CENTER FOR DRUG EVALUATION AND RESEARCH

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OTHER REVIEW(S)

Department of Health and Human Services

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Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology Review (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Review of Study Report No WO40977:

Comparative analysis of ROS1-positive locally advanced or metastatic non-small cell lung cancer between patients treated in entrectinib trials and crizotinib treated patients from real world data

Date:	11 July 2019
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Drug Name(s):	Entrectinib
Subject	Review of the sponsor's final study report comparing clinical trial data to real world data
Application Type/Number:	NDA 212725
Applicant/sponsor:	(b) (4)
OSE RCM #:	2019-730

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LIST OF ABBREVIATIONS

ALK	Anaplastic Lymphoma Kinase
ALKA	ALKA-372-001: "*A phase 1, dose escalation study of entrectinib in adult patients with advanced / metastatic solid tumors*"
BICR	Blinded Independent Central Review
BMI	Body Mass Index
CNS	Central Nervous System
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DEPI	Division of Epidemiology
DOP	Division of Oncology Products
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
IPTW	Inverse Probability of Treatment Weighting
IQR	Interquartile Range
ISE	Integrated Summary of Efficacy
LOT	Lines of Therapy
NOS	Not Otherwise Specified
NSCLC	Non-Small Cell Lung Cancer
NTRK	Neurotropic Tyrosine Kinase
OS	Overall Survival
PFS	Progression Free Survival
QTc	Corrected QT Interval
RWD	Real-World Data
RWE	Real-World Evidence
SD	Standard Deviation
STARTRK-1	RXDX-101-01: "*A phase 1, multicenter, open-label study of oral entrectinib in adult patients with locally advanced or metastatic cancer confirmed to be positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK*"
STARTRK-2	RXDX-101-02: "*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 NTRK 1/2/3, ROS1, or ALK gene rearrangements*"
TTD	Time to Treatment Discontinuation
ULN	Upper Limit of Normal
USA	United States of America

EXECUTIVE SUMMARY

The Division of Oncology Products 2 (DOP2) in the Office of Hematology and Oncology Products (OHOP) consulted the Division of Epidemiology 1 (DEPI) in the Office of Surveillance and Epidemiology (OSE) to review final study report number WO40977, titled "*Comparative analysis of ROS1-positive locally advanced or metastatic non-small cell lung cancer between patients treated in entrectinib trials and crizotinib treated patients from real world data."* DEPI's review of this study report is contained within this document.

This study report compares 53 patients with ROS1-positive NSCLC receiving entrectinib in three single arm clinical trials (ALKA, STARTRK-1, STARTRK-2) and 69 patients with ROS1-positive NSCLC receiving crizotinib in the real world captured by the Flatiron Health Analytic Database. It contains a comparative analysis of time to treatment discontinuation (TTD), progression free survival (PFS), and overall survival (OS).

The primary objectives in DEPI's review of this study report were to address the following two questions: 1) Is the Crizotinib RWE arm sufficient to establish the natural history of disease for ROS1-positive NSCLC? 2) Does the study methodology provided allow for a comparison of treatment outcomes between the entrectinib arm and crizotinib arm in this study?

In review of the first objective, DEPI concluded that the crizotinib arm is unlikely to be generalizable to the entire population of patients with ROS1-positive NSCLC. Its generalizability was limited by the low rate of ROS1 testing in clinical practice and resultant sensitivity (estimated as 15%-30%) and the high proportion of community-treated patients in the selected data source. Additionally, examination of baseline characteristics demonstrates that the crizotinib arm is not sufficiently comparable to the entrectinib clinical trial population.

In review of the second objective, this study identified substantial differences in TTD, PFS, and OS between study arms, all favoring the entrectinib arm. However, differentially implemented study eligibility criteria, resultant differences in baseline criteria, and limitations in statistical modeling due to low sample size make it difficult to determine what proportion of the observed differences in rates of clinical outcomes are due to imbalances in study populations at baseline (i.e. selection bias) versus differential treatment effects of the study drugs. This limits comparison of study arms. Additionally, despite a well-done attempt at defining treatment outcomes, there were limitations. TTD is complicated by treatment beyond disease progression, PFS is limited by missingness in radiographic imaging within electronic medical record data, and OS may be more subject to bias from baseline imbalances.

Based on this review, DEPI provides the following recommendations: 1) While the crizotinib population identified may be representative to patients who currently receive treatment for ROS1-positive NSCLC in the community setting, it is not generalizability to the entire ROS1-positive NSCLC population and it is not generalizable to patients enrolled in entrectinib clinical trials. 2) This study report is not adequate to allow a robust comparison of treatment outcomes between crizotinib and entrectinib study arms. 3) The Applicant should be advised to submit an *a priori* study protocol for future studies, as the current analyses will be considered post-hoc.

**** The final study report has not been submitted to FDA, which is expected to contain multiple secondary and sensitivity analyses. Given the small sample size, it is not expected the final report will containing meaningfully different conclusions from the interim report. A date has not been provided for submission of the final report.*

1 INTRODUCTION

The Division of Oncology Products 2 (DOP2) in the Office of Hematology and Oncology Products (OHOP) consulted the Division of Epidemiology 1 (DEPI) in the Office of Surveillance and Epidemiology (OSE) to review final study report number WO40977, titled "*Comparative analysis of ROS1-positive locally advanced or metastatic non-small cell lung cancer between patients treated in entrectinib trials and crizotinib treated patients from real world data."* The review additionally addresses the following scientific questions:

1. Is the Crizotinib RWE arm sufficient to establish the natural history of disease for ROS1-positive NSCLC?
2. Does the study methodology provided allow for a comparison of treatment outcomes between the entrectinib arm and crizotinib arm in this study?

DEPI's review of this study report is contained within this document.

1.1 BACKGROUND

Lung cancer is the leading cause of cancer-related mortality worldwide. ROS1 is a therapeutic target for medical treatment, present in 1%-2% of patients with non-small cell lung cancer (NSCLC) [Clave S et al, 2016; Stransky N et al, 2014; CSR WO40977]. Crizotinib is currently the only approved ROS1 inhibitor approved for NSCLC in the United States (approved for ROS1-positive NSCLC in March 2016). Entrectinib is a new oral inhibitor of ROS1 with data from three single arm clinical trials.

1.2 REGULATORY HISTORY

The regulatory history for entrectinib (NDA 212725) is described below:

- The Investigational New Drug (IND) application was submitted to FDA in March 2014 (IND #135124)
- Orphan Drug Designation was granted in February 2015
- Priority review was granted in February 2019

Of note, FDA is concurrently reviewing a separate submission (NDA 202726) for entrectinib with the indication of "NTRK fusion-positive solid tumors." RWE was not submitted for NDA 202726.

