During a Treatment Cycle and in the Prior Treatment Cycle

Toxicity since last dose	During treatment cycle	After recovery from toxicity* at the start of subsequent cycle
Hematological Toxicities		
Grade ≤2 Neutropenia (ANC <1500-1000/mm^3) and/or Thrombocytopenia (PLT <75000-50000/mm^3)	If occurs during treatment, maintain daily dose level	Maintain dose level
Uncomplicated Grade 3 Neutropenia (ANC <1000-500/mm^3)	If occurs during treatment, decrease daily dose by one dose level	Maintain dose level
Uncomplicated Grade 3 Thrombocytopenia (PLT < 50,000-25,000/mm^3) or Grade 3 associated to Grade ≥ 2 bleeding	If occurs during treatment, interrupt treatment	Decrease one dose level
Febrile neutropenia : ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38 °C for >1 hour	If occurs during treatment, interrupt treatment	Decrease one dose level
Neutropenic infection: Grade ≥3 infection documented clinically or microbiologically with Grade ≥3 neutropenia	If occurs during treatment, Interrupt treatment	Decrease one dose level
Grade 4 hematological toxicity of any duration	If occurs during treatment, Interrupt treatment	Decrease one dose level
Nausea and/or Vomiting		
Grade ≤2 (in absence of antiemetics)	If occurs during treatment, maintain daily dose level and add antiemetics, if needed. If occurs during rest period, add antiemetics, if needed	Maintain dose level with antiemetics§
Grade ≤2 (in presence of antiemetics)	If occurs during treatment, decrease the daily dose by one dose level, adjust antiemetics, as needed If occurs during rest period, adjust antiemetics, as needed	Maintain dose level with adjusted antiemetics§
Grade ≥3 (in absence of antiemetics)	If occurs during treatment, interrupt one day the drug administration, if needed, decrease the daily dose by one dose level, add antiemetics. If occurs during rest period, add antiemetics	Maintain dose level with antiemetics§
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease one dose level ‡

Diarrhea		
Grade ≤2 (in absence or presence of management of the event §)	If occurs during treatment, maintain daily dose level, add/adjust antidiarrheal treatment, if needed. If occurs during rest period, add/adjust antidiarrheal treatment, if needed	Maintain dose level
Grade ≥3 in absence of management of the event	If occurs during treatment, maintain daily dose level, add antidiarrheal treatment If occurs during rest period, add antidiarrheal treatment	Maintain dose level with antidiarrheal support or if persistent, decrease one dose level
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease one dose level
CNS Toxicities / Neurologic		
Grade ≤1 or no worsening compared to baseline	Maintain dose level	Maintain dose level
Grade 2	If occurs during treatment, decrease the daily dose by one dose level	Decrease one dose level
Grade ≥ 3	If occurs during treatment, interrupt treatment	Decrease one dose level or **Discontinue study treatment‡**
Other Non-Hematological Toxicities (except alopecia)		
Grade ≤1	Maintain daily dose level	Maintain dose level
Grade 2	If occurs during treatment, maintain or decrease the daily dose by one dose level, if clinically indicated	Maintain dose level
Grade ≥ 3	If occurs during treatment, interrupt treatment	Decrease one dose level‡
Grade ≤ 2 hypersensitivity reaction suggestive of anaphylactic reaction	Investigator to discuss with Sponsor before proceeding	
Grade ≥ 3 hypersensitivity reaction suggestive of anaphylactic reaction‡	Treatment discontinuation	Treatment discontinuation
Failure to recover		
Failure to recover to grade ≤ 1 toxicity (except alopecia) or to baseline values, if grade 2 is allowed at study entry, after delaying the initiation of next cycle by > 2 weeks	Monitor until resolved to grade ≤1	Decrease one dose level ‡
§For prophylaxis and management of the events, see details in Supportive Care section of the study ‡ Investigator to discuss with Sponsor before proceeding **Abbreviations:** ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events, NCI = National Cancer Institute; PLT= platelets count		

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After a maximum of a 2-week delay, all toxicities (except for alopecia) were Grade ≤1 or recovered to baseline value, then proceeded with treatment as outlined in Table 89 above. If toxicities did not allow re-treatment after the 2-week delay, an increased delay >2 weeks was discussed between the Investigators and the Sponsor.

Monitoring Plan

For efficacy, the antitumor activity of entrectinib was assessed by the investigator, using RECIST v1.1. Tumor response was assessed every even (per protocol amendment 1) or odd cycle (per protocol amendment 6), every 3 cycles for patients who continued on treatment for 12 cycles or more (per protocol amendment 6), and at the end of last treatment cycle, if more than 4 weeks had passed from last tumor imaging.

Safety assessments including adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, eye examinations, and chest X-rays) were performed at baseline and during the treatment period at different time points, depending on the parameter and on the schedule tested, and/or at the end of treatment. Patients were followed for AEs from the

first dose up to 28 days after the last dose of study treatment or until all drug-related toxicities had resolved or an alternative anticancer therapy was started. See **Table 90** for details.

Table 90: Schedule of Assessments for ALKA-372-001

SCHEDULE OF EVENTS											
Protocol Activities	Pre-Treatment Assessments		Treatment (Week 1, 2 & 3)				Rest (Week 4)	End of		Post Treatment Assessments	
	≤ 28 D	≤ 7 D	D1	D4	D15	D18	D22-28	Every Cycle§	Last Cycle°	28-D FU	Additional FU
Informed Consent 1	X										
Physical examination 2	X		X					X	X		
Medical/Oncologic History 3	X										
Tumor Molecular Characterization 4	X										
Vital Signs, Weight 5		X	X								
ECOG PS 5		X	X								
Height 6		X									
ECG 7		X				C1 & 3			X		
Chest-X-ray (or thorax CT scan) 8	X		If clinically indicated						X		
Laboratory Assessments [x]											
Hematology 9*		X	Twice weekly (weekly from C2 on)					X	X	X (22)	
Blood Chemistry 10*		X	Twice weekly (weekly from C2 on)					X	X	X (22)	
Coagulation 11*		X						X	X	X (22)	
Urinalysis 12		X						Even cycle			
Serum/ Urine Pregnancy Test 13		X							X		
Treatment											
Enrollment 14		X									
NMS-1191372 Administration 15			Daily 4 days on/3 days off								
Efficacy Assessments											
Tumor Imaging 16	X							Even cycle	X		X
Other Clinical Assessments											
Adverse Events 17	X							X	X	X (23)	
Concomitant Medications 18	X							X	X	X	X
Pharmacokinetics											
Plasma sampling 19			X	C1 only	X	X					
Urine sampling 20		X				C1 only					
Exploratory Analysis											

Blood for liquid biopsies **21**	X								X		

Note: (*) Cycle 1, Day 1 assessments: hematology, blood chemistry, need to be repeated on Cycle 1 before the first study drug administration (predose) if they were performed during pretreatment > 1 week before first study drug administration.
§ End of every cycle: i.e., Day 28 or up to Day 42 (in case of 1 or 2 weeks delay in patient re-treatment)
° End of last cycle: i.e., Day 28 (or up to Day 42) of the cycle after which the patient does not receive any additional NMS-1191372 therapy
[X] They can be done ± 1 day from indicated days

Footnotes of Schedule of events	
1.	**Informed consent:** A signed and dated informed consent should be obtained before the patient undergoes any trial related procedure.
2.	**Physical examination** will be done at pretreatment and on Day 1 of each treatment cycle. During Cycle 1, physical examination will be repeated weekly.
3.	**Medical/Oncological History** Includes oncologic history, prior histological/molecular characterization, prior therapies, history of other disease processes (active, controlled or resolved) and concomitant illnesses.
4.	**Tumor molecular characterization:** Patients will be treated based on the molecular diagnosis of local lab performed before study enrollment. All patients must have tumor tissue available for confirmatory analysis (central lab) of ALK positivity. If sufficient tissue is not available, based on Investigator's judgment, patient will be requested to consent to undergo a biopsy to obtain adequate samples. For patients relapsed to Crizotinib, patient will be requested to consent to undergo a tumor biopsy following failure to prior therapy (see details in Section 11.5.1)
5.	**Vital Signs, Weight & ECOG PS:** Blood Pressure/Pulse (supine), Weight (in kg) and performance status (ECOG PS): at pretreatment and on Day 1 of each treatment cycle. The dose to be administered will be adjusted accordingly to the actual weight.
6.	**Height (in cm):** At pretreatment only.
7.	**ECG (12-lead):** Mandatory, as safety assessment, at pretreatment. During treatment on Cycles 1 & 3 on Day 18 between 3 and 6 hours after drug intake, and at the end of the last treatment cycle. On treatment, additional assessments to be performed if clinically indicated.
8.	**Chest X-ray (or thorax CT scan):** Mandatory, as safety assessment, at pretreatment and at the end of the last treatment cycle. On treatment, additional assessments to be performed if clinically indicated. If thorax CT scan is performed at the same time points (i.e., pretreatment and end of last cycle) for tumor assessment, it can be accepted for safety assessment in lieu of chest X-ray. The same method/technique should be used through the whole study.
9.	**Hematology (local lab):** Hb, RBC, PLT, and WBC with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils & differentials other cells). Mandatory, as safety assessment, at pretreatment. During treatment cycles to be done twice weekly in Cycle 1 on Days 4, 8, 11, 15, 18, 22 , 25 & 28 ; weekly from Cycle 2 onwards on Days 8, 15, 22 & 28 . In case of treatment delay to be repeated at the end of each cycle. Hematology tests can be done ± 1 day from indicated days. In case of Grade 3-4 hematological toxicities, hematology tests should be repeated at least every 2-3 days until improvement to Grade 1 or to baseline value.
10.	**Blood Chemistry (local lab):** Fasting glucose, electrolytes (Na, K, Ca, P), BUN or urea, creatinine, creatinine clearance (calculated), total protein, albumin, SGOT (AST), SGPT (ALT), total bilirubin, ALP, amylase, lipase, LDH. Mandatory, as safety assessment, at pretreatment. During treatment cycles to be done twice weekly in Cycle 1 on Days 4, 8, 11, 15, 18, 22, 25 & 28 ; weekly from Cycle 2 onwards on Days 8, 15, 22 & 28 . In case of treatment delay to be repeated at the end of each cycle. Blood chemistry can be done ± 1 day from indicated days. In case of Grade 3-4 events, blood chemistry should be repeated at least every 2/3 days until improvement to Grade 1 or to baseline value.
11.	**Coagulation (local lab):** International Normalized Ratio (INR). Coagulation test should be done at pretreatment, and at the end of every cycle. Mandatory before performing a tumor biopsy.
12.	**Urinalysis (local Lab):** pH, glucose (qualitative, dipstick accepted), protein and blood. At pretreatment and, on treatment, at the end of every even cycle. On treatment, additional assessments to be performed if clinically indicated.
13.	**Serum/Urine Pregnancy Test (local lab):** For women of reproductive potential. At pretreatment and on treatment at the end of last treatment cycle.
14.	**Enrollment:** The Investigator is requested to sign a Request for Enrollment form. His/her signature is the guarantee that the eligibility criteria are met. Patient number and dose level are assigned by the Sponsor. Treatment must be started within 1-3 days from patient enrollment.
15.	**NMS-1191372 administration:** The study drug will be administered once daily for 4 consecutive days a week (i.e., 4 days on /3 days off) for 3 consecutive weeks followed by 1 week of rest for a total of 4 weeks. After an overnight fasting with free access to water, patients will take the study drug with a large glass of plain water without ice. A light breakfast can be served 2 hours later.
16.	**Tumor Imaging (CT scan is the preferred method):** To be done at pretreatment where a total body CT scan including brain is mandatory. On treatment to be repeated at the end of every even cycle (-3 days time window) and at the end of last treatment cycle, if more than 4 weeks has passed from last tumor imaging. Patients with controlled brain metastasis should have a second assessment (performed at least 28 days after the first assessment) confirming the "controlled" status of

	lesion/s. The same method/technique should be used to evaluate the lesion/s through the study. Patients with responding tumors (complete or partial response) must have response confirmed at least 4 weeks after the 1st documentation of response. Post-treatment tumor assessment should be performed every 8 weeks after the last tumor assessment only in patients who have discontinued the study treatment for reasons other than disease progression, until documented PD or starting a new anticancer therapy.
17.	**Adverse Events:** AEs should be assessed and documented at each scheduled clinic visit since patient signs the Informed Consent. To be recorded in the relevant eCRF pages, at baseline (baseline signs and symptoms), and during a given treatment cycle, recorded once at the end of each cycle. For each AE the worst CTC Grade should be reported for a given cycle. Serious adverse events will be reported through an expedite procedure (see details in Section 11.4.1).
18.	**Concomitant Medication:** All concomitant medications should be reported in the relevant eCRF, including supportive care drugs, and drugs used for treating adverse events or chronic diseases. In the follow-up, if an alternative anticancer therapy is initiated, the reporting of the concomitant medication is no further requested.
19.	**PK Plasma Sampling:** (for all patients) blood samples (5 mL/sample) will be collected at the following times: **Cycle 1**, Day 1: at predose (time 0), 1, 2, 4, 6 and 24h from the study drug administration; Day 4: at predose (time 0), 1, 2, 4, 6 and 24h from the study drug administration; Day 15 : at predose (time 0), 1, 2, 4, 6 and 24h from the study drug administration; Day 18: at predose (time 0), 1, 2, 4, 6, 24, 48 and 96h from the study drug administration. **Cycle 2:** samples will be taken on Days 1, 15 and 18, at predose only. Additional blood samples for PK analysis may be collected if, in the opinion of the Investigator and of the Sponsor, an evaluation of PK parameters outside the schedule above is needed for safety reasons. A total of 26 samples corresponding to 130 mL blood will be taken during Cycle 1, and 3 samples corresponding to 15 mL blood during Cycle 2. Additional details are reported in Section 11.4.4.1).
20.	**PK Urine Sampling:** (for patients starting from the dose level in which the first cycle DLT occur). Urine will be collected at baseline and on Cycle 1, Day 18, at 0-6h and 6-24h from NMS-1191372 administration. Additional details related to urine collection are reported in Section 11.4.4.2.
21.	**Blood** (for "liquid biopsies"): Only in ALK positive patients at primary diagnosis, extra blood samples (2 samples for a total of 10 mL) at pretreatment & at the end of treatment are needed to perform the exploratory analysis (see details in Section 11.6).
22.	**28-d Follow up for laboratories abnormalities:** In case hematology, blood chemistry and coagulation abnormalities have not recovered at the end of last cycle, they should be followed-up for 28 days after the last study treatment administration or until they resolve or the Investigator assesses them as chronic or stable, or until alternative anticancer therapy is initiated. In the latest case, the reporting period will end at the time the new treatment is started.
23.	**28-d Follow up for AEs:** the AEs reporting period ends 28 days after the last study treatment administration. The following events should be followed after the end of the reporting period if not resolved: SAEs with outcome 'not recovered' or 'unknown', drug–related AEs (with relationship to the study drug: possible, probable, definite) with outcome 'not recovered' or 'unknown'. They have to be followed until they resolve or the Investigator assesses them as chronic or stable, or until alternative anticancer therapy is initiated. In the latest case, the reporting period will end at the time the new treatment is started.
Abbreviations: AEs=Adverse Events; ALP=alkaline phosphatase; AST/ALT = aspartate aminotransferase/alanine aminotransferase; BUN = blood urea nitrogen; Ca=calcium; CT = Computerized Tomography ECG = electrocardiogram; Hb=hemoglobin; K=Potassium; LDH= Lactic dehydrogenase; MRI = Magnetic Resonance Imaging; NA=Natrium; P=Phosphorus; PLT=Platelets, RBC=Red blood cells; SAEs=Serious Adverse Events; WBC=White blood cells	

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Adverse Event Collection

A DLT was defined as an AE occurring during the first treatment cycle that fulfilled prespecified criteria and grading (generally grades ≥3 in severity) and for which causal relationship to entrectinib could not be excluded; failure to recover (excluding alopecia) after delaying the initiation of next treatment administration by a maximum of 14 days, and failure to complete the first cycle treatment with at least 75% of the planned doses because of a drug related toxicity also met the criteria for a DLT. If a DLT was based on laboratory values alone, then, at a minimum, the laboratory test had to be repeated within 24 hours to confirm DLT. Grading of DLTs was according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

Sample Size Considerations

Initially, an overall sample size of approximately 40 treated patients was anticipated. Since the trial design foresaw that sequential dose-escalation steps are applied to cohorts of 3 to 6 patients up to the identification of the MTD, the total number of patients who would be enrolled and treated would have possibly varied, depending upon the toxicity observed and the resulting influence on cohort size and number of dose levels tested.

An overall sample size of 76 patients were enrolled. For patients enrolled up to and including 30 Nov 2017 with a clinical data cutoff date of 31 May 2018, 58 patients were enrolled at 2

investigative sites; 57 received study drug treatment. Patient enrollment was completed on 20 Mar 2018.

Analysis Datasets
All patients who receive at least one dose of entrectinib will be displayed in the study outputs. The anti-tumor activity of entrectinib will be assessed by considering the objective tumor responses defined according to the RECIST criteria (version 1.1). Patients enrolled but not treated will be identified and described separately.

The data includes patients enrolled up to and including 30 Nov 2017 with a clinical data cutoff of 31 May 2018.

Protocol Amendments

During the course the study, 10 protocol amendments were implemented. Substantial protocol and SAP amendments that were implemented are summarized below:

Original Protocol: (Date: 23 Jan 2012)

Amendment No. 1: (Date: 05 Mar 2012)

Modified the criteria reported in the dose escalation sections that permitted, in the first and second dose level, the simultaneous treatment of the first two patients per dose level.

Amendment No. 2: (Date: 14 Mar 2013)

Manufacturing changes to additional dose form 50mg capsules.

Inclusion criterion permitting prior therapy with ALK inhibitors other than crizotinib previously excluded, and permitting, for patients with CNS involvement, therapy with corticosteroids at stable doses (≤ 4 mg/day dexamethasone or equivalent) for at least 2 weeks.

Amendment No. 3: (Date: 05 Dec 2013)

To switch to treatment in fed condition, and introduction of a new schedule (once daily for 28 consecutive days, q4wks, Schedule B in fed condition) in addition to the current dose escalation (Schedule A, 4 days on/3 days off for 3 consecutive weeks followed by one week of rest, 4-week cycles, fasting condition), and addition of an additional schedule (Schedule C, 4 days on/3 days off, 4-week cycles, fed condition).

Amendment No. 4: (Date: 21 Jan 2014)

To implement an optional twice-daily dosing regimen in Schedule A of the protocol. Schedule A (4-week cycle) is comprised of 3 sequential weeks of 4 days on treatment (administered in fasting condition) followed by 3 days off treatment, with a one-week rest on the fourth week. This optional dosing regimen (administered in fasting condition) is being added to decrease the number of capsules that patients need to take at one time.

Amendment No. 5: (Date: 24 Jun 2014)

To allow the reduction of the intensity of laboratory assessments (hematological and blood chemical assessments) for patients under treatment for a long period of time.

To specify that brain MRI will be performed in glioblastoma patients.

Amendment No. 6: (Date: 14 Nov 2014)

An option has been introduced in the study to evaluate entrectinib when administered as a twice daily dosing regimen, in addition to the once daily dosing regimen, and for enrolling additional patients into a future dose level.

Clarification of DLT: If a DLT is based on lab values alone, then, at a minimum, a repeat value needs to occur within 24 hours to confirm DLT.

To clarify that in all schedules if a patient fails to receive at least 75% of complete first cycle of treatment, for reasons other than treatment-related toxicities, an additional patient must be enrolled at the same dose level.

Inclusion criteria: To allow the inclusion in the trial also of patients with TrkB- and TrkC-positive genetic alterations.

Amendment No. 7: (Date: 26 Feb 2015)

No clinical changes noted.

Amendment No. 8: (Date: 14 Jun 2016)

Enrollment criteria amended to align with global study: modified to enroll other types of TrkA/B/C, *ROS1*, or *ALK* molecular alterations that are of scientific exploratory interest. Only patients with a confirmed molecular alteration of interest will be allowed to enroll, based on agreement between the Investigators and the Sponsor of the study.

To allow for retrospective (ongoing patients) and prospective (newly enrolled patients) blinded independent central review of imaging studies by a third-party imaging laboratory.

Amendment No. 9: (Date: 22 Aug 2016)

To modify the protocol to address the nonclinical embryo-fetal and ocular toxicities findings as described on the Dear Investigator Letter.

Amendment No. 10: (Date: 11 May 2017)

Recommended Patient Information and Informed Consent Form, within the protocol due to changes to the Reference Safety information in the new IB version 7.0.

Data Quality and Integrity: Sponsor's Assurance

Upon further clarifications from entrectinib per FDA’s information requests (IRs), the reviewer was able to:

- Validate Genentech’s analysis dataset and analysis results from legacy dataset

- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy analyses

Compliance with Good Clinical Practices

The study has been conducted according to ICH-GCP E6 and (b) (4) SOPs in agreement with the sponsor. Independent external audits were conducted by (b) (4) and an external third party conducted by the sponsor. The study site could have also been subject to review by the independent ethics committee (IEC), to quality assurance audits performed by sponsor, and/or to inspection by appropriate regulatory authorities to assure compliance with proper study conduct.

Clinical Reviewer Comment: The study was done in outside the U.S. and only 1 patient contributed to the efficacy population for patients with *NTRK*-fusion solid tumors. The above statement was copied from the legacy CSR, submitted to the NDA on 18 Dec 2019 (section 5.3.5.2). See Section 8.1.2 for pooled data and NDA submission Module 2.5 "Clinical Overview" section 1.9 for declaration of GCP.

Financial Disclosure Study ALKA-372-001, entitled, "A Phase I Dose Escalation Study of Entrectinib (RXDX-101) in Adult patients with Advanced/Metastatic Solid Tumors" was conducted in Italy and was not submitted to an IND. There were major deficiencies regarding collection of financial disclosure forms (FDFs), including missing forms for up to 12 (32%) investigators.

Clinical Reviewer Comment: Although there are a number of missing FDFs for investigators in this study, due to the low number of patients enrolled on this trial and subsequently data used for analysis (n=1 for efficacy in the patients with *NTRK*-fusion solid tumors), this reviewer does not believe that the lack of disclosures would have led to significant bias in the efficacy findings. See pooled study results for full details of all missing FDFs (Section 19.2).

19.6.2. RXDX-101-01/STARTRK-1

Trial Design

STARTRK-1, entitled, "A Phase 1, Multicenter, Open-label Study of Oral Entrectinib (RXDX-101) in Adult Patients with Locally Advanced or Metastatic Cancer Confirmed to be Positive for *NTRK*1, *NTRK*2, *NTRK*3, *ROS1,* or *ALK* Molecular Alterations" is a dose-finding, multicenter, open-label study evaluating the safety and efficacy of entrectinib in adult patients with any locally advanced or metastatic solid tumor. The study is comprised of 2 segments, a dose escalation segment and a dose expansion segment. No dose expansion patients were enrolled as of the enrollment cutoff of 30 November 2017. The enrollment cutoff date was set to ensure that patients had approximately 6 months of follow-up at the data cutoff date of 31 May 2018.

In the dose escalation segment, a molecular alteration in *NTRK1/2/3*, *ROS1*, or *ALK* was not a requirement for patient eligibility. As of the data cutoff date of 31 May 2018, 11 centers in the United States, Spain, and South Korea had enrolled patients.

This study segment was performed in sequential cohorts of eligible patients receiving entrectinib orally. Each cycle consisted of treatment for 28 consecutive days in repeated 4-week cycles. Dose escalation continued until a DLT was observed in 2 of 3 or 2 of 6 patients in cycle 1. If 2 of 3 patients experienced a DLT, then enrollment into the cohort stopped. A DLT was defined as an AE occurring during the first treatment cycle that fulfilled prespecified criteria of interest and grading (generally grades ≥3 in severity) and for which causal relationship to entrectinib could not be excluded; failure to recover from the AE within 28 days of onset also met the criteria for a DLT.

During dose escalation, a standard "3+3" patient enrollment scheme was followed with an accelerated titration design. The starting dose was 100 mg/m^2 once daily in the fed condition (entrectinib was administered within 60 minutes following a meal). Dose escalation began with an accelerated phase in which the dose was doubled in successive cohorts until 1 patient experienced a DLT in the first cycle; or 2 patients experienced AEs at least possibly related to entrectinib that were grade ≥2 severity, but not considered to be DLTs and occurred during the first cycle, whichever came first. Once this predetermined toxicity level was met, escalation was planned to be followed by a modified Fibonacci scheme (50%, 40%, or 33% increments). The MTD was the dose level at which 0/6 or 1/6 patients experienced a first-cycle DLT, and at least 2 of 3 or 2 of 6 patients experienced a first-cycle DLT at the next higher dose level (effectively, the MTD was the highest dose associated with a first-cycle DLT in <33% of patients). The RP2D determination was to be based on available safety, tolerability, PK and PD data from different dose levels and schedules tested. Once the RP2D by body surface area (BSA) was established, administration of a flat dose was to be considered in a subgroup of patients if PK and safety data supported the decision.

In the ongoing dose expansion segment, eligible patients are required to have molecular tumors with *NTRK1, NTRK2, NTRK3, ROS1*, or *ALK* molecular alterations. Patients are screened for the presence of molecular alterations by assays available to each clinical site (e.g., NGS, qPRC, FISH, immunohistochemistry). Patients are receiving entrectinib orally for 28 consecutive days in repeated 4-week cycles at the RP2D determined during the dose escalation segment (refer to Summary of Results; the RP2D was determined to be a fixed dose of 600 mg once daily for 28 consecutive days in repeated 4-week cycles). Eligible patients are enrolled into molecularly-defined cohorts under a Simon's 2-stage (minimax) design determined by the type of molecular alteration harbored by the patient's tumor.

Antitumor activity was evaluated by tumor assessment and response determined by RECIST v1.1. Patients had tumor assessments performed by CT or magnetic resonance imaging (MRI) at the end of cycle 1 and approximately every 8 weeks thereafter and at the end-of-treatment visit (if more than 4 weeks passed from the time of previous tumor imaging). The same imaging

method was to be used to evaluate the tumors throughout the entire study. For patients with responding tumors (CR or PR), response confirmation was required to be performed at least 4 weeks after the first documentation of response. For patients with stable disease, tumor measurements were required to meet stable disease criteria of ≥35 days after first administration of entrectinib per the statistical analysis plan (SAP).

Per the protocol, alternate entrectinib formulations at an equivalent dose with similar or improved bioavailability were introduced into the study: during dose escalation, formulations F1 and F2A were used. Blood and urine samples were collected at various time points during the study for PK and PD assessments. Safety was monitored by AEs, laboratory assessments, physical examinations (including height), vital signs (including temperature, systolic/diastolic blood pressure, heart rate, weight, and BSA), ECGs, Eastern Cooperative Oncology Group (ECOG) performance status, and eye examinations. AE monitoring began upon first administration of entrectinib and continued through 30 days after the last administration of entrectinib.

Patients remained on study treatment until disease progression, unacceptable toxicity, or withdrawal of consent. In cases of progressive disease, after discussion with the sponsor, the patient could have continued treatment if the investigator believed that the patient might continue to derive clinical benefit.

Key eligibility criteria

Adult patients (age ≥18) with a histologically or cytologically confirmed diagnosis of relapsed or refractory locally advanced or metastatic solid tumors for whom no alternative effective standard therapy was available or for whom standard therapy was considered unsuitable or intolerable were enrolled.

<u>Dose Escalation Segment</u>:

A molecular alteration in *NTRK1*, *NTRK2*, *NTRK3, ROS1*, or *ALK* was preferred, but not a requirement for patient eligibility.

<u>Dose Expansion Segment</u>:

Eligible patients are required to have locally advanced or metastatic solid tumors harboring the following types of molecular alterations:

1. *NTRK* gene rearrangements (fusions) previously treated with other tropomyosin receptor kinase (TRK) inhibitors
2. *ALK* gene rearrangements with 1198 resistance single-nucleotide polymorphism (SNP)
3. *ALK* alternative transcription initiation (ALK^{ATI})

4. *NTRK/ROS/ALK* overexpression >6 (via RNA)

5. Activating splice variants

6. Other molecular alterations of interest, depending on biological rationale and after discussion with the sponsor

Study Endpoints

Primary Endpoint

Dose Escalation Segment: determine the first cycle DLTs, MTD, and a biologically effective and RP2D of entrectinib administered orally.

Dose Expansion Segment (ongoing): assess ORR, defined as the proportion of patients with complete response (CR) or partial response (PR).

Secondary endpoint

Dose Escalation Segment:

• Safety profile of entrectinib as characterized by AE type, severity, timing, and relationship to study drug, as well as electrocardiogram (ECG) and laboratory abnormalities in the first and subsequent treatment cycles

• Pharmacokinetics (PK) of entrectinib (and its potential metabolites) in plasma

• Antitumor activity of entrectinib as measured by tumor response (ORR) and duration of response (DOR) as well as PFS and overall survival (OS)

• Assay methods to detect molecular alterations (as defined in biomarker assessments), and identify appropriate analytical cutoffs and other relevant biomarker parameters that predict antitumor activity of entrectinib

• Pharmacodynamics (PD) of entrectinib on molecular targets in tumor and surrogate tissue

Dose Expansion Segment (ongoing):

• PFS defined as time from first dose of entrectinib to tumor progression or death due to any cause

• OS defined as time from first dose of entrectinib to death due to any cause

• Disease control rate (hereafter referred to as clinical benefit rate) defined as the proportion of patients with a confirmed CR, PR, or stable disease >6 months

• DOR as defined from the first date a response is identified (either CR or PR) until the date of disease progression

• Intracranial tumor response in patients with central nervous system (CNS) disease

• Safety and tolerability of entrectinib as characterized by AE type, severity, timing, and relationship to study drug, as well as ECG and laboratory abnormalities

• Assay methods to detect molecular alterations (as defined in biomarker assessments), and identify appropriate analytical cutoffs and other relevant biomarker parameters that predict antitumor activity of entrectenib

• PD of entrectinib on molecular targets in tumor and surrogate tissue

• PK of entrectinib (and its potential metabolites) in plasma

Dose Modification and Management Algorithms
All dose reductions should be based on the most severe toxicity observed that is attributable to the study drug. At a starting dose level of 100 mg/m^2/day, no dose reduction is anticipated. If unacceptable toxicity presents, then the patient will be instructed to stop treatment. No more than 1 intra-patient dose reduction is allowed. Doses reduced for drug-related toxicity should not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Recommended dose modifications during Phase 1 treatment cycles are shown in Table 91.

Table 91: Dose Modification Based on the Worst Toxicity Grade (as per NCI CTCAE, Version 4.03) Observed During Phase 1

Toxicity since last dose	During treatment cycle	After recovery from toxicity at the start of subsequent cycle
Hematological Toxicities		
Grade ≤2 Neutropenia (ANC <1500-1000/mm^3) and/or Thrombocytopenia (PLT <75000-50000/mm^3)	If occurs during treatment, maintain daily dose level	Maintain dose level
Uncomplicated Grade 3 Neutropenia (ANC <1000-500/mm^3)	If occurs during treatment, decrease daily dose by 1 dose level	Maintain dose level
Uncomplicated Grade 3 Thrombocytopenia (PLT < 50,000-25,000/mm^3) lasting >7 days or Grade 3 associated to Grade ≥ 2 bleeding	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Febrile neutropenia : ANC <1000/mm^3 with a single temperature of >38.3°C or a sustained temperature of ≥38 °C for >1 hour	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Neutropenic infection: Grade ≥3 infection documented clinically or microbiologically with Grade ≥3 neutropenia	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Grade 4 hematological toxicity of any duration	If occurs during treatment, interrupt treatment	Decrease 1 dose level
Nausea and/or Vomiting		
Grade ≤2 (in absence of antiemetics)	If occurs during treatment, maintain daily dose level and add antiemetics, if needed.	Maintain dose level with antiemetics§
Grade ≤2 (in presence of antiemetics)	If occurs during treatment, decrease the daily dose by 1 dose level, adjust antiemetics, as needed	Maintain dose level with adjusted antiemetics§
Grade ≥3 (in absence of antiemetics)	If occurs during treatment, interrupt 1 day the drug administration, if needed, decrease the daily dose by 1 dose level, add antiemetics.	Maintain dose level with antiemetics§
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease 1 dose level ‡
Diarrhea		
Grade ≤2 (in absence or presence of management of the event §)	If occurs during treatment, maintain daily dose level, add/adjust antidiarrheal treatment, if needed.	Maintain dose level
Grade ≥3 in absence of management of the event	If occurs during treatment, maintain daily dose level, add antidiarrheal treatment	Maintain dose level with antidiarrheal support or if persistent, decrease 1 dose level
Grade ≥3 despite optimal management of the event §	If occurs during treatment, interrupt treatment	Decrease 1 dose level
CNS Toxicities / Neurologic		
Grade ≤1 or no worsening compared to baseline	Maintain dose level	Maintain dose level
Grade 2	If occurs during treatment, decrease the daily dose by 1 dose level	Decrease 1 dose level
Grade ≥ 3	If occurs during treatment, interrupt treatment	Decrease 1 dose level or **Discontinue study treatment**‡
Other Non-Hematological Toxicities (except alopecia)		
Grade ≤1	Maintain daily dose level	Maintain dose level
Grade 2	If occurs during treatment, maintain or decrease the daily dose by 1 dose level, if clinically indicated	Maintain dose level
Grade ≥ 3	If occurs during treatment, interrupt treatment	Decrease 1 dose level‡
Grade ≤ 2 hypersensitivity reaction suggestive of anaphylactic reaction	Investigator to discuss with Sponsor before proceeding	
Grade ≥ 3 hypersensitivity reaction suggestive of anaphylactic reaction‡	Treatment discontinuation	Treatment discontinuation
Failure to recover		
Failure to recover to grade ≤ 1 toxicity (except alopecia) or to baseline values, if grade 2 is allowed at study entry, after delaying the initiation of next cycle by > 2 weeks	Monitor until resolved to grade ≤1	Decrease 1 dose level ‡
§For prophylaxis and management of the events, see details in Supportive Care section of the study ‡ Investigator to discuss with Sponsor before proceeding **Abbreviations:** ANC = absolute neutrophil count; PLT= platelet count		

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Monitoring Plan

Table 92: Schedule of Assessments for Dose escalation

	Screen	Cycle 1[r]					Cycle 2[r]				All Other Cycles[r]		End of Treatment	Safety Follow-Up[q]
Treatment Day	**-30 to -1**	**1**	**7**	**14**	**21**	**28**	**7**	**14**	**21**	**28**	**14**	**28**	**Within 7 days after last dose**	**Within 30 days after last dose**
Informed Consent[a]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Eligibility Assessment[b]	X	X	--	--	--	--	--	--	--	--	--	--	--	--
Physical Examination[c]	X	X	X	X	X	X	--	--	--	X	--	X	X	--
Molecular Characterization of Tumor[d]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Serum Pregnancy Test[e]	X	--	--	--	--	X	--	--	--	X	--	X	X	--
Clinical Safety Laboratory Tests[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	--
ECOG Performance Status[g]	X	X	--	--	--	X	--	--	--	X	--	X	--	--
Vital Signs + Weight (kg)[g]	X	X	X	X	X	X	--	--	--	X	--	X	X	--
12-Lead ECG[h]	X	X	X	--	--	X	--	--	--	X	--	X	X	--
Tumor Biopsy[i]	X	--	--	--	X	--	--	--	--	--	--	--	X	--
Tumor Imaging[j]	X	--	--	--	--	X	--	--	--	--	--	X	X	--
Enrollment[k]	X	--	--	--	--	--	--	--	--	--	--	--	--	--
Entrectinib Dispensation[l]	--	X	--	--	--	X	--	--	--	X	--	X	--	--
PK Assessment[m]	--	X	X	X	--	X	--	--	--	X	--	X	--	--
PD Assessment[n]	--	X	X	X	--	X	--	--	--	X	--	X	X	--
CSF Assessment[o]					X									
Entrectinib Accountability[p]	--	--	X	X	X	X	X	X	X	X	X	X	X	--
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	--	X	X	X	X	X	X	X	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	X	X	X	X	X	X	X	--	--

[a] Includes consent to detect *NTRK1/NTRK2/NTRK3/ROS1/ALK* molecular alterations and participate in the study.

[b] Includes review of medical/oncologic history and inclusion/exclusion criteria.

[c] Physical exam performed during screening (includes height; should be performed within 14 days of initiation of study treatment); during Cycle 1 on Days 1, 7, 14, 21, and 28; on Day 28 of each subsequent treatment cycle; at End of Treatment; and as clinically indicated.

[d] Although it is preferred to enroll patients with solid tumors harboring a *NTRK1, NTRK2, NTRK3, ROS1*, or *ALK* molecular alteration, this will not be an enrollment requirement.

[e] Serum pregnancy test performed for female patients of child-bearing potential during screening; during Cycle 1 on Day 28; on Day 28 of each subsequent treatment cycle; at End of Treatment; and as clinically indicated.

[f] Clinical safety laboratory tests (chemistry, haematology, coagulation, and urinalysis) collected during screening (should be performed within 14 days of initiation of study treatment); during Cycle 1 on Days 1, 7, 14, 21, and 28; during Cycle 2 on Days 7, 14, 21, and 28; during Cycles 3-6 on Days 14 and 28; on Day 28 of each subsequent treatment cycle thereafter; at End of Treatment; and as clinically indicated.

[g] Blood pressure/pulse (supine or seated) and weight (kg) obtained during screening; weekly during Cycle 1 on Days 1, 7, 14, 21, and 28; on Day 28 of each subsequent treatment cycle; and within 7 days of the last dose of study drug. Entrectinib dose to be administered may be calculated according to most recent actual weight measurement. ECOG PS will be evaluated during screening; during Cycle 1 on Days 1 and 28; and on Day 28 of each subsequent cycle.

[h] 12-lead ECG (in triplicate) performed during screening; during Cycle 1 on Days 1 and 7 (pre-dose and at 3 and 6 hours post-dose) and Day 28; on Day 28 of each subsequent treatment cycle; at End of Treatment; and as clinically indicated.

[i] Patients may volunteer to participate in a fine needle aspirate/biopsy of an accessible lesion prior to treatment; on Cycle 1, Day 21; and at End of Treatment for assessment of PD effects of entrectinib on molecular targets.

[j] CT or MRI of thorax and abdomen is mandatory during screening. Due to the high frequency of brain metastasis, brain imaging will be performed during screening in all patients with NSCLC. On treatment to be repeated at the end of Cycle 1, then approximately every 8 weeks thereafter (-7 day window) and at End of Treatment, if more than 4 weeks have passed from last tumor imaging. Tumor assessments may be performed outside of the protocol-defined timepoints at the discretion of the Investigator. The same imaging method/technique should be used to evaluate the lesion(s) throughout the study. Patients with responding tumors (CR or PR) must have response confirmed at least 4 weeks after the first documentation of response. Thereafter, the next radiological assessments will be performed at the end of every two treatment cycles from confirmation. Post-treatment tumor assessment may be performed every 8 weeks after the last tumor assessment only in patients who have discontinued the study treatment for reasons other than disease progression, until documented PD, or starting a new anticancer therapy.

[k] Upon confirmation of study eligibility, the Investigator will complete a Request for Enrollment form for Sponsor review. His/her signature is the guarantee that all eligibility criteria have been met. Treatment must be started within 1-3 days after Sponsor approval of patient enrollment.