1.3 PRODUCT LABELLING

This RWE study report was provided as additional clinical data to support an indication for entrectinib of "*Treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive.*"

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS TO BE REVIEWED

- Study report WO40977 titled "*Comparative analysis of ROS1-positive locally advanced or metastatic non-small cell lung cancer between patients treated in entrectinib trials and crizotinib treated patients from real world data.*"
- The following three study reports were also reviewed specifically for study eligibility criteria:
    - ALKA-372-001 (ALKA): "*A phase 1, dose escalation study of entrectinib in adult patients with advanced / metastatic solid tumors*"
    - RXDX-101-01 (STARTRK-1): "*A phase 1, multicenter, open-label study of oral entrectinib in adult patients with locally advanced or metastatic cancer confirmed to be positive for NTRK1, NTRK2, NTRK3, ROS1, or ALK*"
    - RXDX-101-02 (STARTRK-2): "*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 NTRK 1/2/3, ROS1, or ALK gene rearrangements*"

2.2 CRITERIA APPLIED TO REVIEW

The reviewer used the following guidelines for reference in review of this study report:

(1) FDA Guidance. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices [FDA, 2017]

(2) FDA Guidance. Best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data [FDA, 2013]

(3) FDA Guidance. E 10 Choice of Control Group and Related Issues in Clinical Trials [FDA 2011].

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

This study report contains a comparative analysis of time to treatment discontinuation (TTD), progression free survival (PFS), and overall survival (OS). It compares patients with ROS1-positive NSCLC receiving entrectinib in three single arm clinical trials (ALKA, STARTRK-1, STARTRK-2) and patients with ROS1-positive NSCLC receiving crizotinib in the real world captured by the Flatiron Health Analytic Database.

3.2 STUDY OBJECTIVES

Objectives from Applicant's CSR (page 11 of WO40977)

The primary objective for this study was to perform a comparative analysis between crizotinib and entrectinib among ROS1-positive NSCLC patients using TTD as the primary endpoint.

The secondary objectives for this study were as follows:

- To characterize the demographics, clinical characteristics, and treatment sequences of ROS1-positive NSCLC patients in the real world including those who have been exposed to crizotinib.
- To compare overall survival (OS) and progression-free survival (PFS) between the crizotinib population and the entrectinib populations where appropriate.
- To describe the demographics, clinical characteristics, and outcomes of the ROS1-positive NSCLC patients with and without central nervous system (CNS) metastases at baseline (including time to CNS progression).

  DEPI's Comments

  The primary purpose of DEPI's review is to assess whether the crizotinib RWE arm in Flatiron can be used to approximate the natural history of disease for patients with ROS1-positive NSCLC.

  Given that establishing the natural history of disease for ROS1-positive NSCLC indirectly lends itself to informal comparisons with entrectinib clinical trial patients, DEPI also provides a review of the comparability of these study populations as a secondary aim of this review. However, interpretation of the hazard ratios generated by Cox Proportional Hazard Models were outside the scope of this review.

  Also of note, the third bullet in the Applicant's secondary objectives has not yet been completed or submitted to FDA, and therefore, is not reviewed by DEPI.

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

This was a retrospective study using secondary data, comparing the following two arms of patients with ROS1-positive NSCLC:

- Patients who received entrectinib integrated from three open-label single arm trials (ALKA, STARTRK-1, STARTRK-2); the entrectinib arm.
- Patients who received crizotinib, within the Flatiron Health Analytic Database, a United States RWE source based on electronic medical records from oncology community centers; the crizotinib arm.

3.3.1.2 Population, Data Source & Time Period

Table 1: Study Arm, Study Population, Data Source/Study Design, and Time Period for included data sources

Study Arm / Protocol No.	Study Population	Data Source / Study Design	Time Period
Entrectinib Arm[1]			
ALKA-372-001 (ALKA)	Advanced/metastatic solid tumors including patients with TRKA/B/C, ROS1, or ALK molecular alterations	Phase I, multicenter, open-label clinical trial	Enrolling 19 December 2013 through 2 November 2015
RXDX-101-01 (STARTRK-1)	Solid tumors with NTRK 1/2/3, ROS1, or ALK molecular alterations	Phase I, multicenter, open-label clinical trial	Enrolling 23 June 2015 Through 5 February 2016
RXDX-101-02 (STARTRK-2)	Patients (≥18 years of age) with advanced or metastatic solid tumors that harbor an NTRK 1/2/3, ROS1, or ALK gene rearrangement	Registration-enabling Phase II, global, multicenter, open-label, basket study	Enrolling 3 October 20176 Through 28 April 2017
Crizotinib Arm			
WO40977 (Flatiron RWE)	Patients with ROS1-positive NSCLC in the real-world	Flatiron Health Analytic Database, including 265 community-based clinics and 3 academic networks in the US	Diagnosed 1 January 2011 Through 30 June 2018

[1] While entrectinib clinical trials included multiple molecular alterations, only patients with ROS1-positive NSCLC from entrectinib clinical trials were included in this clinical study report.

* Data from Table 4 of CSR WO40977

3.3.1.3 Selection, Inclusion and Exclusion Criteria

Select differences in eligibility criteria between individual entrectinib clinical trials and the crizotinib flatiron RWE study arm are shown in Table 2 below.

Table 2: Comparison of study eligibility criteria for data sources in the entrectinib arm and crizotinib arm

Eligibility Criteria	ALKA (entrectinib)	STARTRK-1 (entrectinib)	STARTRK-2 (entrectinib)	Flatiron RWE (crizotinib)
ROS1 Testing Method	NGS Testing	NGS Testing	NGS Testing	NGS, fluorescence in situ hybridization, or immunochemistry
ECOG	ECOG <2	ECOG <2	ECOG <2	ECOG <2; patients with missing ECOG were included (55.1% missing)
Live Expectancy	At least 3 months	At least 3 months	At least 4 weeks	No Exclusion
Absolute Neutrophil Count	≥1500/mm^3	≥1500/mm^3	No Exclusion	No Exclusion
Platelets	≥100,000/mm^3	≥100,000/mm^3	No Exclusion	No Exclusion
Hemoglobin	>9.0 g/dL	>9.0 g/dL	No Exclusion	No Exclusion

Serum Creatinine / Creatinine Clearance	≤1.5 ULN / >60 mL/min	Within normal limits / >40 mL/min	No Exclusion	No Exclusion
Total Bilirubin	≤1.5 ULN	≤1.5 ULN	≤2 ULN	No Exclusion
Liver Transaminases (AST/ALT)	≤2.5 ULN; ≤5 ULN if liver metastasis are present	≤2.5 ULN; ≤5 ULN if liver metastasis are present	≤3 ULN; ≤5 ULN if metastasis are present	No Exclusion
Alkaline phosphatase	≤2.5 ULN; ≤5 ULN if liver and/or bone metastasis are present	≤2.5 ULN; ≤5 ULN if liver and/or bone metastasis are present	No Exclusion	No Exclusion
Amylase and Lipase	Within the ULN	No exclusion	No Exclusion	No Exclusion
Pregnancy	Negative within 7 days of treatment initiation	Negative within 7 days of treatment initiation	Negative test	No Exclusion
Serum calcium, magnesium, and potassium	No exclusion	Normal or ≤CTCAE grade 1 with or without supplementation	No Exclusion	No Exclusion
Prior cancer	Excluded within the prior 5 years	Excluded if required therapy within prior 3 years	Excluded prior cancers that would interfere with determination of efficacy	No Exclusion