[l] All patients receive repeated cycles of entrectinib orally. Each cycle consists of treatment for 28 consecutive days in repeated 4-week cycles. The first cohort will be 100 mg/m^2/day. Depending on the entrectinib formulation, administration may occur in either a fasted or fed state (i.e., entrectinib should be administered within 60 minutes following a meal). Sites may dispense sufficient entrectinib to cover approximately 1 treatment cycle at a time, or dispense sufficient entrectinib to last through the next study visit.

[m] Blood sampling for PK assessments collected at the following times during Cycle 1: on Day 1 at pre-dose (time 0), and at 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose; on Day 7 at pre-dose and at 4 hours post-dose; and on Days 14 and 28 at pre-dose, and at 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose. Blood samples will also be collected pre-dose on Day 28 of Cycles 2-6.

[n] Blood sampling for PD assessments collected at the following times during Cycle 1: on Day 1 at pre-dose (time 0) and at 4 and 24 hours post-dose; and on Days 7, 14, and 28 at pre-dose and at 4 hours post-dose. Blood samples will also be collected pre-dose on Day 28 of Cycles 2-6 and at End of Treatment.

[o] On Cycle 1, Day 21, an optional CSF sample may be obtained via lumbar puncture for selected patients with CNS/leptomeningeal metastasis.

[p] Drug accountability performed at each visit of each cycle to ensure patient remains compliant with dosing regimen.

[q] Safety Follow-Up to be performed via phone call to patient. Additionally, each patient will be contacted by telephone approximately every 3 months following study discontinuation until death, loss of follow-up, or withdrawal of consent in order to assess disease progression and survival status.

[r] All study visits scheduled after Cycle 1, Day 1 visit may be completed within a +/- 2 day window.

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Table 93: Schedule of Assessments for Dose expansion

	Screen	Cycles 1 and 2[r]			All Other Cycles[r]	End of Treatment	Safety Follow-Up[q]
Treatment Day	**-30 to -1**	**1[p]**	**14**	**28**	**28**	**Within 7 days after last dose**	**Within 30 days after last dose**
Informed Consent[a]	X	--	--	--	--	--	--
Eligibility Assessment[b]	X	C1	--	--	--	--	--
Physical Examination[c]	X	C1	C1	X	X	X	--
Eye Exam[c]	X			C1		X	
Molecular Characterization of Tumor[d]	X	--	--	--	--	--	--
Serum Pregnancy Test[e]	X	--	--	X	X	X	--
Clinical Safety Laboratory Tests[f]	X	C1	X	X	X	X	--
ECOG Performance Status[g]	X	C1	--	X	X	--	--
Vital Signs + Weight (kg)[g]	X	C1	C1	X	X	X	--
12-Lead ECG[h]	X	C1	--	X	X	X	--
Optional Tumor Biopsy[i]	(X)	--	--		--	(X)	--
Tumor Imaging[j]	X	--	--	C1	q8w	X	--
Enrollment[k]	X	--	--	--	--	--	--
Entrectinib Dispensation[l]	--	C1	--	X	X	--	--
PK Assessment[m]	--	C1		X	X	X	--
PD Assessment[n]	--	C1		X	X	X	--
Entrectinib Accountability[o]	--	--	X	X	X	X	--
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	--	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	--	--

[a] Includes consent to detect *NTRK1, NTRK2, NTRK3, ROS1*, and *ALK* molecular alterations and participate in the study.

[b] Includes review of medical/oncologic history and inclusion/exclusion criteria.

[c] Physical exam performed during screening (includes height; should be performed within 14 days of initiation of study treatment); during Cycle 1 on Days 1, 14, and 28; on Day 28 of each subsequent treatment cycle; at End of Treatment; and as clinically indicated. **Eye exam**: Ophthalmologic exams (which may be performed by an optometrist) will be required at Screening, end of Cycle 1, at the End of Treatment, and as clinically indicated.

[d] Patients will be eligible for study entry based on the molecular diagnosis of tumor samples.

[e] Serum pregnancy test performed for female patients of child-bearing potential during screening; on Day 28 of each cycle; at End of Treatment; and as clinically indicated.

[f] Clinical safety laboratory tests (chemistry, haematology, coagulation, and urinalysis) collected during screening (should be performed within 14 days of initiation of study treatment); during Cycle 1 on Days 1, 14, and 28; during Cycle 2 on Days 14, and 28; on Day 28 of each subsequent treatment cycle thereafter; at End of Treatment; and as clinically indicated.

[g] Blood pressure/pulse (supine or seated) and weight (kg) obtained during screening; during Cycle 1 on Days 1, 14, and 28; on Day 28 of each subsequent treatment cycle; and within 7 days of last dose of study drug.. ECOG PS will be evaluated during screening; during Cycle 1 on Days 1 and 28; and on Day 28 of each subsequent cycle.

[h] 12-lead ECG (in triplicate) performed during screening; during Cycle 1 on Days 1 (pre- and at 4 hours post-dose) and 28; on Day 28 of each subsequent treatment cycle; at End of Treatment; and as clinically indicated.

[i] Optional archival tumor tissue to be sent to Ignyta to evaluate the presence of *NTRK1, NTRK2, NTRK3, ROS1*, or *ALK* molecular alterations (during Screening) or for PD studies (at the End of Treatment)

[j] CT or MRI of thorax and abdomen is mandatory during screening. Due to the high frequency of brain metastasis, brain imaging will be performed during screening in all patients with NSCLC. On treatment to be repeated at the end of Cycle 1, then approximately every 8 weeks thereafter (-7 day window) and at End of Treatment, if more than 4 weeks have passed from last tumor imaging. Tumor assessments may be performed outside of the protocol-defined timepoints at the discretion of the Investigator. The same imaging method/technique should be used to evaluate the lesion(s) throughout the study. Patients with responding tumors (CR or PR) must have response confirmed at least 4 weeks after the first documentation of response. Thereafter, the next radiological assessments will be performed at the end of every two treatment cycles from confirmation. Post-treatment tumor assessment may be performed every 8 weeks after the last tumor assessment only in patients who have discontinued the study treatment for reasons other than disease progression, until documented PD, or starting a new anticancer therapy.

[k] Once study eligibility has been confirmed the patient may be enrolled into the study.

[l] All patients receive repeated cycles (1 cycle = 4 weeks) of entrectinib orally for 28 consecutive days. Depending on the entrectinib formulation, drug administration may occur in a fed or fasted state (i.e., entrectinib should be administered within 60 minutes following a meal). Sites may dispense sufficient entrectinib to cover approximately 1 treatment cycle at a time, or dispense sufficient entrectinib to last through the next study visit.

[m] For all patients, PK samples will be collected prior to the first dose of study drug on Cycle 1 Day 1; pre-dose on Day 28 of each treatment cycle; and at the End of Treatment. In addition, if a new formulation is introduced in the study, serial PK samples (pre dose, 0.5, 1, 2, 4, 6, 8 and 24 hours post-dose) will be collected on Cycle 1, Day 1 and Cycle 1, Day 28 for the first 6 patients enrolled with the new formulation.

If patients with CNS disease dose escalate from 600 to 800 mg QD, serial PK sample collection should be performed at the times noted in the synopsis and Section 13.2.

[n] For all patients, blood and urine samples will be collected prior to the first dose of study drug on Cycle 1 Day 1; pre-dose on Day 28 of each treatment cycle; and at the End of Treatment.

[o] Drug accountability performed at each visit of each cycle to ensure patient remains compliant with dosing regimen.

[p] Cycle 1 has a Day 1 visit; Cycle 2 does not have a Day 1 visit.

[q] Safety Follow-Up to be performed via phone call to patient. Additionally, each patient will be contacted by telephone approximately every 3 months following study discontinuation until death, loss of follow-up, until the patient begins a new course of cancer therapy, or withdrawal of consent in order to assess disease progression and survival status.

[r] All study visits scheduled after Cycle 1, Day 1 visit may be completed within a +/- 2 day window. With this amendment, all patients who were enrolled under the dose escalation phase of the study and are past Cycle 2, will begin to follow the Schedule of Events for the dose expansion phase (Table 2) of the study.

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Adverse Event Collection

Grading of DLTs was according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. An AE is any untoward medical occurrence in a study patient administered a medicinal (investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. New signs and symptoms of underlying disease, or signs and symptoms of emerging disease must be recorded as AEs. AE monitoring for patients will begin upon first administration of entrectenib and will continue through the follow-up telephone contact 30 days following the last administration.

Sample Size Considerations

The accrual goal for each of the previously identified dose-escalation cohorts is 20 patients. For each cohort with exactly 20 patients the lower end of the 90% one-sided upper confidence interval (CI) for a specified number of responses is given in the following table. Thus 3 or more

responses in 20 patients would constitute an isolated signal of activity for that cohort, as stated below in Table 94.

Table 94: Statistical Considerations for Sample Size Calculation

# responses in 20 patients (%)	Lower end of 90% one-sided exact upper confidence interval
2 (10%)	2.7%
3 (15%)	5.6%
4 (20%)	9.0%
5 (25%)	12.7%

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Analysis Datasets

The analysis sets for the dose escalation and dose expansion segments were defined as follows:

- DLT (dose escalation segment only): Patients (1) who experienced a DLT during cycle 1 after at least 1 dose of study drug and (2) who did not experience a DLT, completed cycle 1, and who were compliant with entrectinib treatment administration, having taken a minimum of 80% of study drug doses expected during cycle 1.
- Safety: Patients who received at least 1 dose of entrectinib. Patients who were replaced for evaluation of DLT were still to be included in the safety analysis set if they received at least 1 administration of entrectinib. No patients were replaced for evaluation of DLT.
- Efficacy: Patients who received at least 1 planned dose of entrectinib and who had measurable disease at baseline tumor assessment according to RECIST v1.1. Patients who experienced early discontinuation for any reason prior to the first planned tumor assessment were also included in the efficacy analysis set and were classified with the best response of not evaluable.
- PK: Patients who received at least 1 dose of entrectinib and had evaluable PK data.

Protocol Amendments

During the course the study, 6 protocol amendments were implemented. Substantial protocol and SAP amendments that were implemented are summarized below:

Original Protocol Version 1.0: (Date 25 Feb 2014)

Version No. 2.0: (Date 26 Mar 2014)

This version incorporates FDA comments related to patient safety. The main procedural change concerns the Phase 1 Dose Escalation Segment. The duration of Cycle 1 was changed to 6 weeks instead of 4 weeks. All subsequent cycles are 4 weeks.

Version No. 3.0: (Date 16 April 2014)

This version incorporates changes for clarification concerning study personnel, Phase 1-Cycle 1 timing, visit windows, dose modifications, concomitant medications, recording/reporting of adverse events, table footnotes, and study visit section headings.

Version No. 4.0: (Date 8 Oct 2014)

The requirement for patients to have tumors that harbor molecular alterations of TrkA/B/C, *ROS1*, or *ALK* was removed for patients enrolling in the dose escalation segment of the study. An option was introduced in the Phase 1 segment of the study to evaluate entrectinib when administered as a twice daily dosing regimen, in addition to the once daily dosing regimen included in Version 3.0 of the Protocol. Asymptomatic non-hematological laboratory changes (except renal and liver laboratory values) that can be successfully supplemented (i.e., hypokalemia) were excluded from the definition of a DLT. The requirement was removed for suspending dose escalation once systemic exposure is within 90% of that observed at the MTD dose level with the intermittent dose schedule evaluated in the FIH study. Patients with tumors expressing TrkB and TrkC with associated molecular alterations were enrolled into separate expansion cohorts as opposed to being combined into one cohort. The criteria for enrollment into the 2 ALK cohorts were changed from prior experience with 1 ALK inhibitor to ALK inhibitor-naïve and from prior experience with ≥ 2 ALK inhibitors to prior experience with ≥ 1 ALK inhibitors. The timing of radiological tumor assessments were modified to be performed at the end of Cycle 1, then approximately 8 weeks thereafter (i.e., during each odd cycle). In Version 3.0, the tumor assessments were to be performed during each even cycle.

Version No. 5.0: (Date 23 Apr 2015)

The length of Cycle 1 in the Phase 1 segment was reduced from 42 days to 28 days for all patients. Phase 2a cohorts were modified to the below to support a signal-seeking, exploratory dose expansion cohorts:

• Cohort #1: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor an *NTRK1* rearrangement.

• Cohort #2: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor an *NTRK2* rearrangement.

• Cohort #3: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor an *NTRK3* rearrangement.

• Cohort #4: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding CRC, that harbor an *ALK* rearrangement. Patients with locally advanced or metastatic NSCLC will be excluded from this cohort, except in countries where patients do not have access to approved ALK inhibitors for the treatment of NSCLC.

• Cohort #5: Approximately 20 patients with locally advanced or metastatic solid tumors, excluding NSCLC and CRC, that harbor a *ROS1* rearrangement.

• Cohort #6: Approximately 50 patients with locally advanced or metastatic solid tumors that express TrkA, TrkB, TrkC, ROS1, or ALK with an associated non-fusion, molecular alteration to one of the genes encoding these proteins, which include *NTRK1* (encoding TrkA), *NTRK2* (encoding TrkB), *NTRK3* (encoding TrkC), *ROS1* (encoding ROS1), *ALK* (encoding ALK), *NGF* (encoding NGF), *BDNF* (encoding BDNF), *NTF3* (encoding NT-3), *NTF4* (encoding NT- 4), and *NGFR* (encoding p75).

Thus, the total sample size was increased from N=120 to 150, efficacy endpoints were modified, along with statistical considerations, which was reviewed by the agency and adequate.

Version No. 6.0: (Date 26 Aug 2016)

Due to new nonclinical findings of ocular toxicities, eye exams including at least the visual acuity and slit-lamp tests to monitor for corneal-related visual disturbances during treatment with entrectenib, at Screening, on study, at the End of Treatment, and as clinically indicated to monitor for potential corneal related-visual disturbances.

Added retrospective BICR of tumor scans.

Data Quality and Integrity: Sponsor's Assurance

According to the CSR Section 9.6 submitted to Module 5.3.5.2 RXDX-101-01 “Legacy Clinical Study Report” under Part A “All data quality assurance steps described were used for the dose escalation segment of the study. These same steps will be followed for the dose expansion segment and described in a subsequent CSR when the segment is complete. By signing the protocol, the investigator granted permission to personnel from Ignyta or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.”

Compliance with Good Clinical Practices

Within the text of the protocol was the statement: “The Investigator agrees that the study will be conducted according to the protocol, the US Code of Federal Regulations (CFR), Good Clinical Practice (GCP) (E6) and the ethical principles that have their origin in the Declaration of Helsinki and the ICH guidelines. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the pertinent regulatory authorities.”

Clinical Reviewer Comment: See section 8.1.2 for pooled data and NDA submission Module 2.5 “Clinical Overview” section 1.9 for declaration of GCP.

Financial Disclosure

Study STARTRK-1 (RXDX-101-01, GO40784) entitled, "A Phase 1, Multicenter, Open-Label Study of Oral Entrectinib (RXDX-101) in Adult Patients with Locally Advanced or Metastatic Cancer Confirmed to be Positive for *NTRK*1, *NTRK*2, *NTRK*3, *ROS1*, or *ALK* Molecular Alterations" was conducted in South Korea, Spain, and the United States and was submitted to IND 120500. There were a number of missing FDFs which will be discussed together as pooled data in Section 19.2.

Data Quality and Integrity - Reviewers' Assessment

Upon further clarifications from Genentech in response to FDA's IRs, the reviewer was able to:

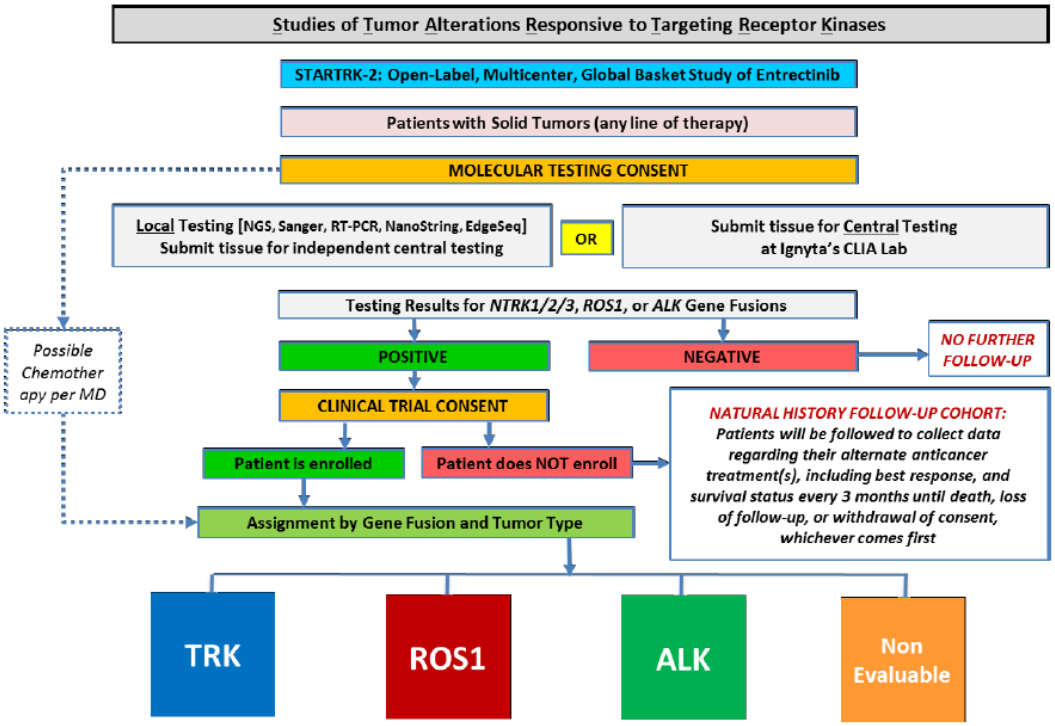
- Reproduce Genentech's analysis dataset and analysis results from legacy dataset
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy analyses

19.6.3. RXDX-101-02/STARTRK-02

Trial Design

STARTRK-2, entitled "An Open-Label, Multicenter, Global Phase II Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements," is an antitumor, global, open-label, multicenter, basket study in adult patients with advanced or metastatic solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene fusion. *NTRK1*, *2*, and *3* gene fusions were treated as a combined *NTRK1/2/3* gene fusion basket. Figure 59 provides the schematics of study design. The primary objective of the study was to determine the ORR of entrectinib, as assessed by BICR, in each patient population basket of solid tumors. The secondary objectives include determining DOR as assessed by BICR in each patient population basket. The patients enrolled into baskets of *NTRK* fusion-positive solid tumors and *ROS1*-positive NSCLC had a data cut off of 31 May 2018. The study and patient enrollment are ongoing as of this date.

Figure 59: STARTRK-2 Basket Study Schema



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Key eligibility criteria

- Histologically- or cytologically-confirmed diagnosis of locally advanced or metastatic solid tumor that harbors an *NTRK*1/2/3, *ROS1*, or *ALK* gene rearrangement that is predicted to translate into a fusion protein with a functional TrkA/B/C, ROS1, or ALK kinase domain, respectively, without a concomitant second oncodriver (e.g., EGFR, KRAS) as determined by Ignyta's CAP/CLIA laboratory or by any nucleic acid-based diagnostic testing method performed at a local CLIA-certified or equivalently-accredited diagnostic laboratory.
- Measurable disease as assessed locally using RECIST v1.1.
- Patients with CNS involvement, including leptomeningeal carcinomatosis, which is either asymptomatic or previously-treated and controlled, are allowed.
- Prior anticancer therapy is allowed (excluding approved or investigational Trk, ROS1, or ALK (non-NSCLC patients only) inhibitors
- Prior radiotherapy is allowed if more than 14 days have elapsed since the end of treatment. Patients who received brain irradiation must have completed whole brain radiotherapy at least 14 days prior and/or stereotactic radiosurgery at least 7 days prior to the start of entrectinib treatment.
- Age ≥ 18, ECOG 0-2.