Prior crizotinib	Allowed[1]	Allowed[1]	Not Allowed, unless presenting with CNS-only progression	Not Allowed
CNS involvement	Controlled CNS involvement accepted in absence of therapy with corticosteroids and/or anticonvulsant	Controlled asymptomatic CNS involvement allowed	Allowed if asymptomatic or previously-treated and controlled	No exclusion
Resolution of all acute toxic effects of any prior anticancer therapy	Required	Required	Not specifically mentioned	No Exclusion
Age	≥18 years	≥18 years	≥18 years	≥18 years
Symptomatic Brain Metastasis or leptomeningeal involvement	Excluded	No Exclusion	No Exclusion	No Exclusion
Other Specific Recent Medical Conditions	In prior 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure,	In prior 6 months: myocardial infarction, unstable angina, coronary / peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident	In prior 3 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure,	No Exclusions

	cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis	or transient ischemic attack, symptomatic bradycardia, requirement for anti-arrhythmic medication.	cerebrovascular accident or transient ischemic attack, stroke, symptomatic bradycardia, uncontrolled arrhythmias requiring medication	
Major surgery	Excluded in prior 4 weeks	Excluded if incomplete recovery	Excluded if incomplete recovery	No Exclusion
Gap between diagnosis and treatment date	4 weeks must have elapsed since prior chemotherapy; or 5 half-lives in absence of toxicity; 6 weeks for nitrosureas, mitomycin C, and liposomal doxirubicin	2 to 4 weeks after prior cytotoxic chemotherapy; 6 weeks for nitrosureas, mitomycin C, and liposomal doxorubicin; 7 days from prior non-cytotoxic cancer therapy in absence of toxicity; at least 4 weeks since completion of antibody-directed therapy	2 weeks or 5 half-lives from prior treatment, whichever is shorter; 4 weeks since antibody directed therapy	Patients with a gap >90 days were excluded
Prior Radiotherapy	Allowed if no more than 25% of bone marrow reserve has been irradiated	Allowed if >14 days had elapsed since end-of-treatment visit.	Allowed if >14 days had elapsed since end of treatment	No Exclusion

Positive test for concomitant oncodriver mutation (i.e. EGFR, ALK, DRAS, and BRAF)	Excluded	Excluded	Excluded	Excluded
QTc interval prolongation	History of prolonged QTc interval prolongation; risk factors for torsade de pointes; other concomitant medications that may prolong QTc	Non-pharmacologically induced prolonged QTc interval; history of additional risk factors for torsade de pointes	Excluded history of non-pharmacologically induced QTc interval prolongation; additional risk factors for torsade de points	No Exclusion
Peripheral neuropathy	No Exclusion	Excluded Grade 2	Excluded Grade 2	No Exclusion
Active infections	Excluded	Excluded	Excluded	No Exclusion
Active gastrointestinal disease	Excluded	Excluded	Excluded	No Exclusion
Interstitial lung disease, interstitial fibrosis	Excluded	Excluded	Excluded	No Exclusion
Other severe acute or chronic medical or psychiatric condition	Excluded	Excluded	Excluded	No Exclusion

[1] While ALKA and STARTRK-1 allowed prior crizotinib use, page 7 of CSR WO400977 describes the entrectinib arm using the following statement: "the patients had no previous exposure to another ROS1 inhibitor such as crizotinib." No information is provided on exclusion of any ROS1-positive patients treated with entrectinib in the CSR.

DEPI Comments on Study Eligibility Criteria

The entrectinib clinical trials had many eligibility criteria that either were not or could not be replicated in the crizotinib RWE arm. It is unknown to what extent these criteria decrease generalizability of the entrectinib clinical trial program to the total population of treated ROS1-positive real-world patients.

These differences in eligibility criteria can have measurable and unmeasurable influences on the final population studied. The measurable influence can be assessed through a study attrition table. For example, STARTRK-2, which contributed 37 of 53 (69.8%) patients in the entrectinib arm of this study, appears to have directly excluded only 12 patients (page 58 of CSR RXDX-101-02). Of 219 total screened patients in STARTRK-2, 207 were enrolled (206 treated). Unmeasured differences typically revolve around the impact of these criteria on referral for clinical trial inclusion and cannot be measured.

3.3.2 Outcomes

3.3.2.1 Treatment Discontinuation

In clinical trials, Time to Treatment Discontinuation (TTD) was defined as the time from entrectinib initiation to permanent treatment discontinuation, which could have occurred due to death, toxicity, withdrawal of consent, and first documentation of radiographic progression.

Treatment beyond disease progression is common in the real-world, as there may be additional clinical benefit from continued treatment. Using only the date of treatment discontinuation would therefore not match TTD in the entrectinib arm. Therefore, TTD in the crizotinib RWE arm was defined as the time from crizotinib initiation to whichever of the following events occurred first: initiation of a new therapy, death within 7 days of the last administration, the last day of treatment prior to a gap ≥60 days, and documentation of disease progression (radiographic progression, clinician note documenting loss of clinical benefit, or both).

DEPI Comments on TTD Outcome

Treatment beyond progression complicates interpretation of this outcome. Generally, treatment beyond disease progression in the real-world would bias towards longer treatment duration with the crizotinib RWE study arm. Though potentially substantial differences in treatment ascertainment and adherence between study arms would have unpredictable effects on the study findings.

Differences in defining progression free survival as a censoring criterion could also result in bias. Using both radiographic imaging and investigator assessment in the entrectinib arm would be expected to produce a more similar definition to that in the crizotinib RWE study arm.

3.3.2.2 Progression Free Survival

Progression free survival was determined using two methods in clinical trials. First, it was determined solely by radiographic progression (i.e., blinded independent central review, BICR). A second definition included both radiographic progression and investigator-assessed progression, which also includes a documentation of “loss of clinical benefit.”

Because radiographic data is not completely available in electronic medical records, progression was defined in the crizotinib RWE arm using a combination of radiographic records and clinical

notes, where progression was defined at documentation of disease progression, loss of clinical benefit, or both.

DEPI's comments on PFS outcome

Defining PFS as a combined outcome using radiographic imaging and investigator assessment in the entrectinib arm provides a more similar outcome definition to the crizotinib study arm. Use of a more ambiguously defined PFS outcome based on clinician notes for crizotinib may have resulted in earlier documentation of PFS; while at the same time, missingness in radiographic imaging for crizotinib could result in later documentation of PFS.

3.3.2.3 Overall Survival

Overall survival was defined as the time from treatment initiation to death from any cause in both study arms. Censoring was on the last activity date (i.e. last visit date) if a patient was still ongoing treatment at study end or death could not be confirmed.

DEPI Comments on OS Outcome

The completeness of capture for this outcome was not described for the crizotinib or entrectinib study arms. Upon review of the literature, a validation study for capture of mortality was conducted using FlatIron EMR data among patients with advanced NSCLC [Curtis MD et al, 2018]. The study compared the combination of four data streams (structured EMR data, linkage to social security death index, unstructured EMR data, and commercial death data) to the National Death Index. It found this methodology had a sensitivity of 89.7%, a specificity of 97.3%, a positive predictive value of 97.9% and a negative predictive value of 87.1%. Agreement of dates of death between this approach and the NDI were 93.4% (exact day) and 97.0% (±15 days). It is not known whether this exact approach was used in the current study. Additionally, this report does not detail whether mortality had a differential capture in the crizotinib RWE arm versus the entrectinib clinical trial arm. Generally, both arms should have an acceptable capture of death.

3.3.3 Exposure

This study compares patients with ROS1-positive NSCLC treated with entrectinib in three single arm clinical trials versus patients with ROS1-positive NSCLC treated with crizotinib in the real world.

DEPI Comments on Exposure

Both study arms should have nearly complete capture of drug exposure. However, the real-world cohort likely had poor sensitivity for identifying ROS1-positive NSCLC.

3.3.4 Covariates

The following covariates are specified in the Applicant's protocol.

Table 3: Covariates used in statistical modeling for analyses of TTD, PFS, and OS

Prognostic Variables Defined A Priori	**Rationale for Use**	**Grouping**
Age	Demographic	Continuous (primary analysis) Categorical (sensitivity analysis; <65 and ≥ 65)
Gender	Demographic	Male; female
Race/ethnicity	Demographic	Other; white (other includes Asian and Hispanic/Latino)
Smoking status	Clinical: As a proxy of severity of disease at baseline (in the absence of ECOG)	History of smoking and no history of smoking
Brain metastases at baseline	Clinical: Known prognostic factor affecting the outcome of the treatment*	Yes or No
Prior LOT	Clinical: Known prognostic factor affecting outcome of treatment	≤ 2 LOT and >2 LOT

ECOG = Eastern Cooperative Oncology Group; LOT = Lines of therapy

* Data from Table 9 of CSR WO40977

DEPI's Comments

Given the small sample size, multiple covariates with imbalances at baseline are not included as covariates for statistical modeling. Additionally, the covariates in Table 5A and Table 5B do not completely capture all imbalances expected to result from the differential study eligibility criteria. For example, the Applicant could have included an assessment of available baseline laboratory data. Covariates including race/ethnicity, smoking status, brain metastases, and prior lines of therapy (LOT) are likely to be ascertained differentially based on study arm.

3.3.5 Sample Size/Power

Calculations for sample size and study power was not provided.

3.3.6 Statistical Analysis

Primary Analyses

Comparisons between groups were done using chi-squared tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.

Time to event analyses (TTD, PFS, OS) were conducted using Kaplan-Meier analyses and Cox Proportional Hazards Models. These were conducted both for the full study population and for a trimmed inverse probability of treatment weighted pseudo-population as described in the following bullet.

Adjusted analyses used the covariates in section 3.3.4 to calculate a propensity score for each patient, as the probability of treatment with entrectinib. Inverse probability of treatment weighting was applied to the propensity score to create a pseudo-population where the treatment is independent of the covariates included in calculation of the propensity score. Patients with weights above the 99th percentile were removed from the analysis.

DEPI Comments

The IPTW adjustment approach is intended to address only the covariates listed in section 3.3.4 of this review. This is not expected to fully account for the differences in baseline characteristics between the study arms. Additionally, this adjustment approach cannot address differences in selection criteria, which represent an unaddressed source of bias in this study.

3.3.7 Sensitivity Analyses

Table 4: Completed and Ongoing Sensitivity Analyses

Sensitivity analyses	Rationale	Status	PS and Time-to-Event Model specification
Age	As a categorical variable (e.g., $<65, \geq 65$)	Impact on results completed	Same prognostic factors as main analysis
Prior targeted therapy exposure	Using prior targeted therapy instead of line of therapy for covariate adjustment and to derive propensity score	Impact on results completed	Same prognostic factors as main analysis except for line of therapy
Restricted follow-up time	Restricted to population with at least 12 months of potential follow-up after starting crizotinib treatment	Impact on results completed	Same prognostic factor as main analysis
Missing ECOG*	restricted to patients with non-missing ECOG values	Impact on results completed; subgroup analysis ongoing	Same prognostic factor as main analysis except for smoking that is replaced by ECOG in 2 categories ECOG = 0 and ECOG = 1-2)
Brain metastasis	Yes vs. no	Ongoing, subgroup analysis	Same prognostic factors as main analysis
Matching methods	Caliper matching	Ongoing	Same prognostic factors as main analysis
Difference in scan frequency for estimation PFS	Scan frequency between arms (trial vs. RWD)	Ongoing	Same prognostic factors as main analysis
Different genetic testing methods	Restricted to crizotinib RWD arm patients with confirmed FISH test only	Ongoing	Same prognostic factors as main analysis
Covariate selection	Stepwise variable selection	Ongoing (on PS development and Cox models)	Depends on model performance

ECOG = Eastern co-operative Oncology Group; FISH = fluorescence in situ hybridization; PS = propensity score; RWD = real-world data

* Data from Table 10 of CSR WO40977

DEPI Comments

The above completed sensitivity analyses were not highly informative. The remainder of the provided sensitivity analyses are ongoing and thus have not been reviewed by DEPI.

3.4 STUDY RESULTS

3.4.1 Baseline Characteristics

Population Characteristics at baseline are shown in Table 5A and Table 5B for the entrectinib clinical trial and crizotinib RWE study arms.

Table 5A: Baseline Characteristics

Category	Sub–category	Trial Entrectinib (N = 53)	RWD Crizotinib (N = 69)
Gender n (%)	Female	34 (64.15)	39 (56.52)
	Male	19 (35.85)	30 (49.48)
Race n (%)	Asian	19 (35.85)	6 (8.7)
	White	31 (58.5)	41 (59.42)
	Black or African American	2 (3.77)	8 (11.59)
	Hispanic or Latino	1 (1.89)	10 (14.49)
	Not Provided	0 (0.0)	4 (5.8)
Age (%)	18-34 years old	3 (5.66)	0 (0)
	35-64 years old	39 (73.58)	32 (46.38)
	≥ 65 years old	11 (20.75)	37 (53.62)
Age Median (IQR) (Age = Year of First Treatment Start = Birth Year)		53 (46–61)	65 (55–73)
BMI (%)	Underweight < 18.5 (kg/m²)	2 (3.7)	0 (0)
	Normal 18.5 < 25 (kg/m²)	25 (47.17)	15 (21.74)
	Overweight 25 < 30 (kg/m²)	14 (26.42)	18 (26.09)
	Obese ≥ 30 (kg/m²)	12 (22.64)	14 (20.29)
	Not Provided	0 (0)	22 (31.88)
BMI Mean (SD; baseline assessed ≤ 30 days before first treatment)		25.93 (5.05)	27.77 (5.57)
Smoking Status n (%)	History of smoking	22 (41.51)	38 (55.07)
	No history of smoking	31 (58.49)	31 (44.93)
Clinical practice Type n (%)	Community	31 (58.49)	54 (78.26)
	Academic	22 (41.51)	15 (21.74)
Location of clinical practice n (%)	Asia Pacific	19 (35.8)	0 (0)
	Europe	19 (35.8)	0 (0)
	USA	15 (28.3)	69 (100.0)