- Peripheral neuropathy Grade ≥ 2.
- History of non-pharmacologically induced prolonged QTc interval

Study Endpoints

Primary Endpoint:
To determine the ORR of entrectinib, as assessed by BICR, in each patient population basket of solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement

Secondary Endpoints:

- To determine the DOR, time to response (TTR), and clinical benefit rate (CBR) of entrectinib, as assessed by BICR, in each patient population basket of solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement
- To determine the intracranial tumor response of entrectinib and CNS progression-free survival (CNS-PFS) in patients presenting with measurable CNS disease at baseline, as assessed by BICR using RANO or RANO-BM, as applicable
- To estimate the PFS and OS of patients with solid tumors that harbor an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement treated with entrectinib
- To evaluate the safety and tolerability of entrectinib when administered at the RP2D in patients with solid tumors that harbor an *NTRK1/2/3*, *ROS1,* or *ALK* gene rearrangement
- To assess the population PK of entrectinib and to explore correlations between PK, response, and/or safety findings in patients with *NTRK1/2/3*, *ROS1*, *or ALK* gene rearrangements
- To evaluate the effect of entrectinib on ventricular repolarization
- To assess treatment-related symptoms and general health status using validated instruments of patient reported outcomes

Dose Modification and Management Algorithms
If toxicities that are possibly related to entrectinib are not easily managed or corrected, and are not tolerable to the patient, or if there are AEs that are not acceptable in the Investigator's judgment, the patient should have study treatment interrupted until the AE resolves to Grade ≤ 1. If study treatment is interrupted, dose reduction (if mandated) should occur when study treatment is resumed. All dose reductions should be based on the most severe toxicity observed that is attributable to entrectinib. If needed, dose reductions may occur in decrements of 200 mg and no more than 2 dose reductions will be allowed; therefore, the possible daily doses of entrectinib are listed in Figure 60:

Figure 60: Schema of Dose reduction for Toxicity

Dose Level	Dose (mg QD)
RP2D	600
- 1	400
-2	200

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Entrectinib treatment may be interrupted for a maximum of 28 days to allow sufficient recovery from any toxicity if the patient is still deriving clinical benefit in the judgment of the Investigator.

As such, for patients with CNS disease who have been on study for at least 2 cycles of treatment (i.e., 8 weeks) with a best response of SD per RECIST v1.1 and without treatment-related Grade ≥ 2 adverse events, dose escalation to 800 mg daily will be allowed as per Investigator's discretion after discussion with the Sponsor.

Dose modifications for toxicities are described in Figure 61.

Figure 61: Dose Modifications for Entrectinib-Related Adverse Events

Toxicity*	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at same dose level	Continue at same dose level For prolonged or intolerable CNS toxicity, withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment	Withhold dose until toxicity is ≤ G1 or has returned to baseline, then reduce by 1 dose level and resume treatment; or discontinue treatment as per the Investigator's discretion
Hematologic	Continue at same dose level	Continue at same dose level	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then resume treatment at the same dose level or reduce by 1 dose level as per the Investigator's discretion Grade 3 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption	Withhold dose until toxicity is ≤ G2, or has returned to baseline, then reduce the dose by 1 dose level and resume treatment Grade 4 lymphopenia without other dose-limiting events (e.g., opportunistic infection) may continue study treatment without interruption
Prolonged QTc	Continue at same dose level	Interrupt entrectinib until recovery to baseline Assess and correct electrolytes and concomitant medications Continue at same dose level	Interrupt entrectinib until recovery to baseline Assess and correct electrolytes and concomitant medications. Reduce dose by 1 dose level and resume treatment. If an alternative cause for QTc prolongation is found and corrected, resume at same dose level	Discontinue treatment permanently
Pneumonitis (in absence of disease progression, pulmonary embolism, positive cultures or radiation effect)	Withhold dose until toxicity is Grade 0, then resume treatment at same dose Discontinue treatment permanently if pneumonitis recurs	Withhold dose until toxicity is Grade 0, then resume treatment at same dose Discontinue treatment permanently if pneumonitis recurs	Discontinue treatment permanently	Discontinue treatment permanently

*dose modifications to be based on worst toxicity grade as per NCI CTCAE v4.0

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Monitoring Plan

Figure 62: Schedule of Assessments

	Screening [a]	Cycle 1		Cycles 2-3 (+/- 2d)		Cycle 4+ (+/- 2d)	End of Treatment [c]	Safety Follow-Up [d]	Survival Follow-Up
Treatment Day	-30 to -1	1 [a]	15	1	15 [b]	1	~ 7 days after last dose	~ 30 days after last dose	~ Every 3 months
Baseline Assessments									
Molecular testing informed consent [1]	No time limit								
Tumor biopsy [2]	(X)						(X)		
Clinical trial informed consent [3]	X								
Eligibility assessment [3]	X								
Physical examination [4]	X	(X)	X	X	(X)	X	(X)	(X)	
Eye exam [5]	X			C2			(X)		
Serum pregnancy test [6]	X			X		X	(X)		
Laboratory Studies									
US: Triplicate ECGs [7]	X	X		X		X	(X)		
JPN: Triplicate ECGs [8]	X	X		X		X	(X)		
ROW: Single ECG [9]	X	X		X		X	(X)		
Clinical laboratory assessments [10]	X	(X)	X	X	(X)	X	(X)	(X)	
Coagulation and lipid panel [10]	X								
PK samples [11]		X		X		X	(X)		
a. **JPN**: PK Sub-Study [12]		X		X		X	(X)		
PD samples [13]		X		X		X	(X)		
Tumor Markers [14]	X	(X)		X		X	(X)		
Imaging Assessments (+/- 7 days) [15]									
CT/MRI brain	X			(C2)		(q8w)	(X)		(q8w)
CT/MRI chest, abdomen, (pelvis)	X			C2		q8w	(X)		(q8w)
Bone scan	(X)			(C2)		(q8w)	(X)		(q8w)
Other Clinical Assessments									
ECOG, body weight, and vital signs [16]	X	(X)	X	X	(X)	X	(X)	(X)	
Adverse events and conmeds [17]	X	X	X	X	(X)	X	(X)	X	
Entrectinib compliance assessment			X	X	(X)	X	(X)		
Entrectinib dispensing and dosing [18]		X		X		X			
Post-study survival status [19]									X
Patient Reported Outcomes									
Quality of life questionnaires [20]		X		X		X	(X)		

Footnotes

(X) = optional or as applicable
1. **Molecular Testing Informed Consent:** Pre-study participation consent to detect *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangements (test performed at Ignyta's CAP/CLIA laboratory in San Diego, California, USA, or alternatively, local testing using any nucleic acid-based diagnostic testing method that relies on direct assessment of gene rearrangements and is performed at a CLIA-certified or equivalently-accredited diagnostic laboratory will be accepted) in order to determine eligibility to proceed to the clinical trial consent process. Local or central determination of gene rearrangements to determine eligibility can be performed in advance with no time limit, and molecular testing does not trigger the Screening window. For patients enrolled via local molecular testing, submission of patient tumor sample (archival or fresh tissue, unless medically contraindicated) is required for independent central molecular testing at Ignyta's CAP/CLIA laboratory.
2. **Tumor Biopsy:** Biopsies may be performed during Screening for patients who enrolled via local molecular testing but do not have enough leftover tumor tissue to submit to Ignyta. Also, if clinically feasible and patient has consented to the biopsy, additional tissue at the time of progression will be collected to gain insights into potential mechanisms of resistance.
3. **Clinical Trial Informed Consent and Eligibility Assessment:** Following central determination of an *NTRK1/2/3*, *ROS1*, or *ALK* gene rearrangement, patients can proceed to consent to the main study and perform Screening assessments, including a thorough review of their prior medical and oncologic history.
4. **Physical Examination:** During Screening, a complete physical examination of major body systems, including known and suspected sites of disease, should be performed. During subsequent visits, abbreviated physical exams will be sufficient.
5. **Eye exam:** Ophthalmologic exams including at least the visual acuity and slit-lamp tests (which may be performed by an optometrist) will be required at Screening, Cycle 2 Day 1, at the End of Treatment, and as clinically indicated.
6. **Serum Pregnancy Test:** To be performed in all female patients of child-bearing potential during Screening, Day 1 of every cycle, at the End of Treatment, and as clinically indicated.
7. **ECG (US):** Three consecutive 12-lead ECGs performed approximately 2 minutes apart will be collected during Screening, on Days 1 of Cycles 1-3 pre-dose and 4 hours (+/- 15 minutes) post-dose, only pre-dose on Days 1 of each treatment cycle thereafter, at the End of Treatment, and as clinically indicated.
8. **ECG (JPN):** In the same patients participating in the JPN PK Sub-Study[12], three consecutive 12-lead ECGs performed approximately 2 minutes apart will be collected during Screening, on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 pre-dose and 4 hours (+/- 15 minutes) post-dose coinciding with the PK samples; thereafter, triplicate ECGs need to be collected only pre-dose on Days 1 of each treatment cycle, at the End of Treatment, and as clinically indicated. **After the required number of patients have been enrolled in the Japan PK Sub-Study, all subsequent newly enrolled patients** will only require triplicate ECGs performed approximately 2 minutes apart during Screening, pre-dose on Days 1 of each treatment cycle, at the End of Treatment, and as clinically indicated. The Sponsor will communicate appropriately when the Japan PK Sub-Study is completed.
9. **ECG (ROW):** A single 12-lead ECG should be performed during Screening, on Days 1 of Cycles 1-3 pre-dose and 4 hours (+/- 15 minutes) post-dose, only pre-dose on Days 1 of each treatment cycle, at the End of Treatment, and as clinically indicated.
10. **Clinical laboratory Assessments:** Hematology, biochemistry, and urinalysis assessments will be performed during Screening, on Days 1 and 15 of Cycle 1, Day 1 of each subsequent treatment cycle thereafter, at the End of Treatment, and as clinically indicated. Standard coagulation and lipid panels will be required at Screening and as clinically indicated on-study. All laboratory assessments will be performed locally at each institution.
11. **PK Samples:** Blood samples for determination of population PK will be collected pre-dose on Day 1 of each treatment cycle and at the End of Treatment. Additionally, if clinically feasible, a PK sample should be obtained at the time of any serious and/or unusual adverse events that may be causally related to the study drug.

US: After each set of triplicate ECGs collected on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1, an additional PK blood sample will be collected at 4 hours (+/- 15 minutes) post-dose to match the time of the post-dose ECGs. **ROW:** After each set of ECGs are collected on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1, an additional PK blood sample will be collected at 4 hours (+/- 15 minutes) post-dose to match the time of the post-dose ECGs
12. **Japan PK Sub-Study:** In at least 6 patients (3 male, 3 female), blood samples will be collected at 0 (pre-dose), 0.5, 1, 2 hours (+/- 5 minutes), 4 (**prior to blood sample collection, record triplicate 12-lead ECGs approximately 2 minutes apart**), 6, 8 hours (+/- 15 minutes), and 24 hours (+/- 1 hour) post-dose on Cycle 1 Day 1 and on Cycle 2 Day 1. At Cycle 3 Day 1, an additional PK blood sample will be collected at 4 hours (+/- 15 minutes) post-dose to match the time of the post-dose ECGs. Thereafter, starting with Cycle 4, only pre-dose samples will be collected on Day 1 of each subsequent treatment cycle and at the End of Treatment. **After the required number of patients have been enrolled in the Japan PK Sub-Study, all subsequent newly enrolled patients** will only require pre-dose PK samples on Day 1 of each treatment cycle and at the End of Treatment. The Sponsor will communicate appropriately when the Japan PK Sub-Study is completed.
13. **PD Samples:** Blood and urine samples for exploratory biomarker analyses will be collected along with the clinical laboratory samples on Day 1 of each treatment cycle and at the End of Treatment.
14. **Tumor Markers:** Blood and urine samples should be collected as per Standard of Care (SOC) for each patient's particular tumor type and recorded in the eCRF at Screening, on Day 1 of each treatment cycle, at the End of Treatment, and as clinically indicated.
15. **Imaging Assessments:** CT or MRI of the brain, chest, abdomen, +/- pelvis (depending on tumor type), as well as a bone scan* (if applicable) should be performed during Screening according to the standard of care for each particular tumor type, e.g., for NSCLC patients, only CT or MRI scans of the brain, chest and abdomen are expected. * Sodium fluoride (NaF) PET scan may also be performed; FDG PET or PET/CT can be used in NSCLC patients and other patients with PET-avid tumors, but the CT potion of a PET/CT may not be used in lieu of a diagnostic CT, unless it is performed with IV contrast. Please consult with the Imaging Manual for further details on required scans per tumor type. On treatment scans are to be performed at the end of Cycle 1 (Cycle 2 Day 1 +/- 2 days), then approximately every 8 weeks thereafter (+/- 7-days) and at End of Treatment (if more than 4 weeks have passed since the last imaging assessment). Tumor assessments may also be performed outside of the protocol-defined time points at the discretion of the Investigator. Patients with responding tumors (CR or PR) must have response confirmed at least 4 weeks after the first documentation of response. All anatomical areas that were scanned during Screening should be assessed at every on-study time point using the same imaging modality in order to determine tumor response as per RECIST v1.1. In addition to submitting all scans for BICR within 1 week of collection, local assessment of tumor response should also be performed by the Investigator.
16. **Vital Signs:** Blood pressure and pulse can be assessed either in the supine or seated position. Body weight should be collected at every clinic visit, while height is only required at Screening.
17. **Adverse Events and Concomitant Medications/Treatments:** Patients must be followed for adverse events from the first day of study treatment until at least 30 days after the last dose of study drug, or until all serious or study drug-related toxicities have resolved or are deemed "chronic" or "stable", whichever is later. Only serious adverse events related to study procedures need to be reported from the time of the main informed consent. Concomitant medications and concurrent treatments should be documented at Screening and at every clinic visit.
18. **Entrectinib Dispensing and Dosing:** Entrectinib bottles will be dispensed at the start of each new cycle of treatment. Entrectinib will be self-administered orally at home (except on clinic days), on a continuous daily dosing regimen at a dose of 600 mg per day (three 200-mg capsules per day). On Day 1 clinic visit days, entrectinib should be taken at the clinic after all the pre-dose assessments have been conducted, at the direction of the study research nurse. On Day 15 and other visits (e.g., imaging days), entrectinib should be taken at home according to the patient's daily routine.

19.	**Post-Study Survival Status:** Patients discontinuing study treatment due to documented radiographic progression will enter the survival follow-up period, where survival status and subsequent anticancer therapy information (including best response) will be collected every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first. Survival can be collected via telephone call or medical chart review. Patients discontinuing study treatment prior to documented radiographic progression will also enter the survival follow-up period, where they will continue to have schedule disease assessments approximately every 8 weeks until documentation of radiographic progression, the start of a subsequent anticancer therapy, or decision to no longer treat (e.g., supportive care), whichever is first. At that time, survival status (and subsequent anticancer therapy information, including best response, if appropriate) will be collected every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first.
20.	**Patients Reported Outcomes:** All patients will complete the QLQ-C30 and EQ-5D quality of life questionnaires at the clinic **PRIOR to any other clinical activity** on Cycle 1 Day 1, Day 1 of each subsequent treatment cycle thereafter, and at the End of Treatment. **NSCLC** and **mCRC** patients enrolled across all baskets will also complete the lung cancer and colorectal cancer specific modules, QLQ-LC13 and QLQ-CR29, respectively, along with the other 2 questionnaires.
a.	**Cycle 1 Day 1 Assessments:** Assessments in parenthesis (X) do not need to be completed if they have been performed during the Screening period within the past 7 days.
b.	**Day 15 Assessments:** These safety visits will be performed during Cycles 1-3 and are optional at Cycles 2 and 3 as per Investigator's discretion. Starting at Cycle 4, patients will be seen in the clinic once a month, at the start of each new cycle of treatment.
c.	**End of Treatment Assessments:** Assessments in parenthesis (X) do not need to be completed if they have been performed within the past 7 days (within the last 2 weeks for patient reported outcomes and 4 weeks for tumor assessments, respectively).
d.	**Safety Follow-Up:** Patients should be evaluated in clinic approximately 30 days after the last dose of study drug. Physical examination (including ECOG and vitals) and clinical laboratory assessments should be performed as clinically indicated. Adverse events should be followed until all serious or study drug-related toxicities have resolved or are deemed "chronic" or "stable", whichever is later.
e.	**Screening Assessments:** Assessments that have been performed as part of standard of care, **prior to obtaining informed consent AND** that are within the past 7 days of Screening **AND** within 30 days of the first dose of study drug, may be used for Screening and do not have to be repeated.

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Adverse Event Collection

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a medicinal product, regardless of causal attribution. An AE can therefore be any of the following:

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition),

Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

Assessment of adverse events will include type, incidence, severity (graded by the NCI CTCAE, v4.0), timing, seriousness, and relatedness. Adverse events will be assessed at every clinic visit.

Sample Size Considerations

For each basket, a true response rate of 20% or less is considered insufficient to warrant further study, whereas a true response rate of 40% or more is considered worthy of further study. The number of patients evaluated in each stage and the minimum number of responders needed to meet the primary endpoint were determined based on a sequential testing technique with at least 80% power and 1-sided $\alpha = 0.025$.

Based on the above design considerations, the first stage will enroll up to 13 patients per basket. Patients are enrolled sequentially and the stage is deemed successful on the 4th responder. If the first stage is not successful, then enrollment in that basket will be terminated.

Otherwise, up to an additional 49 patients will be enrolled into the second stage.

- If within a particular basket, the 14th responder is observed prior to the enrollment of the 49th response-evaluable patient in stage 2, the basket will be deemed as having met the primary endpoint (ruling out an objective response rate of 20%).
- In contrast, the basket will be deemed as not meeting the primary endpoint if the full complement of 49 response-evaluable patients have been enrolled in stage 2 and 14 responders have not been observed at 13 weeks post the date of Cycle 1 Day 1 for the 49th response evaluable patient.
- Under these conditions, if the true response rate is 20%, the probability of stopping enrollment during the first stage is 75%. Conversely, if the true response rate is 40%, then the probability that enrollment will be terminated during the first stage is equal to 17%.

Analysis Datasets

Each basket cohort of patients will be treated as its own separate patient population with the following definitions:

- Natural History Follow-Up Cohort: All gene rearrangement positive patients who were screened and were not enrolled into the study
- Safety Analysis Population [SA]: All eligible patients who enroll into a defined basket and have received at least one dose of entrectinib will be the primary population for evaluating patient characteristics, treatment administration, and safety endpoints for each particular basket
- Efficacy Analysis Population [EA]: The response-evaluable patient population will be defined as all patients in the SA who had measurable disease at baseline per investigator. The EA population will be used for the primary efficacy analyses
- CNS Response Population [CRP]: CNS response population will be defined as all patients in the EA who had measurable CNS disease at baseline
- Patient Report Outcomes Population [PRO]: All patients in the SA who completed the QLQ-C30 and EQ-5D questionnaires on Cycle 1 Day 1 and answered at least one question on an on-study time point thereafter
    - For NSCLC or mCRC baskets, the PRO population will include all NSCLC or mCRC patients who also completed the QLQ-LC13 or QLQ-CR29 questionnaires, respectively, on Cycle 1 Day 1 and answered at least one question on an on-study time point thereafter, in addition to the QLQ-C30 and EQ-5D questionnaires as described above
- Population Pharmacokinetics Populations [POP-PK]: All patients in the SA who have at least one PK sample collected during the study

Protocol Amendments

Original Protocol Version 1: (Date 30 July 2015)

Version 2: (Date 2 Nov 2015)

- Allow local molecular testing for enrollment into the study
- Allow patients with non-measurable disease (evaluable disease only) to also be enrolled into the study, to contribute to safety and pharmacokinetics (PK); this basket will not be assessed for the primary endpoint.
- Revise other inclusion and exclusion criteria to maximize enrollment of these rare patient
- Including blood cell count restrictions removed as there were not hematologic toxicities at that point, and bilirubin and creatinine clearance thresholds were increased as entrectenib had not been shown to affect hepatic or renal function.
- Add post-dose ECGs and time-matched post-dose PK samples for patients enrolled outside the US and Japan
- Add precautionary language on the concomitant use of acid-reducing agents
- For the master Clinical Trial Informed Consent Form (version 03 August 2015), additional information was provided with regards to alternative treatments for NSCLC patients in the "What other choices…" section

Version 3: (Date 9 Sept 2016)

- Due to new nonclinical findings of embryo-fetal and ocular toxicities, the amendment and Dear Investigator letter included a reinforcement of the existing pregnancy restrictions and contraceptive precautions with additional mandatory monthly serum pregnancy tests in all female patients of childbearing potential, and to add ophthalmologic exams (Screening, Cycle 2 Day 1, at the End of Treatment, and as clinically indicated), including at least the visual acuity and slit-lamp tests to monitor for corneal-related visual disturbances during treatment with entrectinib.
- Appendix 1 (Molecular Testing) was updated based on the FDA/CDRH approval of the Ignyta Trailblaze Pharos™ assay as an investigational device for use in STARTRK-2 under IDE G160133. With this approval, the Ignyta *NTRK1/2/3, ROS1, ALK* Gene Rearrangements Assay was changed from a 2-step test using immunohistochemistry (IHC) followed by next generation sequencing (NGS) to just one step using NGS. All references to the 2-step test were changed accordingly throughout the protocol.
- In an effort to maximize the enrollment of these rare patients, the "non-measurable disease" basket was renamed "non-evaluable for the primary endpoint" basket, to allow for the protocol eligibility criteria, e.g., ECOG performance status > 2, dual primary cancers where one cancer's mutation status is unknown, or dual oncogenic drivers, e.g., ALK fusion and EGFR mutation. Patients with non-measurable disease will continue to be enrolled to this basket.

- Recognizing that CNS metastases are common in many solid tumors and that recent data with tyrosine-kinase inhibitors suggest that dose intensification may be necessary to overcome incomplete target inhibition in the CNS, intra-patient dose escalation in patients with CNS disease who have been on study for at least 2 cycles of treatment with a best response of Stable Disease (SD) per RECIST v1.1 AND without treatment-related Grade ≥ 2 adverse events will be allowed as per Investigator's discretion after discussion with the Sponsor.
- As a way to more efficiently assess whether entrectinib has anticancer activity in other (non-NSCLC and non-mCRC) solid tumors, the statistical analysis methodology for all evaluable baskets (NSCLC, including CNS-only progression post crizotinib, mCRC, other solid tumors) was harmonized to one single statistical design based on a 2-stage sequential testing design. While the original statistical assumptions for the main baskets (a true response rate of 20% or less is considered insufficient to warrant further study, whereas a true response rate of 40% or more is considered worthy of further study) were preserved, the number of patients evaluated in each stage and the minimum number of responders needed to meet the primary endpoint were re-calculated based on a sequential testing technique with at least 80% power and 1-sided alpha=0.025.

Version 4: (Date 3 Aug 2017)
The protocol was revised to expand the *ROS1* fusion-positive, *ROS1* inhibitor-naïve NSCLC basket size to include an additional 90 patients by adjusting the statistical assumptions for this patient population relative to crizotinib

Data Quality and Integrity: Sponsor's Assurance

Section 14.3 in the protocol states, "After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented."

Compliance with Good Clinical Practices

Section 15 of the protocol states, "This study will be conducted in accordance with the U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

Clinical Reviewer Comment: See section 8.1.2 for pooled data and NDA submission Module 2.5 "Clinical Overview" section 1.9 for declaration of GCP.

Financial Disclosure

Study STARTRK-2 (RXDX-101-02, GO40782) entitled, "An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3, ROS1,* or *ALK* Gene Rearrangements" was conducted in Australia, Hong Kong, Japan, Singapore, South Korea, Taiwan, Belgium, France, Germany, Italy, Netherlands, Poland, Spain, Switzerland, United Kingdom, and the United States and was submitted to IND 120500 and IND 135124. A signed financial disclosure form (FDF) was not obtained for 573 (31.8%) investigators in Study STARTRK-2, and 2 PIs that enrolled patients in the *NTRK* efficacy population. Many IRs were sent to the applicant and teleconferences to attempt to reconcile the FDFs or show due diligence. See Section 19.2for full review of the pooled data regarding missing FDFs.

Of the investigators who responded, disclosable financial interests were recorded by 2 out of 1801 (<1%) of investigators in Study STARTRK-2, as in **Error! Reference source not found.** below:

Table 95: Investigators with a Positive Financial Disclosure

Study Protocol	Roche Site Number	Ignyta Site Number	Number of Patients Enrolled at Site	Investigator Name	Investigator Type	Disclosure
STARTRK-2	(b) (6)				Principal Investigator	Payment received from Roche/GNE greater than $25,000 for speaking/ consultation fees
STARTRK-2					Sub-Investigator	(b) (6) is a Genentech employee and holds significant equity interests in Roche/GNE that exceeds $50,000

Source: Response to IR dated 7 June 1019

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Seizure prophylaxis with non-enzyme-inducing anti-epileptic drugs (non-EIAEDs) is allowed during the study for patients with controlled asymptomatic CNS involvement. Treatment with antidiarrheal drugs was outlined by Grade in the protocol. Prophylactic use of G-CSF or initiation of erythropoietin may be instituted according to the American Society of Clinical Oncology guidelines in patients who are having difficulty with severe neutropenia or anemia.

As for treatment compliance, see Section 8.1.2 for pooled data from all registration studies.

Data Quality and Integrity - Reviewers' Assessment

Upon further clarifications from entrectinib per FDA's IRs, the reviewer was able to:

- Reproduce Genentech's analysis dataset and analysis results from legacy dataset
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA's major efficacy analyses

19.6.4. RXDX-101-03 / STARTRK-NG

Trial Design

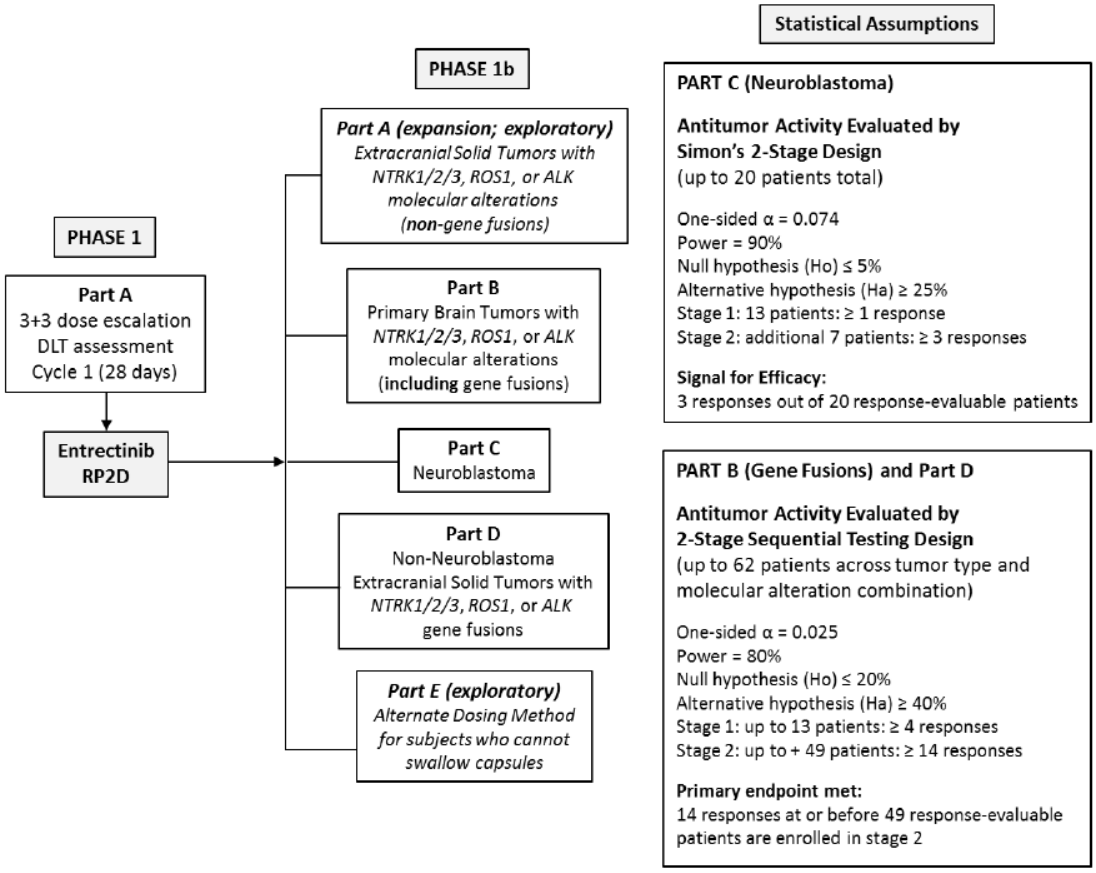
STARTRK-NG, entitled "A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, with or without TRK, *ROS1*, or *ALK* Fusions" is a 5-part, multicenter, open-label dose escalation study in pediatric subjects with relapsed or refractory extracranial solid tumors (Phase 1; Part A), with expansion cohorts (Phase 1b) in subjects with primary brain tumors harboring *NTRK1/2/3, ROS1*, or *ALK* molecular alterations (Part B), neuroblastoma (Part C), and other non-neuroblastoma, extracranial solid tumors harboring *NTRK1/2/3, ROS1*, or *ALK* gene fusions (Part D). In addition, an exploratory cohort (Part E) will enroll subjects who are otherwise eligible but unable to swallow capsules.

Dose escalation: Entrectinib was administered orally with food, QD, in repeated 4-week cycles. The starting dose in Part A was 250 mg/m^2 on a continuous daily dosing regimen. Up to four dose levels were evaluated. A "3+3" patient enrollment scheme was followed during the dose escalation.

The RP2D was planned to be determined from DLT(s) derived from clinical and laboratory observations in the first treatment cycle (28 days). The MTD was defined as the dose level immediately below the dose level at which ≥ 2 patients from a cohort of 3 to 6 patients experienced a DLT. After MTD was established, based on the DLT assessment and an overall acceptable safety profile at the MTD, this dose was selected as the RP2D for evaluation in the Phase 1b portion of the study.

Dose expansion: Phase 1b was designed to enroll additional patients with specific tumor types and molecular alterations. All patients in Phase 1b were planned to receive entrectinib at the pediatric RP2D, except for Part E, who were to initially receive entrectinib via alternative dosing methods at the -1 dose level de-escalation from the RP2D.

Figure 63: Study Design



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For DLT evaluation, toxicity will be graded according to the NCI CTCAE; Version 4.03. Peripheral motor and sensory neuropathy will be graded according to the pediatric specific grading criteria. The DLT evaluation period will start from the Cycle 1 Day 1 and end on Cycle 1 Day 28.

Tumor assessments included magnetic resonance imaging (MRI) or computed tomography (CT) scans, metaiodobenzylguanidine (MIBG) scans, with/without bone marrow aspirates and biopsies. Tumor responses in patients were evaluated using RECIST version 1.1, Curie score, or RANO, depending on the tumor type.

Patients were allowed to continue entrectinib until clinical, laboratory or radiographic evidence of disease progression, development of unacceptable toxicity, or discontinuation at the discretion of subject/parent/guardian or Investigator.

The study is ongoing.

Key eligibility

- Children, adolescents, and young adult patients with relapsed or refractory extracranial solid tumors (Phase 1; Part A), with additional expansion parts (Phase 1b) in children, adolescents, and young adult patients with primary brain tumors harboring *NTRK1/2/3*,

ROS1, or *ALK* molecular alterations (Part B), neuroblastoma (Part C), and other non-neuroblastoma, extracranial solid tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* gene fusions (Part D).

- In addition, an exploratory cohort (Part E) enrolls patients who were otherwise eligible but unable to swallow capsules.
- Patients ≥2 years and <22 years of age were eligible for Part A through Part D, and patients from birth to <22 years of age were eligible for Part E.

Study Endpoints

Primary objective: to determine the MTD or RP2D of entrectinib in pediatric patients (children and adolescents) with relapsed or refractory solid tumors.

Secondary objectives:

1. To describe the safety profile of entrectinib as characterized by AE type, severity, timing and relationship to entrectinib treatment, as well as electrocardiogram (ECG) and laboratory abnormalities in the first and subsequent treatment cycles

2. To characterize the PK of entrectinib in plasma

3. To determine the ORR, DOR, TTR, CBR, and PFS in all enrolled patients (Parts A [expansion], C, and D) receiving entrectinib at the RP2D, using RECIST v1.1 and the Curie Scale, as applicable

4. To determine the intracranial tumor response, DOR, TTR, and CNS-progression free survival (CNS-PFS) in Parts B and D patients receiving entrectinib at the RP2D and presenting with measurable CNS primary or secondary disease at baseline, using RANO or RANO-BM, respectively.

Dose Modification and Management Algorithms

Up to 2 dose reductions due to treatment-related toxicity will be permitted in individual participants.

Definitions and dose modifications related to prolonged QTc were written into the protocol.

For dose-limiting somnolence or cognitive disturbance:

• If the toxicity resolves to Grade < 2 or baseline within 14 days (≤ 14 days) of drug discontinuation, the subject may resume treatment with a dose reduction

• If the toxicity does not resolve to Grade < 2 or baseline within 14 days of drug discontinuation, the subject must be removed from protocol therapy

For all other non-hematologic dose-limiting toxicity:

• If the toxicity resolves to Grade ≤ 2 or baseline within 14 days (≤ 14 days) of drug discontinuation, the subject may resume treatment with a dose reduction

• If the toxicity does not resolve to Grade ≤ 2 or baseline within 14 days of drug discontinuation, the subject must be removed from protocol therapy.

• Two dose modifications for toxicity are permitted. If DLT recurs or new DLT is observed after 2 dose reductions, the subject must be removed from protocol therapy. This includes subjects who have had their dose increased by intra-subject dose escalation.

• Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

Monitoring Plan

Figure 64: Schedule of Assessments

	Screen	Cycle 1 (Assessments ±1 day)				Cycles 2-6 (±2 days)		Cycle 7+ (±2 days)	End of Protocol Therapy	Safety Follow-Up[a]
Treatment Day	-14 d	1[b]	8	15	22	1	15*	1	Within 7 days of last dose	~ 30 days after last dose and q3mo
Informed Consent	X									
Eligibility Assessment	X	X								
Enrollment	X									
Vital Signs	X	(X)	X	X	X	X	X	X	X	(X)
Performance Status, Ht, Wt	X	(X)				X		X	X	(X)
Physical Examination	X	(X)	X	X	X	X	X	X	X	(X)
Eye Examination	X					C2			X	
Serum Pregnancy Test[c]	X	(X)				X		X	X	
Urinalysis	X	(X)				X		X		
Clinical Safety Lab Tests (Section 7.2)	X	(X)	X	X	X	X	X	X	X	(X)
12-Lead ECG[d]	X	X			X	X			X	
Tumor Evaluation (Parts A and E)[e]	X					Post C2, 4, 6		Post C9, 12, 16, 20 then every 6th cycle	X	
Tumor Evaluation (Parts B, C, and D)[f]	X					Post every even-numbered cycle, starting with C2			X	
Dispense Entrectinib		X				X		X		
Patient Diary		X	X	X	X	X	X	X	X	
Pill Count by study team						X		X	X	
Concomitant Meds	X	X	X	X	X	X	X	X	X	X
AE Review	X	X	X	X	X	X	X	X	X	X
PK Assessment[g]		X	X	X	X	X		X		
PIA[h]		X		X						
PD Assessment[i]		X				X		X	X	
Archival Tissue/ Molecular Testing	X								X	

[a] Safety follow-up includes long-term survival follow-up, which may be performed via phone call to subject/family/treating physician, every 3 months until death, loss of follow-up, or withdrawal of consent to assess disease progression and survival status. Assessments in parenthesis (X) are optional.
[b] Cycle 1 Day 1 Assessments in parenthesis (X) do not need to be completed if they were performed during the Screening period within the past 7 days.
[c] Serum pregnancy test performed for female subjects of child-bearing potential
[d] On Day 1 of Cycle 1, ECG assessments will be completed prior to first dose of drug and 4 hours after first dose of drug. If Screening ECG was done within 48 hours of Cycle 1 Day 1, the ECG prior to the first dose of drug on Day 1 does not need to be repeated. Pre-dose Day 22 of Cycle 1, Day 1 of Cycles 2-6 and at the End of Treatment visit.
[e] Tumor evaluation for subjects in Parts A and E will be performed at Screening, at the end of Cycles 2, 4, 6, 9, 12, 16, 20, 24, and then every 6 cycles until discontinuation from the study (End of Treatment visit).
[f] Tumor evaluation for subjects in Parts B, C, and D will be performed at Screening, at the end of every even-numbered cycle, e.g., Cycles 2, 4, 6, 8, etc., until discontinuation from the study (End of Treatment visit).
[g] Pharmacokinetics (PK): PK samples (2 mL each) will be collected on Cycle 1 Day 1 pre-dose [time 0] and at 1, 2, 4, 6, and 24 hours [Cycle 1 Day 2 pre-dose] post-dose; Cycle 1 Days 8, 15 and 22 pre-dose [trough]; on Cycle 2 Day 1 (*or Cycle 3 Day 1, if Cycle 2 Day 1 not collected*) pre-dose [time 0] and at 1, 2, 4, 6, and 24 hours [Cycle 2 Day 2 pre-dose] post-dose; and on Day 1 of every cycle thereafter pre-dose [trough]. Additionally, if clinically feasible, a PK sample should be obtained at the time of any serious and/or unusual adverse events that may be causally related to the study drug.
[h] Plasma inhibitory assay samples (5 mL each) will be collected on Cycle 1 Day 1 pre-dose [time 0] and at 4 hours post-dose, and pre-dose on Cycle 1 Day 15.
[i] Pharmacodynamics (PD): Blood samples (10 mL) for exploratory biomarker analyses will be collected pre-dose on Day 1 of each new treatment cycle starting with Cycle 1, and at the End of Treatment visit.
[*] During dose expansion, at the Investigator's discretion, Cycles 2-6 Day 15 visits are optional depending on the subject's clinical status. If the clinic visit is performed, complete the visit assessments. If the subject does not visit the clinic visit, a phone call may be used in lieu of a clinic visit to assess adverse events and concomitant medications.

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Adverse Event Collection

Safety was evaluated on an ongoing basis through a list of assessments including monitoring of AEs per CTCAE v3, laboratory evaluations, vital signs, and performance status throughout the study. Other assessments including PK and molecular testing were performed.

Sample Size considerations

Phase 1 (Part A) Planned: approximately 6 – 30 patients; Enrolled: 16 patients

Phase 1b (Part B and D) Planned: Part A will remain open as an exploratory cohort to allow enrollment of subjects with non-gene fusion, molecular alterations of interest that are not eligible for Part D. Part C: Approximately 7-24 subjects with relapsed or refractory neuroblastoma. Part B (gene fusions) and Part D: Enrollment as per a 2-stage sequential testing design, with up to 62 subjects per tumor type and molecular alteration combination. Part E: Exploratory cohort for subjects who are unable to swallow capsules.

For each specific patient population, a true response rate of 20% or less is considered insufficient to warrant further study, whereas a true response rate of 40% or more is considered worthy of further study. The number of subjects evaluated in each stage and the

minimum number of responders needed to meet the primary endpoint were determined based on a sequential testing technique with at least 80% power and 1-sided $\alpha = 0.025$.
Based on the above design considerations, the first stage will enroll up to 13 subjects per basket. Subjects are enrolled sequentially and the stage is deemed successful on the 4th responder. If the first stage is not successful, then enrollment in that basket will be terminated. Otherwise, up to an additional 49 subjects will be enrolled into the second stage.