* Data from Table 11 of CSR WO40977

Table 5B: Baseline Characteristics

Category	Sub–category	Trial Entrectinib (N=53)	RWD Crizotinib (N=69)
Histology n (%)	Non-squamous cell carcinoma	53 (100)	64 (92.75)
	Squamous cell carcinoma	0	3 (4.35)
	NOS	0	2 (2.9)
ECOG n (%; baseline assessed ≤30 days before First Treatment Start Date for RWD)	0	20 (37.74)	16 (23.19)
	1	27 (50.94)	8 (11.59)
	2	6 (11.32)	7 (10.14)
	Missing		38 (55.07)
Brain Mets at baseline n (%; before or on First Treatment Start)	Yes	23 (43.4)	17 (24.64)
	No	30 (56.6)	52 (75.36)
Total Number of Mets sites (Note: Other Met is considered as 1) before or on Index Date n (%)	<2	27 (50.9)	50 (72.5)
	≥2	26 (49.1)	19 (27.5)
Number of prior LOT	≤2 LOT	40 (75.47)	63 (91.3)
	>2 LOT	13 (24.53)	6 (8.7)
Any prior target therapies n(%)	Yes	9 (16.98)	11 (15.94)
Any prior chemotherapies n(%)	Yes	34 (64.15)	21 (30.43)

BMI = body mass index; IQR = interquartile range; LOT = lines of therapy; n = number; RWD = real-world data; SD = standard deviation; USA = United States of America

* Data from Table 11 of CSR WO40977

DEPI Comments on Baseline Characteristics

Notable differences at baseline were observed between entrectinib clinical trial patients and crizotinib treatment in the real-world. Entrectinib treated patients were younger (median age 53 years versus 65 years), more female (64.2% vs 56.5%), more Asian (35.9% vs 8.7%), less likely to have a history of smoking (41.5% vs 55.07%), more likely to receive treatment in academic center (41.5% vs 21.7%), and less likely to be of US nationality (28.3% vs 100%). However, entrectinib treated patients were also more likely to present with brain metastasis (43.4% vs 24.6%), have ≥2 metastasis at baseline (49.1% vs 27.5%), and have >2 prior lines of therapy (24.5% vs 8.7). It is also notable that 55.1% (n=38) of patients in the crizotinib RWE arm have a missing ECOG score. Imbalances between treatment arms may be attributed to differences in selection criteria and variability due to small sample size.

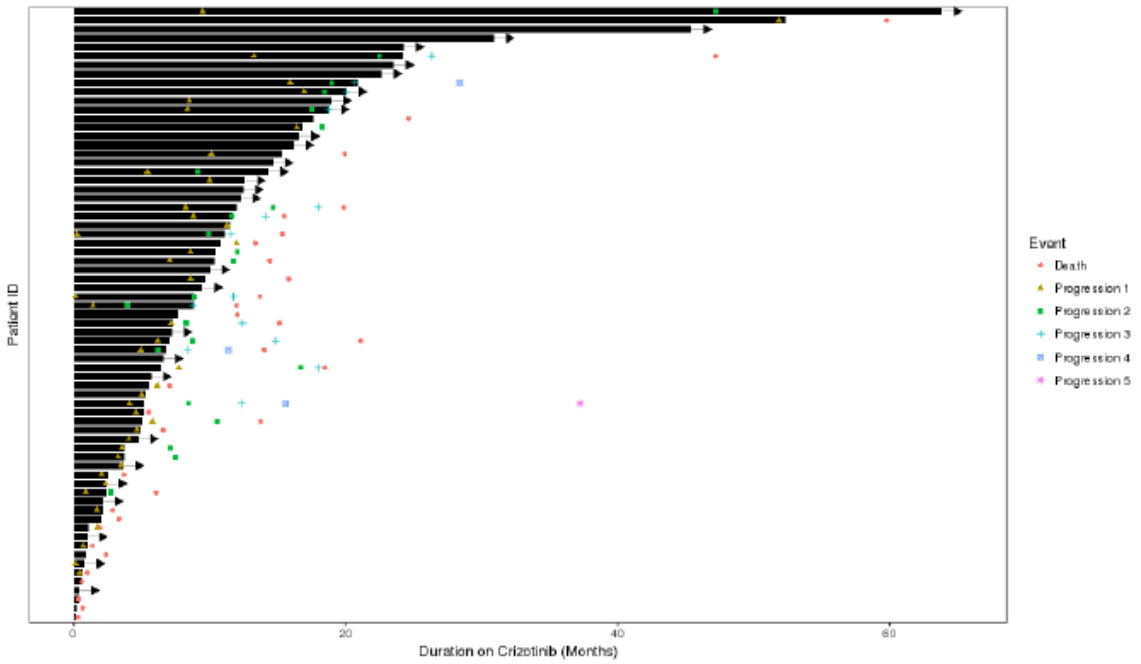
Inverse probability of treatment weighting was successful in creating a pseudo-population balanced on specific factors included in the propensity score calibration (i.e.

gender, race, age, brain metastasis at baseline, prior lines of therapy, and history of smoking); see Table 12 from CSR WO40977. However, given the small sample size and limited number of covariates included in this approach, it is unlikely the weighted population can account for the totality of the differences in study arms at baseline.

3.4.2 Reasons for Censoring and Treatment Beyond Progression in Crizotinib RWE study arm

The below graph (Figure 1) provides a depiction of the timing between disease progression, death, and treatment discontinuation.

Figure 1: Swimmer plot of crizotinib treated patients, indicating patients with treatment beyond progression (TBP)



* Data from Figure 6 of CSR WO40977

DEPI Comments

This graph demonstrates commonplace crizotinib treatment beyond disease progression, necessitating a drug discontinuation definition that additionally censors at disease progression.

Additionally, this graph demonstrates that most censoring between months 8-12 in the crizotinib RWE arm is due to first progression. A crude assessment from this plot suggests that, of the 17 patients censored during this time period, roughly 12 are first progression of disease. This is relevant to interpretation of differences in Kaplan Meier plots that appear during this time window in Sections 3.4.3 and 3.4.4 below.