- If within a particular basket, the 14th responder is observed prior to the enrollment of the 49th response-evaluable subject in stage 2, the basket will be deemed as having met the primary endpoint (ruling out an objective response rate of 20%).
- In contrast, the basket will be deemed as not meeting the primary endpoint if the full complement of 49 response-evaluable subjects have been enrolled in stage 2 and 14 responders have not been observed at 13 weeks post the date of Cycle 1 Day 1 for the 49th response evaluable subject.
- Under these conditions, if the true response rate is 20%, the probability of stopping enrollment during the first stage is 75%. Conversely, if the true response rate is 40%, then the probability that enrollment will be terminated during the first stage is equal to 17%.

Analysis Datasets

- Enrolled Population: All patients enrolled in this study with a cut-off date of 31 Nov 2017
- Safety population: All enrolled patients who received at least one administration of entrectinib. The phase 1 dose escalation efficacy analysis was conducted using this safety population.
- DLT-Evaluable population: Patients who had received at least 75% of the prescribed dose during Cycle 1 (≥ 21 of 28 days) or experienced DLT at any time within 28 days after receiving the first dose or who discontinued study drug due to toxicity within 28 days after receiving the first dose. Patients who discontinued entrectinib treatment due to progressive disease or other reason not related to toxicity were replaced if they had not received 75% of the prescribed dose during Cycle 1.
- Pharmacokinetic Evaluable Population: All patients who received any dose of entrectinib and who had at least one quantifiable post-baseline PK sample available

Protocol Amendments

Original Submission: (Date: 5 Nov 2015)

Version 2: (Date: 18 Nov 2015)
Revised to clarify the dose modification criteria threshold to resume study drug treatment for DLTs, specifically, entrectinib-related DLTs of somnolence or cognitive disturbance.

- Somnolence and cognitive disturbance were added as exceptions to the rule for defining dose-limiting toxicities that are due to failure to recover to Grade ≤ 2 or baseline.
- The dose modification rules for dose-limiting toxicities were revised to point out specific rules for prolonged QTc, somnolence, and cognitive disturbance

Version 3: (Date: 30 Nov 2016)

- To expand the Phase 1b portion of the study beyond neuroblastoma, as a way to more efficiently assess whether entrectinib has anticancer activity in pediatric cancers which harbor *NTRK*, *ROS1*, or *ALK* molecular alterations, especially gene fusions. Antitumor endpoints and statistical methods were added accordingly. In addition, retrospective blinded independent central review of tumor assessments will be performed for a select group of subjects, e.g., gene fusion-positive subjects and neuroblastoma responders.
- To move Part B (Primary Brain Tumors) to the Phase 1b portion of the study; all subjects enrolled in Part B will receive entrectinib at the RP2D determined in Part A without the need to confirm that dose in a mini dose escalation.
- A separate cohort (Part E) was created to accommodate subjects ages ≥ 2 years and < 22 years who are unable to swallow capsules and all subjects < 2 years who otherwise meet all other eligibility criteria for the other parts. Alternative dosing methods will be applied.
- Due to new nonclinical findings of embryo-fetal and ocular toxicities (Dear Investigator Letter, August 2016), the protocol was amended:
    - To reinforce the existing pregnancy restrictions and contraceptive precautions with at least 2 methods of contraception and to extend the restriction to at least 90 days following the last dose of study drug
    - To add ophthalmologic exams (i.e., visual acuity test), in the Schedule of Assessments (Screening, Cycle 2 Day 1, at the End of Treatment, and as clinically indicated) to monitor for corneal-related visual disturbances during treatment with entrectinib
- Planning for the upcoming introduction of a pediatric-specific formulation, additional collection of blood samples was added to better understand the pharmacokinetics of entrectinib in pediatric subjects receiving the current adult formulation (capsules) versus future formulation(s).

Version 4: (Date: 24 March 2017)

1. Amended to establish a PK bridge between intact capsules vs. capsule contents mixed with a small amount of food to ensure a safe starting dose in patients treated in Part E:
2. Since the effect of fat content and food volume on entrectinib administered using alternative dosing method (e.g., capsule content mixed with a small amount of food) is unknown, a meal with a standardized fat content and volume in Part E will be used
3. For patients who do not require seizure prophylaxis therapy with enzyme inducers, a table was added to counsel providers and patients avoid the co-administration of strong or moderate CYP3A inhibitors and inducers.

Data Quality and Integrity: Sponsor's Assurance

Described in Section 13 of the protocols within the CSR submitted in Module 5.3.5.2.

Compliance with Good Clinical Practices

Per Section 3.4 of the protocols within the CSR submitted in Module 5.3.5.3, "This study was conducted in accordance with GCP, and investigators were trained according to applicable Sponsor SOPs."

Clinical Reviewer Comment: See section 8.1.2 for pooled data and NDA submission Module 2.5 "Clinical Overview" section 1.9 for declaration of GCP.

Financial Disclosure

Study STARTRK-NG (RXDX-101-03, CO40778) entitled, "A Phase 1/1b, Open-Label, Dose-Escalation and Expansion Study of Entrectinib (RXDX-101) in Children and Adolescents with Recurrent or Refractory Solid Tumors and Primary CNS Tumors, with or without TRK, ROS1, or ALK Fusions" was conducted in the US and was submitted to IND 120500. A signed financial disclosure was not obtained for 34 (12%) investigators in Study CO40778 (STARTRK-NG). A positive FDF was received for the following investigator:

Figure 65: Positive FDF

STARTRK-NG	(b) (6)	Sub-Investigator	(b) (6) has received payment from Roche/GNE greater than $25,000 in a calendar year for speaking fees

Source: NDA submission and IR dated 7 June 2019

Details regarding missing FDFs across all studies is discussed in detail in Section 19.2.

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/s/

KELIE M REECE
08/13/2019 12:46:13 PM

CLAIRE E MYERS
08/13/2019 12:49:41 PM

WHITNEY S HELMS on behalf of STEPHANIE L AUNGST
08/13/2019 12:50:15 PM

WHITNEY S HELMS
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JOHN K LEIGHTON
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08/13/2019 01:11:29 PM

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08/13/2019 01:12:59 PM

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08/13/2019 01:17:55 PM

XINYUAN ZHANG
08/13/2019 01:19:14 PM

YUCHING N YANG
08/13/2019 01:53:42 PM

GUOXIANG SHEN
08/13/2019 01:55:12 PM

HONG ZHAO
08/13/2019 01:56:28 PM
I concur.

HONG ZHAO
08/13/2019 01:56:28 PM
I concur.

NAM ATIQUR RAHMAN
08/13/2019 02:51:33 PM
I concur with the recommendation.

SIRISHA L MUSHTI
08/13/2019 02:55:46 PM

LISA R RODRIGUEZ
08/13/2019 03:04:47 PM

RAJESHWARI SRIDHARA
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LEIGH J MARCUS
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MARTHA B DONOGHUE
08/13/2019 04:19:49 PM

PATRICIA KEEGAN
08/13/2019 05:01:28 PM

GIDEON M BLUMENTHAL
08/13/2019 05:31:01 PM

Clinical Consultation

To: Kelie Reece, PhD, RPM, DOP2

From: Jacqueline Karp, MD, Clinical Reviewer, DBRUP

Through: Theresa Kehoe, MD, Clinical Team Leader, DBRUP
Audrey Gassman, MD, Deputy Director, DBRUP

Subject: NDAs 212725 and 212726

Date: July 24, 2019

Materials Reviewed: Relevant submissions under NDAs 212725 and 212726, Relevant literature

Reason for Consultation

The Division of Oncology Products 2 (DOP2) is currently reviewing two NDAs (212725 and 212726) for the new molecular entity entrectinib (trade name Rozyltrek), a kinase inhibitor indicated for the treatment of adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) and adult and pediatric patients 12 years of age and older with certain neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive solid tumors. Entrectinib is administered as a 600 mg oral dose daily in both adult and pediatric patients.

A safety concern that emerged during DOP2's review of entrectinib clinical trial data was an increased fracture incidence with entrectinib therapy. Across the clinical trials of entrectinib, fractures were reported in 16/337 (5%) of adult patients and 7/30 (23%) of pediatric patients who received entrectinib.

DOP2 has requested a consultation from the Division of Bone, Reproductive and Urologic Products (DBRUP) regarding this safety concern. Specifically, DOP2 has asked DBRUP to provide labeling recommendations regarding bone toxicity and to provide recommendations for postmarketing study requirements to further characterize the fracture risk.

Biologic Plausibility

The mechanism of action of entrectinib involves inhibition of the neurotrophic tropomyosin receptor 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), anaplastic lymphoma kinase (ALK), Janus kinase (JAK)2, and tyrosine kinase non-receptor 2 (TNK2).

In addition to their known key role in nervous system development and maintenance, neurotrophins (e.g. nerve growth factor, NGF) and their receptors (e.g., TRKA, TRKB and TRKC) are also involved in skeletal tissue formation and healing. Studies have shown that neurotrophins and their receptors are widely expressed in skeletal tissues and have suggested their involvement in chondrogenesis and osteogenesis (Su et al., 2017). A study by Tomlinson et al. (2017) demonstrated that communication between osteoblasts and sensory nerves through nerve growth factor-TRKA signaling is essential for load-induced bone formation in mice, suggesting a key role for TRKA in this process. Since neurotrophins and their receptors have a known role in skeletal metabolism, and since entrectinib inhibits neurotrophic tyrosine receptor kinases, it is biologically plausible that entrectinib therapy may have deleterious effects on bone tissue and therefore confer an increased risk of fracture.

The JAK (Janus kinase) family of tyrosine kinases including JAK 2 and TNK2 (other targets of entrectinib) is also thought to have a key role in the regulation of skeletal development and bone metabolism (Li et al., 2013). Although the significance of the JAK family in the musculoskeletal system has not been fully characterized, evidence suggests that JAK signaling pathways may also be involved in regulation of bone homeostasis and the bone response to mechanical loading. Additionally, many cytokines that activate JAK signaling are known to affect osteoblast and osteoclast differentiation and proliferation. The inhibitory effect of entrectinib on JAK tyrosine kinases adds to the biologic plausibility that entrectinib therapy may have adverse effects on bone tissue and confer an increased propensity to fracture.

The only other drug in the same specific class as entrectinib is larotrectinib, which was approved for similar indications in 2018. Larotrectinib also inhibits TRKA, TRKB and TRKC. Of note, no increased fracture incidence has been observed in clinical trials and postmarketing experience with larotrectinib. Different inhibitory activities at TRKA, TRKB and/or TRKC between the two products could explain the disparate results. Clinical pharmacology data suggest that entrectinib may be a more potent inhibitor of TRKA, TRKB and TRKC, as the IC50 values were 0.1 to 25 nM for entrectinib and 5 to 11 nM for larotrectinib. Additionally, the fact that larotrectinib does not inhibit JAK2 and TNK2 could also explain the disparate results between the two products regarding fracture incidence.

Relevant Nonclinical Studies

In the nonclinical studies of entrectinib, no major bone safety issues were identified. In repeat dose toxicology studies in rats and dogs, no gross or histological changes were observed in bone tissue. In a 13-week juvenile rat toxicology study, femur lengths in males and females were slightly decreased at the highest tested dose (16 mg/kg/day) on post-natal day 98 and this was still apparent at postnatal day 128. However, the terminal body weights were also significantly decreased in this dose group, and the decreased femur lengths were considered to be secondary to an effect on overall growth and not specific to bones. Histological evaluation revealed no microscopic findings to explain the decreased femur lengths. In an embryofetal development study in rats, skeletal abnormalities were observed (bent bones and reduced ossification). The

growth effect observed in the juvenile rat study and the skeletal abnormalities observed in the embryofetal rat studies may be due to an inhibitory effect of entrectinib on bone growth and modeling. Although the histologic studies in animals did not reveal any bone effects, a bone effect is still possible, as histologic evaluation may not identify primary quantitative effects on bone formation or effects on the quality of the bone tissue.

Nonclinical studies of other JAK inhibitors have identified adverse bone effects. The following are examples of such drugs:

- Ruxolitinib, a JAK inhibitor under investigation for the topical treatment of atopic dermatitis, demonstrated significant adverse bone effects in juvenile rat toxicity studies. These studies showed that ruxolitinib, relative to control, was associated with declines in serum P1NP, a marker of bone formation activity; reduced bone mineral content (BMC) and cross-sectional bone area by peripheral quantitative computed tomography (pQCT), in the metaphysis and the diaphysis of the tibia, with no reduction in volumetric bone mineral density (BMD); shorter bone lengths in both femur and spine; and transverse radio-opaque lines in the tibia. Effects on body weight were observed in conjunction with the bone changes. The data suggested adverse effects of ruxolitinib on longitudinal as well as appositional bone growth mediated by potential effects on growth plate chondrocytes and/or osteoblasts consistent with reduced bone growth in the axial and appendicular skeleton. The main issue raised by these data was that bone growth may be interrupted or slowed by the drug.
- Baricitinib, a JAK1/2 inhibitor approved for the treatment of rheumatoid arthritis (RA), demonstrated decreases in rates of bone growth in juvenile rat studies. These decreases were considered secondary to lower body weight gain. There were no generalized abnormalities of trabecular or cortical bone or the physis.
- Upadacitinib and filgotinib, JAK1 inhibitors under investigation for the treatment of RA, have not demonstrated abnormal bone findings in juvenile animal toxicity studies.
- Tofacitinib, a JAK 1/3 inhibitor approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis and ulcerative colitis, has not demonstrated bone or cartilage pathology in juvenile and adult rat toxicity studies.

Summary of Entrectinib Development Program and Fracture Data

Entrectinib was studied in one dose-finding trial in adults [ALKA (n=57)], one dose-finding and activity-estimating trial in adults, [STARTRK-1 (n=76)], one dose-finding and activity-estimating trial in pediatric and young adult patients [STARTRK-NG (n=16)], and one fixed-dose, single arm, activity-estimating trial in adults [STARTRK-2 (n=206)]. All clinical trials were open-label with no comparator.

For the NTRK indication, entrectinib may be approved under accelerated approval based on tumor response rate and durability of response. Continued approval will be contingent upon verification of clinical benefit observed in confirmatory trials. For the ROS1 indication, entrectinib is under consideration for regular approval.

Postmarketing studies of entrectinib will be required to further characterize certain risks (e.g., cardiac risks, potential effects on growth and development and neurological outcomes) and confirm clinical benefits for the population approved under accelerated approval.

The NDA safety dataset included 355 patients (337 adults and 18 pediatric patients) who were enrolled in the abovementioned entrectinib clinical trials. Of these patients, 172 (48%) were exposed to entrectinib for 6 months or longer and 84 (24%) were exposed to exposed for 1 year or longer.

The concern for an increased fracture risk with entrectinib therapy arose late during the NDA review cycle, when 2 cases of atraumatic femoral neck fractures in patients in the STARTRK-NG study were presented at the annual American Society of Clinical Oncology meeting in June 2019 (Robinson et al.). The identification of these cases prompted a further investigation into fracture events across the entrectinib program.

The applicant evaluated this fracture safety signal by conducting a cumulative review of the clinical trial and company drug safety databases to identify all events of fractures reported in entrectinib-treated patients. That review included patients who were not part of the NDA dataset (which had a cutoff of May 31, 2018) in order to provide a comprehensive analysis of the fracture risk. The search had a clinical cutoff date of March 8, 2019 for Studies STARTRK-1 and ALKA, March 31, 2019 for Studies STARTRK-2 and STARTRK-NG and May 3, 2019 for the company drug safety database. The analysis included a total of 528 patients (498 adults, 30 pediatric patients) that have been treated with entrectinib across the 4 clinical studies. The composite term "fractures" used in the search for fracture events included the following MedDRA preferred term (PTs): humerus fracture, foot fracture, ankle fracture, femoral neck fracture, stress fracture, fibula fracture, fracture, rib fracture, spinal fracture, wrist fracture, femur fracture, pathological fracture, tibia fracture, lower limb fracture.

The search retrieved a total of 38 patients with reported events indicative of fractures from the clinical trial database. Upon review of the retrieved events, 4 were determined to be adverse events of joint dislocation (2), meniscus injury (1), and rotator cuff injury (1). These 4 events were therefore subsequently excluded from the fracture analysis.

Of the 34 patients (27 adults and 7 pediatric patients) identified from the cumulative search and review of retrieved events, 15 patients were from outside of the original NDA dataset (11 adults and 4 pediatric patients). Fracture events were considered serious in 15 of the patients (12 adults and 3 pediatric patients).

Narratives submitted for these 34 patients are summarized as follows:

<u>Pediatric Patients</u>:

- 10 year old male patient with left proximal tibia fracture on study day 225 and second left proximal tibia fracture on study day 297 (unclear whether this was a recurrent fracture or new fracture)
- 10 year old female patient with 2nd right metatarsal fracture on study day 130

- 7 year old male patient with right lower limb fracture on study day 54
- 8 year old female patient with tibia fracture on study day 121
- 6 year old male patient with left femur fracture on study day 75 and second left femur fracture after a fall on study day 83 (appears to be a new fracture)
- 4 year old female with bilateral femoral neck fractures on study day 85 with no antecedent trauma
- 9 year old male patient with bilateral femoral neck fractures on study day 221

Adults:

- 22 year old woman with metatarsal fracture on study day 563
- 66 year old woman with ankle fracture on study day 53
- 23 year old woman with tibial stress fracture on study day 42 and additional/recurrent (unclear) tibial stress fractures on study days 100, 281, 366 and 574
- 53 year old woman with humerus fracture on study day 340
- 70 year old woman with bilateral jaw fractures (parasymphysial) on study day 253
- 68 year old woman with unspecified fracture on study day 104; noted to have osteoporosis
- 57 year old man with medial tibial plateau fracture on study day 117; no trauma noted
- 68 year old woman with left humerus fracture on study day 11 and 100 (unclear whether recurrent or new)
- 33 year old woman with left ankle fracture on study day153
- 38 year old woman with right pathologic femoral neck fracture on study day 38
- 41 year old man with spine fracture on study day 74
- 29 year old man with right humerus fracture on study day 98
- 64 year old woman with rib fracture on study day 85
- 81 year old woman with spinal compression fracture on study 61; noted to have osteoporosis
- 54 year old man with left toe fracture on study day 185
- 72 year old woman with right hip stress fracture on study day 31 after fall; noted to have osteoporosis
- 80 year old woman with right hip stress fracture on study day 7 after mechanical fall; noted to have prior stress fracture of right hip
- 59 year old woman with wrist fracture on study day 114 after a fall
- 67 year old woman with left pathologic femoral neck fracture on study day 262 and right femoral neck fracture on study day 499 after a fall
- 67 year old woman with left ankle and fibula fracture on study day 163 after fall
- 64 year old woman with pathologic left femoral neck and shaft fractures on study day 48 after fall from bed and left proximal tibia stress fracture on study day 49
- 31 year old man with spinal fracture on study day 302
- 27 year old man with pathologic right femur shaft fracture on study day14 after fall
- 60 year old woman with pathologic right humerus fracture on study day 15 after injury; noted to have osteoporosis
- 80 year old woman with lumbar compression fracture on study day 91 after fall

- 51 year old woman with left bimalleolar ankle fracture on study day 121, left foot fracture on study day 138; noted to have osteoporosis
- 68 year old woman with right hip fracture on study day 380 after fall; noted to have avascular necrosis of right hip

Median duration to occurrence of fracture was 4 months (range: 1.8-7) in pediatric patients and 3.8 months (range 0.3-19) in adults. The percentage of patients whose fractures required casting or surgery cannot be determined given the limited information available in the narratives. By the time of data cut-off, 5 (71%) of pediatric patients and 17 (63%) of adults were reported to have complete healing of their fractures. Although the action taken with entrectinib following fracture events was not reported in every narrative, it appears that nearly all patients continued entrectinib following fracture events. Most patients who underwent surgical treatment of fractures had entrectinib temporarily withheld at the time of surgery.

Of note, review of pharmacokinetic data from individual patients who had fracture events revealed that their systemic exposure to entrectinib was not higher than that of the overall trial populations.

Assessment

Overall, information in the narratives regarding the underlying conditions and events preceding the fractures was limited. Therefore, it is difficult to make a causality assessment of the fracture events in many of the individual patient narratives. Evaluation of the totality of information available across all fracture events suggests many could be drug-related, as most fractures did not seem to have had an alternative cause. Most fractures did not appear to be due to tumor pathology at the fracture site and most patients who experienced a fracture did not appear to have significant underlying risk factors for fracture (only 5 of the adult patients with a fracture were reported to have a history of osteoporosis). Of particular concern is that all fractures in pediatric patients were associated with minimal or no trauma, whereas most fractures in adults occurred in the setting of a fall or other trauma to the affected area. This suggests that entrectinib may have a differential effect on the growing versus mature skeleton. In some adult and pediatric patients, there appeared to be either recurrent or multiple events of fractures. These findings suggest not only a role of entrectinib in fracture, but potentially a detrimental effect of entrectinib on fracture healing.

While the 5% incidence rate of fractures observed in adults in the entrectinib clinical trials does not appear to exceed the background fracture incidence rate in adults with solid tumors (estimated to be as high as 18%), the 23% incidence rate of fractures observed in pediatric patients was unexpectedly high, as the corresponding estimated background rate is approximately 6%.

Given the unexpected rate of fractures in pediatric patients and the lack of an alternative explanation for most fracture events (e.g., known tumor pathology at the fracture site, major trauma) in the entrectinib clinical trials, entrectinib likely <u>does</u> increase the risk of fractures. There is biologic plausibility for this risk, given the implicated role of entrectinib's target

receptors in bone development and formation as described above. In addition, the risk seems to be increased in pediatric patients.

The etiology of the fracture risk is not well-understood. Although the nonclinical studies demonstrated a growth effect in juvenile rats (which may or may not be related to a defect in bone formation), the nonclinical studies did not demonstrate any specific bone toxicity. It is possible that the histologic evaluations of bone tissue may not have been adequate to reveal quantitative effects on bone growth and formation or adverse effects on bone quality (e.g., mineralization).

As the etiology of fracture risk and severity of the risk are unknown, we recommend that additional evaluations be conducted. The following section describes the specific recommendations for additional nonclinical and clinical evaluations to further characterize the bone toxicity and fracture risk of entrectinib.

Recommendations Regarding Additional Studies

Nonclinical

These recommended nonclinical studies could help to identify a potential adverse effect of entrectinib on bone metabolism, and perhaps provide information on the mechanism of action of such an effect.

- Conduct a short-term study in young growing rats to determine the effects of entrectinib on longitudinal bone growth and mineralization by static histomorphometry, e.g. in the proximal tibia. (refer to Schenk et al.,1986). Effects on the growth plate, bone and osteoid volume, and trabecular parameters should also be determined in this study.

- Conduct a study of adequate duration (e.g. 2-3 months) to evaluate the effect of entrectinib on bone tissue in young adult rats using bone densitometry, static and dynamic histomorphometry and biomechanical strength testing. Because DXA and areal bone mineral density data may be confounded by entrectinib's potential effects on growth, quantitative computed tomography (QCT) of the long bones may be performed, also because this technique can provide data on both cortical and cancellous bone compartments. Bone mechanical tests should be performed of both cancellous and cortical bone sites, and data on both extrinsic and intrinsic strength parameters, which are independent of bone size, should be obtained. The correlation between bone mineral content (BMC) and bone strength parameters for control vs. treated groups may also provide relevant information.

Clinical

The following assessments should be performed in the ongoing and planned trials of entrectinib in all adult and pediatric patients.

- Initial and serial assessments of bone mineral density (BMD) with dual x-ray absorptiometry (DXA) scans. DXA should be performed every 6-12 months. The DXA scans should analyze areas where there are standardized DXA placement procedures and normative data available for assessment (i.e. lumbar spine, femoral neck, and total hip). Analyses should be based on scans with standard (supine) patient positioning. Adequate quality control measures should be established for DXA scans performed in the trials (as described by Faulkner et al., 1995). Serial DXA scans in patients who are continuing entrectinib therapy will not be as informative as those in patients who are initiating entrectinib therapy (since initiating patients will have a baseline BMD available for comparison). However, serial DXA scans in patients continuing entrectinib could still provide useful information regarding durability of a potential drug effect on BMD.

- Initial and serial serum bone formation and resorption markers (N-terminal propeptide of Type I Collagen [P1NP], osteocalcin, bone-specific alkaline phosphatase [BSAP] and carboxy-terminal cross-linked telopeptides of type 1 collagen [CTX-1]). Because levels vary with time of day and in response to meals, these markers should be measured in standardized conditions, preferably in the morning after an overnight fast. Similar to BMD, markers of bone turnover will be more informative in patients initiating entrectinib, but also may provide useful information regarding durability of a potential drug effect.

- Initial and serial measures of calcium metabolism markers (e.g. vitamin D, parathyroid hormone) to evaluate a potential role of entrectinib in calcium metabolism and skeletal homeostasis.

Additionally, given the potential effect of entrectinib on growth and skeletal formation, we recommend the following additional assessments in pediatric patients in the ongoing and planned entrectinib trials:

- Assessment of linear growth at least every 6 months. Height measurements should be conducted according to recommendations in *Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children*.
- Assessment of potential impairment of bone growth with serial hand/wrist and knee X-rays. With growth impairment, sclerotic lines, usually referred to as growth arrest or "Harris" lines, develop adjacent and parallel to growth plates (Park, 1964; Ogden, 1984). The appearance of these lines may be helpful in assessing possible growth plate effects of entrectinib. These lines typically are not apparent on X-ray until approximately 6 weeks following a triggering event (Jacobson et al., 2012). Therefore, for patients starting entrectinib therapy, initial X-rays should be performed 6 weeks following the entrectinib start date. X-rays should be performed at 6-month intervals and should use a consistent side (left or right) for all scans.

If there continues to be uncertainty regarding the nature of entrectinib's effects on bone tissue after evaluation of adequate data from the abovementioned assessments, peripheral quantitative computed tomography (pQCT) of the distal radius and/or tibia should be considered, as this

assessment would provide more specific information on bone geometry and differential effects on cortical versus trabecular bone compared to DXA. pQCT is not recommended as an initial assessment, however, given the additional burden, radiation exposure and expense associated with this procedure.

Fractures should be included as adverse events of interest in all trial protocols. For any patient who experiences a fracture, a detailed narrative of the event and patient's history should be provided, to include information regarding the underlying fracture risk (e.g., menopausal status, diagnosis of osteoporosis), presence of tumor pathology at the fracture site, and events preceding the fracture (e.g., falls or other injuries).

Labeling Recommendations

At the labeling meeting on July 15, 2019, DOP2 and DBRUP drafted the following text to describe the fracture risk in the Warnings and Precautions section of the USPI:

(b) (4)

References

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/s/

JACQUELINE E KARP
07/24/2019 02:25:13 PM

THERESA E KEHOE
07/24/2019 02:46:41 PM

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07/24/2019 02:57:02 PM

Medical Officer's Review of NDA 212725
Ophthalmology Consult

NDA 212725	Submission Date	December 18, 2019
	Consult Request Date:	May 9, 2019
Consult Review	Review completed:	May 15, 2019

Product Name: ROZLYTREK (entrectinib)

Sponsor: Genentech

Requested:
"In Section 5.4 of label for Entrectinib (ROZLYTREK), the following information will be included.

Section 5.4 Vision Disorders:

(b) (4)

[redacted]

Questions to Consult Team:
1.Please provide input regarding discontinuation/ interruption of drug for vision disorders.
2. Please provide input regarding the ophthalmological evaluations to evaluate vision loss and other vision disorders associated with Entrectinib.

I will also provide the consulting team with a clean version of the most recent label and the Summary of Clinical Safety. We will be sending the first draft of the label to the Applicant next Friday, May 17."

Reported Ocular Adverse Events from all studies (355 patients):

MedDRA Preferred Term		
EYE DISORDERS		
Total number of patients with an event	97	
Total number of events	171	
VISION BLURRED	31	Likely related to dry eye condition
PHOTOPHOBIA	18	Likely related to dry eye condition
DIPLOPIA	11	Likely related to dry eye condition
DRY EYE	10	Likely related to dry eye condition
EYE PAIN	9	Likely related to dry eye condition
VISUAL IMPAIRMENT	7	Likely related to dry eye condition
CATARACT	4	Likely age related
PHOTOPSIA	4	Associated with vitreous detachments, likely age related
VITREOUS FLOATERS	4	Likely age related
CONJUNCTIVITIS ALLERGIC	3	Potential drug related allergic event
PERIORBITAL OEDEMA	3	Potential drug related event
VITREOUS DETACHMENT	3	Likely age related
CONJUNCTIVAL HYPERAEMIA	2	Likely related to dry eye condition
EYE SWELLING	2	Potential drug related event
EYELID OEDEMA	2	Potential drug related event
GLAUCOMA	2	Unlikely to be related
LACRIMATION INCREASED	2	Likely related to dry eye condition
ASTHENOPIA	1	Likely related to dry eye condition
BLINDNESS	1	Attr buted to radiation necrosis of a left parieto-occipital lobe lesion
CATARACT CORTICAL	1	Unlikely to be related
CHALAZION	1	Unlikely to be related
CONJUNCTIVAL HAEMORRHAGE	1	Unlikely to be related
CORNEAL EROSION	1	Likely related to dry eye condition
EYE DISORDER	1	Unknown- single event
EYE IRRITATION	1	Likely related to dry eye condition
EYE PRURITUS	1	Likely related to dry eye condition
HALO VISION	1	Likely related to dry eye condition
KERATITIS	1	Likely related to dry eye condition
LACRIMATION DECREASED	1	Likely related to dry eye condition
MEIBOMIAN GLAND DYSFUNCTION	1	Likely related to dry eye condition
METAMORPHOPSIA	1	Unknown- single event
MYDRIASIS	1	Unknown- single event
PATHOLOGIC MYOPIA	1	Unlikely to be related
PRESBYOPIA	1	Likely to be age related
RETINAL HAEMORRHAGE	1	Unknown- single event
STRABISMUS	1	Unlikely to be drug effect on eye
TRICHIASIS	1	Unknown- single event
VITREOUS ADHESIONS	1	Likely to be age related
XEROPHTHALMIA	1	Likely related to dry eye condition

Reviewer's Comments: *The reported ocular adverse events are mostly suggestive of the product causing signs and symptoms of dry eye syndrome. In addition, there are some allergic type reactions and some periorbital swelling. The majority of the remaining ocular events are typically observed as a result of aging.*

The following information is recommended to be conveyed in the package insert:

(b) (4)

Response to Questions:

1. Please provide input regarding discontinuation/ interruption of drug for vision disorders.

Response: *The vast majority of reported ocular events are likely to be attributed to drug effects causing signs and symptoms of dry eye, periorbital/lid edema, brain metastases or events commonly seen in an older population. Dry eye signs and symptoms can usually be treated with ocular demulcents (artificial tears). Discontinuation of ROZLYTREK is unlikely to be necessary. Brain metastases and events related to aging would not warrant discontinuation of ROZLYTREK. The mechanism of action causing periorital/lid edema is unknown and discontinuation of ROZLYTREK would need to be evaluated on a case by case basis.*

2. Please provide input regarding the ophthalmological evaluations to evaluate vision loss and other vision disorders associated with Entrectinib.

Response: *Slit lamp examinations and visual acuity assessments are the most effective means of monitoring the majority of reported ocular adverse events.*

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/

WILEY A CHAMBERS
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Consultative Review

Subject: Consultation Request
Original NDAs [212725 & 212726]

From: Brian Trummer, MD, PhD (Reviewer)
Division of Neurology Products (DNP), CDER

Through: Nick Kozauer, MD (Associate Director)
Division of Neurology Products, CDER

To: **Kelie Reece, RPM**
Division of Oncology Products 2

Material Reviewed:
-Responses to FDA Request for Information Dated 30 January 2019, IR-07, NDA 212725.
-Responses to FDA Request for Information Dated 23 April 2019, IR-31, NDA 212726
-NDA 212725 & NDA 212726 Entrectinib Mid Cycle Meeting 3/7/2019 Powerpoint
-Section 2.5 Clinical Overview
-Midcycle NDA 212725-6 Clinical Statistical Powerpoint 3/7/2019
-75 days safety update report for Entrectinib 04 March 2019
-Section 2.7.4 Summary of Clinical Safety

Date Received: 12/18/2018

Date Reviewed: 4/11/2019

Background

This document provides responses to questions posed to the Division of Neurology Products (DNP) by the Division of Oncology Products 2 (DOP2) in consultation requests regarding New Drug Application (NDA) reviews for entrectinib for the treatment of metastatic non-small cell lung cancer that is ROS1-positive (NDA 212726) and adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive, (b) (4) or metastatic solid tumors who have either progressed following prior therapies or (b) (4) (b) (4). The focus of the consultation requests relates to the

evaluation and labeling of neurologic adverse events (AEs) that were observed in the development program.

Entrectinib, is a small molecule adenosine triphosphate (ATP) competitive, selective inhibitor of tropomyosin related kinases, ROS1, ALK.

Consult Questions and Answers:

1. Pertaining to the neurological adverse events in this NDA described in the 4 pivotal studies:

a. *Is it possible that these neurological AEs are related to the MOA of the drug entrectinib?*

   Yes, some of the neurological AEs may be related to the mechanism of action of entrectinib. The most common treatment-related adverse events for entrectinib were fatigue/asthenia (46%), dysgeusia (42%), paresthesias (29%), nausea (28%), and myalgias (23%) [1]. Additionally, it appears that the frequent neurologic adverse events of fatigue, dysgeusia, constipation, nausea, and paresthesia were reversible after stopping the drug [2].

   Mechanistically, entrectinib targets TRKA/B/C which are receptors for growth factors such as NGF, BDNF, and NT-3 [3]. BDNF has been shown to have a role in regulating the developmental and mature taste system and maintaining adult hippocampal neurogenesis [4]. In a phase 2 study of alectinib, an anaplastic lymphoma kinase (ALK) inhibitor at 300mg twice daily in 46 patients with ALK-positive NSCLC, a commonly reported adverse event included grade 1 or 2 dysgeusia [5]. Some publications have argued that CNS penetration of a TRKB inhibitor could result in ataxia and other serious neurologic adverse effects [6]. Loratinib, an anaplastic lymphoma kinase (ALK) inhibitor that has pan-TRK as additional targets, has been reported to have neurological adverse events of peripheral neuropathy in 21% [7]. Belizatinib, an ALK inhibitor that has been reported to have Pan-TRK as additional targets, had reported adverse events of fatigue (26.1%), headache (17.4%), decreased appetite (15.2%), asthenia (13%) and dysgeusia (10.9%) [7]. Fatigue and peripheral neuropathy have been reported with other small molecules that target pan-TRK receptors. Therefore, there is significant mechanistic and class effect rationale for how entrectinib could cause a range of neurologic adverse effects.

b. *Do these appears to be class effects, as seen in similar drug larotrectinib?*

   Common nervous system adverse reactions of dizziness (all grades - 28%; Grade 3-4 – 1%) and headache (all grades 14%; no Grade 3-4) are included in Section 6 of the prescribing information (PI) for larotrectinib. Additionally, falls, although not directly attributed to ataxia, were reported in 10% of patients, with one event coded as a Grade 3-4. Additionally, Section 5.1 (Neurotoxicity) of the larotrectinib PI discusses Grade 3 adverse reactions of delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). A Grade 4

encephalopathy was reported in one patient. Additionally, neurologic adverse reactions that lead to dose modification in that development program included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor.

The neurologic AE profile that was observed in the larotrectinib development programs has a significant overlap with the neurologic AE profile observed in the entrectinib program. This observation, along with the mechanistic plausibility discussed in the response to Question 1a, suggest potential class effects.

c. *Is there evidence to suggest whether or not these neurological AEs are related to the presence of CNS metastatic disease?*

Appendix 1 and Appendix 2 adapted from an IR response from the sponsor present the frequency for each neurological adverse event in those with metastatic disease compared with those without metastatic disease, as well as a breakdown by prior radiation therapy status.

These data suggest that many of the reported adverse reactions are present in similar incidence rates regardless of the presence of brain metastases at enrollment. Two adverse reactions, dysgeusia and paresthesia occur at somewhat higher rates in patients without CNS metastatic disease at baseline. Mechanistically, it is unclear why these adverse reactions would be elevated in patients without CNS metastasis.

It is well known that treatments with brain radiation results in progressive impairment in memory, executive functions, and attention [8]. Therefore, identifying which patients received prior radiation therapy vs those that did not may further assist in determining if cognitive disorder is associated with drug treatment or something else, such as metastasis or radiation therapy. As seen in Appendix 2, five adverse reactions: dizziness, headache, paresthesia, balance disorder, and confusional state occur at somewhat higher rates in those patients with CNS metastasis at baseline who had prior radiation therapy relative to those with CNS metastasis at baseline who did not receive prior radiation therapy. In the USPI Response Document for 212726, comment 8, in response to cognitive disorders, “adult patients who had brain metastases at baseline had an overall higher frequency (39%) of these events when compared to those without (24.9%).” It is plausible that some of the increased incidence in cognitive disorders in patients with brain metastases at baseline may be due to their receiving prior radiation (elevating confusional state to 11.1% vs 4.2% in those not receiving prior radiation).

Taken together, in answering your question, it would appear that presence of CNS metastatic disease itself is not driving the finding of neurological AEs. Rather, neurological AEs are potentially drug-related, and some AEs occurring at higher rates in those with CNS metastasis previously treated with radiation therapy.

d. *Do the composite terms to subdivide nervous system effects into cognitive vs psychiatric AEs appear rational? Why or why not?*

The proposed groupings are generally acceptable. However, upon reviewing the tables from 20190208-NDA 212725 Response to IR07 Clinical questions, the terms “confusional state” and “mental status changes” should be moved from Psychiatric Disorders to Neurological Disorders.

e. *Do you have further recommendations to reclassify the AE terms related to the nervous system*

The application groups nervous system AE terms under the following categories: 1) Cognitive disorders AEs 2) Peripheral sensory neuropathy AEs 3) Dysesthesia AEs 4) Ataxia AEs, and 5) Syncope. Falls also occur in 8.4% of treated patients. These groupings, as well as the terms that are included in each category, are generally acceptable; however, we would suggest altering the components of cognitive disorders (discussed below) and including an evaluation of impaired taste (discussed below).

Cognitive Disorders:

Currently, the primary review team is using the following preferred terms for cognitive disorder: confusional state, somnolence, cognitive disorder, insomnia, disturbance in attention, memory impairment, psychomotor retardation, psychomotor skills impaired.