3.4.3 Time to Treatment Discontinuation (TTD)

TTD is provided below in Table 6 for the entrectinib arm, the unweighted crizotinib RWE arm, and the IPTW weighted crizotinib RWE arm. This table censors for progression in the entrectinib arm using both radiographic imaging and investigator-assessment.

Table 6: Median TTD in entrectinib and crizotinib arms (unweighted and weighted)

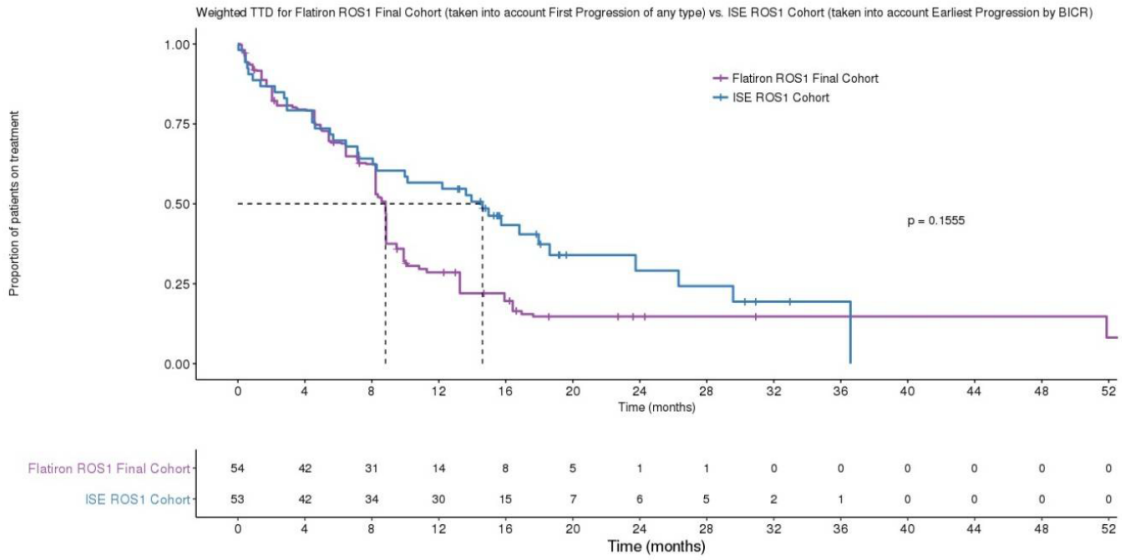
Treatment arm	Patients	Events	Median TTD	95% CI
Entrectinib	53	36	14.61	8.29-23.75
Crizotinib Unweighted	69	50	8.36	6.18-10.13
Crizotinib Weighted*	54	42	8.82	8.22-9.9

TTD = time to treatment discontinuation; * N on reweighted sample; Progression events from both radiographic imaging and investigator-assessment

* Data from Table 14 of CSR WO40977

Of note, the accompanying Kaplan Meier plot for TTD includes a definition for PFS in the entrectinib arm using only radiographic progression (Figure 2).

Figure 2: Kaplan Meier Estimates of Weighted TTD across Study Arms (BICR)



BICR = blinded independent central review; ISE = integrated summary of efficacy; TTD = time to treatment discontinuation

* Data from Figure 8 of CSR WO40977

DEPI Comments

Rates of treatment discontinuation are similar through 8 months of follow-up and differentiate substantially between months 8-12. Review of the Swimmer Plot (Figure 1) shows that most censoring between months 8-12 is due to disease progression. This CSR does not provide the frequency of radiographic testing or physician visits in the real-world, although this is listed as an ongoing sensitivity analysis. It is possible the rapid differentiation during this time period may be due to a measurement bias from a lower frequency of patient assessment in the real world.

3.4.4 Progression Free Survival (PFS)

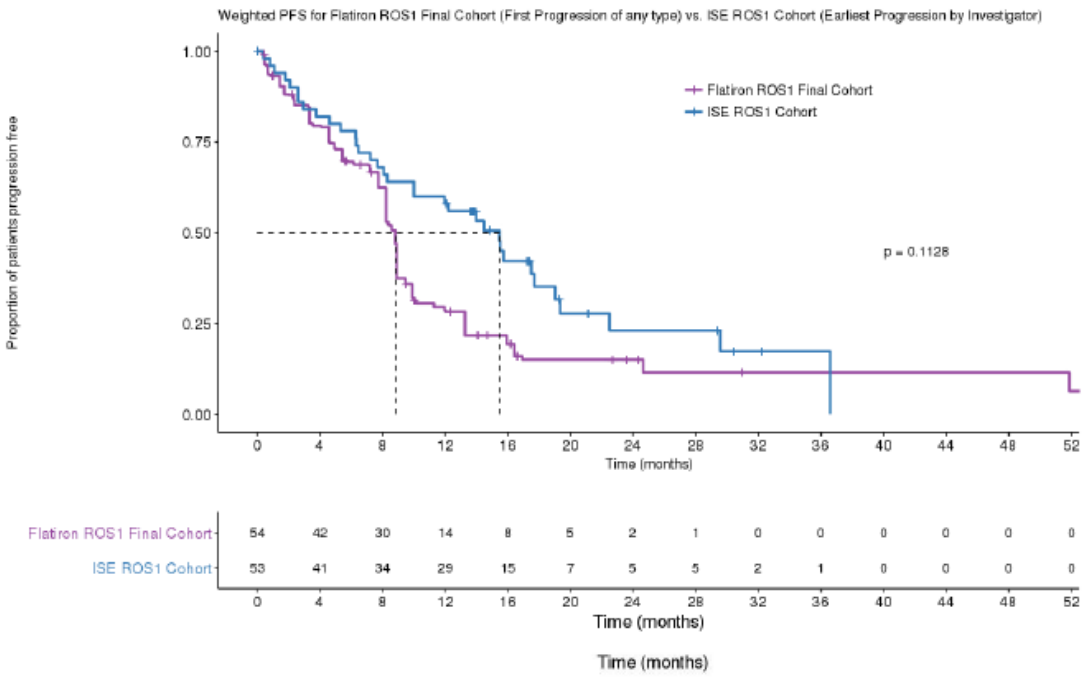
The below Table 7 and Figure 3 provide the PFS results using a combined radiographic imaging and investigator assessed definition in the entrectinib arm. Results using only radiographic progression are provided in Figure 9 and Table 15 of CSR WO40977.

Table 7: Median PFS (investigator-assessed) in Entrectinib and Crizotinib Study Arms (unweighted and weighted)

Treatment arm	Patients	Events	Median PFS (95% CI)
Entrectinib	53	25	19.0 (12.2-NE)
Crizotinib Unweighted	69	50	8.49 (6.18-10.13)
Crizotinib Weighted*	54	42	8.82 (8.22-9.9)

* Data from Table 17 of CSR WO40977

Figure 3: Kaplan Meier Estimates of Weighted PFS Across Study Arms (Investigator-Assessed)



ISE = integrated summary of efficacy; PFS = progression-free survival.