For reference, the following table, reproduced from the application, presents the applicant’s analyses of cognitive disorders:

Table 13 Overview of Cognitive Disorders Adverse Events (Safety Population)

MedDRA Preferred Term	NCI-CTCAE Grade	NTRK- Adult (N= 68)	ROS1 NSCLC-Adult (N= 134)	Other Adult (N= 137)	Pediatric (N= 16)	Total (N= 355)
Cognitive disorder	All	3 (4.4%)	11 (8.2%)	14 (10.2%)	0	28 (7.9%)
	1	2 (2.9%)	5 (3.7%)	10 (7.3%)	0	17 (4.8%)
	2	0	4 (3.0%)	2 (1.5%)	0	6 (1.70%)
	3	1 (1.5%)	2 (1.5%)	2 (1.5%)	0	5 (1.40%)
Confusional state	All	7 (10.3%)	8 (6.0%)	11 (8.0%)	0	26 (7.3%)
	1	6 (8.8%)	4 (3.0%)	7 (5.1%)	0	17 (4.8%)
	2	0	3 (2.2%)	2 (1.5%)	0	5 (1.4%)
	3	1 (1.5%)	1 (0.7%)	2 (1.5%)	0	4 (1.1%)
Disturbance in attention	All	4 (5.9%)	6 (4.5%)	6 (4.4%)	1 (6.3%)	17 (4.8%)
	1	4 (5.9%)	6 (4.5%)	5 (3.6%)	1 (6.3%)	16 (4.5%)
	3	0	0	1 (0.7%)	0	1 (0.3%)
Memory impairment	All	3 (4.4%)	9 (6.7%)	1 (0.7%)	0	13 (3.7%)
	1	2 (2.9%)	8 (6.0%)	1 (0.7%)	0	11 (3.1%)
	2	1 (1.5%)	1 (0.7%)	0	0	2 (0.6%)
Amnesia	All	1 (1.5%)	5 (3.7%)	3 (2.2%)	0	9 (2.5%)
	1	1 (1.5%)	5 (3.7%)	3 (2.2%)	0	9 (2.5%)
Mental status changes	All	2 (2.9%)	2 (1.5%)	2 (1.5%)	0	6 (1.7%)
	1	1 (1.5%)	0	0	0	1 (0.3%)
	3	1 (1.5%)	2 (1.5%)	2 (1.5%)	0	5 (1.4%)
Mental disorder	All	0	1 (0.7%)	0	0	1 (0.3%)
	1	0	0	0	0	0
	2	0	0	0	0	0
	3	0	1 (0.7%)	0	0	1 (0.3%)
Hallucination	All	0	2 (1.5%)	2 (1.5%)	0	4 (1.1%)
	1	0	2 (1.5%)	1 (0.7%)	0	3 (0.8%)
	2	0	0	1 (0.7%)	0	1 (0.3%)
Delirium	All	0	1 (0.7%)	2 (1.5%)	0	3 (0.8%)
	1	0	0	2 (1.5%)	0	2 (0.6%)
	3	0	1 (0.7%)	0	0	1 (0.3%)
Hallucination, visual	All	1 (1.5%)	0	0	0	1 (0.3%)
	1	1 (1.5%)	0	0	0	1 (0.3%)

Note: Entrectinib- cognitive impairment AEGT were utilized to capture potential events of interest of cognitive disorders AE. Entrectinib- cognitive impairment AEGT include the PTs of altered state of consciousness, amnesia, amnestic disorder, cognitive disorder, confusional state, delirium, disorientation, disturbance in attention, hallucination, hallucination auditory, hallucination visual, hallucinations mixed, impaired reasoning, incoherent, judgement impaired, memory impairment, mental disorder, mental impairment, mental status changes.

The cognitive disorders grouping should include the MedDRA preferred terms of: cognitive disorder, memory impairment, disturbance in attention, aphasia, amnesia. The preferred terms of confusional state, delirium and mental status change, current coded as psychiatric adverse events, are also most appropriately grouped with cognitive disorders. We would recommend not including déjà vu, somnolence, insomnia, psychomotor retardation, and psychomotor skills impaired in cognitive disorders grouping. Also, the terms hallucination, and hallucination visual should be removed from the cognitive disorders grouping. Whether the vague term of mental disorder would be appropriate to include in

the cognitive disorders grouping is unclear and would depend upon the nature of the preferred terms.

Impaired Taste:
Dysgeusia is also a relevant neurologic AE that was observed in the development program at a high rate and should be presented in labeling. An analysis of impaired taste should be conducted to include a grouping of the MedDRA terms ageusia, hypogeusia, and dysgeusia. Of note, it is interesting that anosmia was apparently not reported in the development program given the high rate of dysgeusia, as anosmia is known to contribute to dysgeusia in many instances. We recommend considering asking the applicant if they are aware of any association with its drug and anosmia that were not described in the application.

We speculate that anosmia may have been indirectly captured by dysgeusia as taste has a significant olfactory component. Anosmia can result in significant hazards, ranging from burning pots or pans to ingesting spoiled food and inability to detect a gas leak[9]. Although there is insufficient evidence to support describing this risk in labeling, we would recommend the consideration of a prospective assessment of anosmia in the future development of this product for other indications.

2. Do you have any recommendations regarding conveying the risk of neurological AEs in product labeling?

We would recommend using a consistent approach to the presentation of neurologic AEs as was used for the larotrectinib PI, particularly given the presumed class effects of these drugs. The most serious AEs could be similar described in Section 5 (to include patients with Grade 3-4 AEs, patients discontinuing, and patients requiring dose reductions), with the common neurologic AE profile presented in Section 6.

3. Is there additional information that DOP2 should ask for during the NDA review?

We have no additional recommendations at this time.

4. Are there postmarketing safety surveillance or risk mitigation strategies DOP2 should consider?

We do not have any current recommendations for additional safety surveillance or risk mitigation strategies beyond clear labeling that describes the potential for the risk of neurologic AEs, as discussed in this review.

References:

1. Drilon, A., et al., *Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1).* Cancer discovery, 2017. **7**(4): p. 400-409.
2. Iyer, R., et al., *Entrectinib is a potent inhibitor of Trk-driven neuroblastomas in a xenograft mouse model.* Cancer letters, 2016. **372**(2): p. 179-186.
3. Liu, D., et al., *Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of NTRK, ROS1, and ALK fusion-positive solid tumors.* Therapeutics and clinical risk management, 2018. **14**: p. 1247-1252.
4. Meng, L., et al., *Targeting the BDNF/TrkB pathway for the treatment of tumors.* Oncology letters, 2019. **17**(2): p. 2031-2039.
5. Awad, M.M. and A.T. Shaw, *ALK inhibitors in non-small cell lung cancer: crizotinib and beyond.* Clinical advances in hematology & oncology : H&O, 2014. **12**(7): p. 429-439.
6. Morgensztern, D., et al., *Molecularly targeted therapies in non-small-cell lung cancer annual update 2014.* J Thorac Oncol, 2015. **10**(1 Suppl 1): p. S1-63.
7. Le, T. and D.E. Gerber, *ALK alterations and inhibition in lung cancer.* Seminars in cancer biology, 2017. **42**: p. 81-88.
8. Greene-Schloesser, D., et al., *Radiation-induced brain injury: A review.* Frontiers in oncology, 2012. **2**: p. 73-73.
9. Santos, D.V., et al., *Hazardous events associated with impaired olfactory function.* Arch Otolaryngol Head Neck Surg, 2004. **130**(3): p. 317-9.

Appendix 1: Nervous System Disorders and Psychiatric Disorders by Investigator CNS Disease at Baseline

MedDRA System Organ Class MedDRA Preferred Term	Patients without CNS Disease at Baseline (N=217)	Patients with CNS Disease at Baseline (N=138)
Total number of patients with at least one adverse event	192 (88.5%)	116 (84.1%)
Overall total number of events	728	512
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	185 (85.3%)	112 (81.2%)
Total number of events	643	434
DYSGEUSIA	108 (49.8%)	47 (34.1%)
DIZZINESS	74 (34.1%)	49 (35.5%)
PARAESTHESIA	52 (24.0%)	21 (15.2%)
HEADACHE	38 (17.5%)	25 (18.1%)
NEUROPATHY PERIPHERAL	19 (8.8%)	12 (8.7%)
PERIPHERAL SENSORY NEUROPATHY	20 (9.2%)	9 (6.5%)
COGNITIVE DISORDER	16 (7.4%)	12 (8.7%)
SOMNOLENCE	16 (7.4%)	10 (7.2%)
BALANCE DISORDER	11 (5.1%)	14 (10.1%)
HYPERAESTHESIA	12 (5.5%)	12 (8.7%)
ATAXIA	8 (3.7%)	9 (6.5%)
DISTURBANCE IN ATTENTION	13 (6.0%)	4 (2.9%)
HYPOAESTHESIA	8 (3.7%)	7 (5.1%)
SYNCOPE	7 (3.2%)	7 (5.1%)
MEMORY IMPAIRMENT	6 (2.8%)	7 (5.1%)
AMNESIA	3 (1.4%)	6 (4.3%)
DYSARTHRIA	6 (2.8%)	3 (2.2%)
TREMOR	5 (2.3%)	4 (2.9%)
APHASIA	2 (0.9%)	6 (4.3%)
SEIZURE	1 (0.5%)	7 (5.1%)
PRESYNCOPE	3 (1.4%)	3 (2.2%)
PERIPHERAL MOTOR NEUROPATHY	5 (2.3%)	0
DYSAESTHESIA	2 (0.9%)	2 (1.4%)
HYDROCEPHALUS	0	4 (2.9%)
HYPERSOMNIA	2 (0.9%)	2 (1.4%)

Investigator text for AEs encoded using MedDRA v21.0.
Patients with investigator CNS disease at baseline include patients with primary brain tumor and patients with CNS metasta

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MedDRA System Organ Class MedDRA Preferred Term	Patients without CNS Disease at Baseline (N=217)	Patients with CNS Disease at Baseline (N=138)
BRAIN OEDEMA	0	3 (2.2%)
DIZZINESS POSTURAL	3 (1.4%)	0
DYSKINESIA	0	3 (2.2%)
FACIAL PARALYSIS	0	3 (2.2%)
HEMIPARESIS	0	3 (2.2%)
AGEUSIA	1 (0.5%)	1 (0.7%)
ALLODYNIA	1 (0.5%)	1 (0.7%)
MIGRAINE	2 (0.9%)	0
NEURALGIA	2 (0.9%)	0
SCIATICA	1 (0.5%)	1 (0.7%)
AKATHISIA	1 (0.5%)	0
APHONIA	1 (0.5%)	0
ASTERIXIS	0	1 (0.7%)
AUTONOMIC NERVOUS SYSTEM IMBALANCE	0	1 (0.7%)
CAUDA EQUINA SYNDROME	0	1 (0.7%)
CEREBELLAR ATAXIA	1 (0.5%)	0
CEREBRAL HAEMORRHAGE	0	1 (0.7%)
CEREBRAL INFARCTION	0	1 (0.7%)
CEREBROVASCULAR ACCIDENT	1 (0.5%)	0
CERVICOBRACHIAL SYNDROME	0	1 (0.7%)
DEPRESSED LEVEL OF CONSCIOUSNESS	0	1 (0.7%)
DIZZINESS EXERTIONAL	1 (0.5%)	0
DYSGRAPHIA	0	1 (0.7%)
DYSMETRIA	0	1 (0.7%)
ENCEPHALOPATHY	0	1 (0.7%)
FINE MOTOR SKILL DYSFUNCTION	1 (0.5%)	0
GENERALISED TONIC-CLONIC SEIZURE	0	1 (0.7%)
HYPOGEUSIA	1 (0.5%)	0
HYPOSMIA	1 (0.5%)	0
LIMBIC ENCEPHALITIS	0	1 (0.7%)
METABOLIC ENCEPHALOPATHY	1 (0.5%)	0
MYOCLONUS	1 (0.5%)	0

Investigator text for AEs encoded using MedDRA v21.0.
Patients with investigator CNS disease at baseline include patients with primary brain tumor and patients with CNS metastas

MedDRA System Organ Class MedDRA Preferred Term	Patients without CNS Disease at Baseline (N=217)	Patients with CNS Disease at Baseline (N=138)
NERVOUS SYSTEM DISORDER	0	1 (0.7%)
PERONEAL NERVE PALSY	1 (0.5%)	0
PHRENIC NERVE PARALYSIS	1 (0.5%)	0
PSYCHOMOTOR SKILLS IMPAIRED	0	1 (0.7%)
RESTLESS LEGS SYNDROME	1 (0.5%)	0
SENSORY DISTURBANCE	0	1 (0.7%)
SPINAL CORD COMPRESSION	1 (0.5%)	0
TRIGEMINAL NEURALGIA	0	1 (0.7%)
VASOGENIC CEREBRAL OEDEMA	0	1 (0.7%)
VISUAL FIELD DEFECT	1 (0.5%)	0

Investigator text for AEs encoded using MedDRA v21.0.
Patients with investigator CNS disease at baseline include patients with primary brain tumor and patients with CNS metas

MedDRA System Organ Class MedDRA Preferred Term	Patients without CNS Disease at Baseline (N=217)	Patients with CNS Disease at Baseline (N=138)
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	51 (23.5%)	40 (29.0%)
Total number of events	85	78
CONFUSIONAL STATE	14 (6.5%)	12 (8.7%)
INSOMNIA	16 (7.4%)	8 (5.8%)
ANXIETY	8 (3.7%)	9 (6.5%)
DEPRESSION	4 (1.8%)	6 (4.3%)
AGITATION	4 (1.8%)	3 (2.2%)
MENTAL STATUS CHANGES	0	6 (4.3%)
LIBIDO DECREASED	3 (1.4%)	2 (1.4%)
HALLUCINATION	0	4 (2.9%)
DELIRIUM	1 (0.5%)	2 (1.4%)
IRRITABILITY	2 (0.9%)	1 (0.7%)
MOOD SWINGS	0	2 (1.4%)
ABNORMAL DREAMS	1 (0.5%)	0
AFFECT LABILITY	0	1 (0.7%)
AFFECTIVE DISORDER	0	1 (0.7%)
CATATONIA	1 (0.5%)	0
COMPLETED SUICIDE	1 (0.5%)	0
DEJA VU	1 (0.5%)	0
DEPRESSED MOOD	0	1 (0.7%)
ENURESIS	0	1 (0.7%)
EUPHORIC MOOD	1 (0.5%)	0
HALLUCINATION, VISUAL	1 (0.5%)	0
MENTAL DISORDER	0	1 (0.7%)
MOOD ALTERED	1 (0.5%)	0
NIGHTMARE	1 (0.5%)	0
PERSISTENT DEPRESSIVE DISORDER	1 (0.5%)	0
PSYCHOMOTOR RETARDATION	1 (0.5%)	0
SLEEP DISORDER	1 (0.5%)	0
STARING	1 (0.5%)	0

Investigator text for AEs encoded using MedDRA v21.0.
Patients with investigator CNS disease at baseline include patients with primary brain tumor and patients with CNS

Appendix 2: Nervous System Disorders and Psychiatric Disorders by Prior CNS Radiation, patients with Investigator CNS Disease at Baseline

MedDRA System Organ Class MedDRA Preferred Term	Prior Radiation Therapy (all) (N=90)	No Prior Radiation Therapy (N=48)
Total number of patients with at least one adverse event	76 (84.4%)	40 (83.3%)
Overall total number of events	399	113
NERVOUS SYSTEM DISORDERS		
Total number of patients with at least one adverse event	74 (82.2%)	38 (79.2%)
Total number of events	334	100
DIZZINESS	34 (37.8%)	15 (31.3%)
DYSGEUSIA	31 (34.4%)	16 (33.3%)
HEADACHE	19 (21.1%)	6 (12.5%)
PARAESTHESIA	18 (20.0%)	3 (6.3%)
BALANCE DISORDER	12 (13.3%)	2 (4.2%)
COGNITIVE DISORDER	8 (8.9%)	4 (8.3%)
HYPERAESTHESIA	7 (7.8%)	5 (10.4%)
NEUROPATHY PERIPHERAL	8 (8.9%)	4 (8.3%)
SOMNOLENCE	8 (8.9%)	2 (4.2%)
ATAXIA	5 (5.6%)	4 (8.3%)
PERIPHERAL SENSORY NEUROPATHY	4 (4.4%)	5 (10.4%)
HYPOAESTHESIA	7 (7.8%)	0
MEMORY IMPAIRMENT	5 (5.6%)	2 (4.2%)
SEIZURE	6 (6.7%)	1 (2.1%)
SYNCOPE	6 (6.7%)	1 (2.1%)
AMNESIA	3 (3.3%)	3 (6.3%)
APHASIA	5 (5.6%)	1 (2.1%)
DISTURBANCE IN ATTENTION	4 (4.4%)	0
HYDROCEPHALUS	3 (3.3%)	1 (2.1%)
TREMOR	2 (2.2%)	2 (4.2%)
BRAIN OEDEMA	1 (1.1%)	2 (4.2%)
DYSARTHRIA	3 (3.3%)	0
DYSKINESIA	3 (3.3%)	0
FACIAL PARALYSIS	3 (3.3%)	0
HEMIPARESIS	2 (2.2%)	1 (2.1%)
PRESYNCOPE	3 (3.3%)	0

Investigator text for AEs encoded using MedDRA v21.0.
Patients with investigator CNS disease at baseline include patients with primary brain tumor and patients with CNS metastases.

MedDRA System Organ Class MedDRA Preferred Term	Prior Radiation Therapy (all) (N=90)	No Prior Radiation Therapy (N=48)
DYSAESTHESIA	2 (2.2%)	0
HYPERSOMNIA	2 (2.2%)	0
AGEUSIA	1 (1.1%)	0
ALLODYNIA	1 (1.1%)	0
ASTERIXIS	0	1 (2.1%)
AUTONOMIC NERVOUS SYSTEM IMBALANCE	0	1 (2.1%)
CAUDA EQUINA SYNDROME	1 (1.1%)	0
CEREBRAL HAEMORRHAGE	0	1 (2.1%)
CEREBRAL INFARCTION	0	1 (2.1%)
CERVICOBRACHIAL SYNDROME	1 (1.1%)	0
DEPRESSED LEVEL OF CONSCIOUSNESS	1 (1.1%)	0
DYSGRAPHIA	0	1 (2.1%)
DYSMETRIA	1 (1.1%)	0
ENCEPHALOPATHY	1 (1.1%)	0
GENERALISED TONIC-CLONIC SEIZURE	1 (1.1%)	0
LIMBIC ENCEPHALITIS	0	1 (2.1%)
NERVOUS SYSTEM DISORDER	1 (1.1%)	0
PSYCHOMOTOR SKILLS IMPAIRED	1 (1.1%)	0
SCIATICA	1 (1.1%)	0
SENSORY DISTURBANCE	1 (1.1%)	0
TRIGEMINAL NEURALGIA	1 (1.1%)	0
VASOGENIC CEREBRAL OEDEMA	1 (1.1%)	0

Investigator text for AEs encoded using MedDRA v21.0.
Patients with investigator CNS disease at baseline include patients with primary brain tumor and patients with CNS metastases.

MedDRA System Organ Class MedDRA Preferred Term	Prior Radiation Therapy (all) (N=90)	No Prior Radiation Therapy (N=48)
PSYCHIATRIC DISORDERS		
Total number of patients with at least one adverse event	29 (32.2%)	11 (22.9%)
Total number of events	65	13
CONFUSIONAL STATE	10 (11.1%)	2 (4.2%)
ANXIETY	7 (7.8%)	2 (4.2%)
INSOMNIA	6 (6.7%)	2 (4.2%)
DEPRESSION	5 (5.6%)	1 (2.1%)
MENTAL STATUS CHANGES	4 (4.4%)	2 (4.2%)
HALLUCINATION	3 (3.3%)	1 (2.1%)
AGITATION	3 (3.3%)	0
DELIRIUM	2 (2.2%)	0
LIBIDO DECREASED	2 (2.2%)	0
MOOD SWINGS	2 (2.2%)	0
AFFECT LABILITY	1 (1.1%)	0
AFFECTIVE DISORDER	0	1 (2.1%)
DEPRESSED MOOD	0	1 (2.1%)
ENURESIS	1 (1.1%)	0
IRRITABILITY	1 (1.1%)	0
MENTAL DISORDER	1 (1.1%)	0

Investigator text for AEs encoded using MedDRA v21.0.
Patients with investigator CNS disease at baseline include patients with primary brain tumor and patients with CNS metastases.

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/

KELIE M REECE
05/03/2019 08:38:16 PM