* Data from Figure 10 of CSR WO40977

DEPI Comments

Similar to the outcome of TTD, a large differentiation in PFS is observed between months 8-12. The rapid nature of this change may be due in some part due to measurement bias from different frequencies of radiographic imaging between the two groups.

3.4.5 Overall Survival (OS)

Median overall survival is provided in Table 8, although it was not estimated in the entrectinib arm due to a low number of events. A Kaplan Meier curve for overall survival is provided in Figure 4.

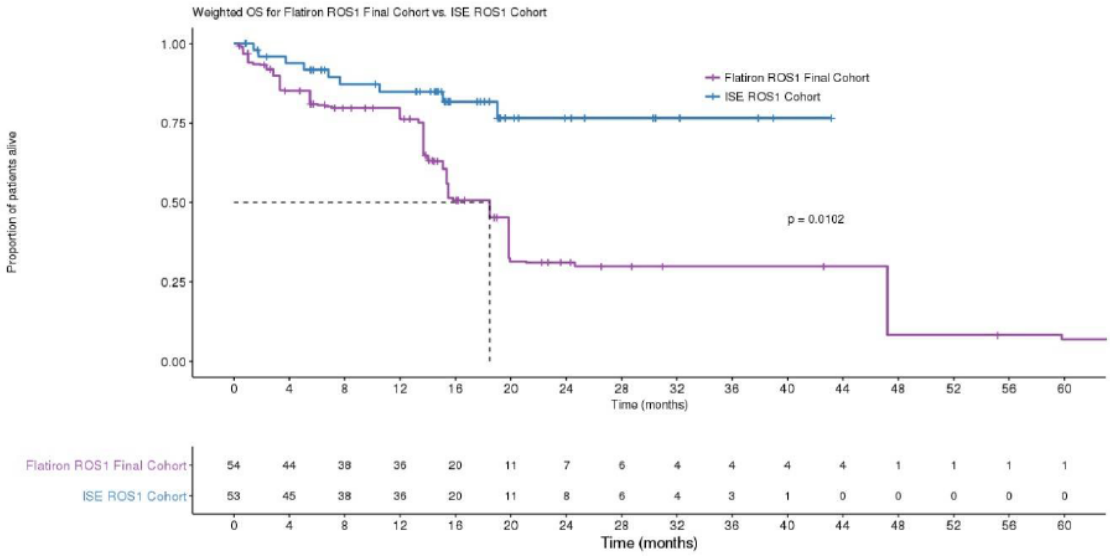
Table 8: Median OS in entrectinib and crizotinib arms (unweighted and weighted)

Treatment arm	Patients*	Events	Median OS (95% CI)
Entrectinib	53	9	NE
Crizotinib Unweighted	69	33	19.87 (15.1-NE)
Crizotinib Weighted*	54	34	18.49 (15.1-19.93)

OS = overall survival; NE = not estimated

* Data from Table 18 of CSR WO40977

Figure 4: Kaplan Meier Estimates of OS for entrectinib and crizotinib (weighted OS for the crizotinib arm)



ISE = integrated summary of efficacy; OS = overall survival

* Data from Figure 11 of CSR WO40977

DEPI Comments

Although a substantial difference in overall survival is suggested by the Kaplan Meier plot, this analysis is underpowered. Further, the Applicant has not demonstrated that IPTW adequately account for imbalances between study arms, which could influence OS.

3.5 STUDY CONCLUSIONS

The Applicant concluded that:

1. The primary analysis showed evidence of lower risk of treatment discontinuation with entrectinib compared to crizotinib (HR = 0.64, 95%CI: 0.4-1.02
2. Using real world progression as a proxy for PFS, the analysis also showed that entrectinib is associated with a longer PFS (19.0 months compared to 8.8 months); (HR 0.44, 95%CI: 0.26-0.74)
3. As the data are still immature (with only 17% events) in the entrectinib trial arm and 48% events in the crizotinib arm and the median OS not yet reached at the time of this submission, comparisons in OS between the trial arm and the RWD arm could not be drawn. However, the median OS observed in the RWD crizotinib arm was 18.5 months (95%CI: 15.1-19.9), suggesting a preliminary improvement in OS.

DEPI Comments

Substantial differences in rates of clinical outcomes were observed between study arms. However, given limitations, the study conclusions are overstated and not adequately supported by the data. See Discussion for specific questions addressed regarding these conclusions. See Appendix for a list of key study limitations.

4 DISCUSSION

Is the Crizotinib RWE arm sufficient to establish the natural history of disease for ROS1-positive NSCLC?

Only 150 patients had a positive test for ROS1 of 48,935 total NSCLC cases (0.3%). ROS1 alterations are known to have a prevalence is 1-2%, suggesting this RWE cohort captures between 15%-30% of the total ROS1-positive population. This low sensitivity is likely due selective ROS1 testing, which the Applicant suggests is more common among non-smokers and females. It should also be noted this cohort is primarily community-based. As a result, the crizotinib arm may adequately represent community treated patients who receive ROS1 testing and test positive; however, this population is unlikely to be generalizable to the entire population of patients with ROS1-positive NSCLC. The Applicant does provide two additional cohorts to support the similarity of their crizotinib arm to other available cohort studies, the Asian Cohort and the EUROS1 cohort (See Figure 12, page 45 of CSR WO40977). These cohorts were not reviewed by DEPI.

Does the study methodology provided allow for a comparison of treatment outcomes between the entrectinib arm and crizotinib arm in this study?

There are substantial differences in eligibility criteria by arm, resultant differences in population characteristics at baseline, and inadequate covariate adjustment in statistical modeling due to low sample size. As a result, it is challenging to determine what proportion of the observed differences in rates of treatment outcomes (TTD, PFS, and OS) between study arms is due to differences in the study populations (i.e. selection bias) versus true differences in this clinical endpoint between treatments.

This study report provides a generally acceptable definition of study outcomes given limitations of available data. However, TTD is complicated by treatment beyond disease progression, PFS is limited by missingness in radiographic imaging in EMR data, and OS may be more subject to bias from baseline imbalances.

Of note, the ongoing sensitivity analysis that evaluates differences in frequency of radiographic imaging between the study arms could provide additional information on the presence of measurement bias for estimation of PFS.

5 CONCLUSION

The crizotinib arm is unlikely to be generalizable to the entire population of patients with ROS1-positive NSCLC. Examination of baseline characteristics demonstrates the crizotinib arm is not sufficiently comparable to the entrectinib clinical trial population.

Substantial differences in study outcomes (TTD, PFS, and OS) were noted, favoring the entrectinib arm. However, comparisons between the entrectinib and crizotinib study arms were limited by differentially implemented study eligibility criteria, resultant differences in baseline criteria, and limitations in statistical modeling due to low sample size. These limitations make it difficult to determine what proportion of the observed differences in rates of clinical outcomes are due to imbalances in study populations (i.e. selection bias) versus differential treatment effects of the study drugs.

Finally, because this study report was submitted to FDA without prior review of a study protocol, all analyses are considered post-hoc.

6 RECOMMENDATIONS

1. While the crizotinib population identified may be representative to patients who currently receive treatment for ROS1-positive NSCLC in the community setting, it is not generalizability to the entire ROS1-positive NSCLC population and it is not generalizable to patient enrolled in entrectinib clinical trials.

2. This study report is not adequate to allow a robust comparison of treatment outcomes between crizotinib and entrectinib study arms.

3. The Applicant should be advised to submit an a priori study protocol before submission of a study report to FDA for review.

7 REFERENCES

Clave S, Gimeno J, Munoz-Marmol AM, et al. ROS1 copy number alterations are frequent in non-small cell lung cancer. Oncotarget 2016;16(7):8019-28.

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Food and Drug Administration / Center for Devices and Radiologic Health. Use of real-world evidence to support regulatory decision-making for medical devices; guidance for industry and FDA staff. 31 August 2017. Accessed on 15 April 2019. Available at: < https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>.

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Food and Drug Administration / Center for Drug Evaluation and Research (CDER) & Center for Biologics Evaluation and Research (CBER). E 10 choice of control group and related issues in clinical trials; guidance for industry and FDA staff. May 2001. Accessed 15 April 2019. Available at: < https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073139.pdf>.

Stransky N, Cerami E, Schalm S, et al. The landscape of kinase fusions in cancer. Nat Commun 2014;5:4846.

8 APPENDIX: SUMMARY OF KEY LIMITATIONS

Selection Bias

This is the greatest threat to study validity for the comparison of study arms. Substantial differences in baseline covariates were observed. While this is a generally well-done study report, it is unlikely these differences can be overcome with the provided analyses.

Missing Data Among Covariates and Missing Covariates

The Applicant did not try to replicate all the study eligibility criteria in this RWE protocol, likely because data to implement them are missing for many inclusion and exclusion criteria in the crizotinib RWE arm. It would have been useful for the Applicant to evaluate all eligibility criteria to the extent possible, especially baseline laboratory data. It is noteworthy that ECOG was missing in 55.1% of patients in the crizotinib arm.

Statistical Modeling

Not all covariate imbalances were included in the statistical modeling, which was limited by sample size.

Measure of Study Outcomes

This study report provides a generally acceptable definition of study outcomes given limitations of available data. It does have limitations. TTD is complicated by treatment beyond disease progression, PFS is limited by lack of radiographic imaging in EMR data, and OS may be more subject to bias from baseline imbalances.

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/s/

STEVEN BIRD
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SUKHMINDER K SANDHU on behalf of SIMONE P PINHEIRO
07/16/2019 03:59:27 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 9, 2019

TO: Patricia Keegan, MD
Division Director
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

and

Ann T. Farrell, MD
Division Director
Division of Hematology Products (DHP)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: John A. Kadavil, Ph.D.
Deputy Director
DGDBE, OSIS

SUBJECT: Routine inspection of Celerion Arizona, Tempe, AZ supporting clinical studies RXDX-101-15 (NDA 212725 and NDA 212726) NON-RESPONSIVE

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of studies RXDX-101-15 (NDA 212725 and NDA 212726) NON-RESPONSIVE conducted at Celerion Arizona, Tempe, AZ.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. NON-RESPONSIVE NON-RESPONSIVE NON-RESPONSIVE. The final classification for Celerion Arizona, Tempe, AZ, USA is Voluntary Acton Indicated (VAI).

1.1. Recommendation

NON-RESPONSIVE

NON-RESPONSIVE However, the inspectional findings were isolated in nature and do not impact the reliability of data from study RXDX-101-15. Therefore, data from study RXDX-101-15 and other studies of similar design (open-label) are reliable to support a regulatory decision.

I conclude that data from the audited study RXDX-101-15 (NDA 212725 & NDA 212726) are reliable to support a regulatory decision. NON-RESPONSIVE NON-RESPONSIVE .

2 Inspected Studies:

NDA 212725 and NDA 212726
Study Number: RXDX-101-15
Study Title: "A 2-Part, Open-Label, Randomized, 2-Period, Single-Dose Study to Assess the Relative Bioavailability of 2 Entrectinib Formulations Under Fasting Conditions and the Effect of Food on the Entrectinib F06 Formulation in Healthy Adult Male Subjects"
Dates of conduct: 02/16/2018 – 06/6/2018

NON-RESPONSIVE

Clinical site: Celerion Arizona
2420 West Baseline Road
Tempe, AZ
FEI#: 3009853739

ORA investigator Michelle Hines (b) (4) inspected Celerion Arizona, 2420 West Baseline Road Tempe, AZ from May 28 to June 5, 2019.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

3 Inspectional Findings

NON-RESPONSIVE

At the conclusion of the inspection, investigator Hines did not observe objectionable conditions and did not issue Form FDA 483 to the clinical site. NON-RESPONSIVE

NON-RESPONSIVE

4. Conclusion:

After reviewing the inspectional findings at Celerion Arizona, I conclude the following:

- The data from study RXDX-101-15 are reliable. I recommend that data from study RXDX-101-15 should be accepted for further agency review.
- NON-RESPONSIVE

  In addition, I recommend that data from other blinded studies conducted at Celerion Arizona since the previous inspection (b) (4) should not be accepted for agency

review without an inspection to authenticate the dosing records.

Final Classification:

VAI – Celerion Arizona,
Tempe, AZ
USA
FEI#: 3009853739

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/CDER-OSISBEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
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ORA/OMPTO/OBIMO/ORABIMOW.Correspondence@fda.hhs.gov

Draft: XFL 06/24/2019; 7/5/2019; 7/9/2019
Edit: MFS 06/25/2019 and 07/05/2019; JAK 07/05/2019 and 07/08/2019

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL/Celerion, Tempe, AZ, USA

OSIS File #: 8372 (NDA 212725)
8373 (NDA 212726)
NON-RESPONSIVE

FACTS: 11908319

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/s/

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MICHAEL F SKELLY
07/09/2019 02:57:20 PM

JOHN A KADAVIL
07/09/2019 03:02:21 PM

Clinical Inspection Summary

Date	June 12, 2019
From	Yang-min (Max) Ning, M.D., Ph.D. Susan Thompson, M.D. Kassa Ayalew, M.D., M.P.H. OSI/DCCE/GCPAB
To	Leigh Marcus, M.D. Martha Donoghue, M.D. Shanthi Marur, M.D. Erin Larkins, M.D. Kelie Reece, Ph.D., RPM OCE/OHOP/DOP2
NDA #	212725 and 212726
Applicant	Genentech, Inc.
Drug	Entrectinib capsules (ROZLYTREK)
NME	Yes
Therapeutic Classification	Inhibitor of tyrosine kinases, including neurotrophic tyrosine receptor kinases (NTRK) and proto-oncogene tyrosine-protein kinase (ROS1)
Proposed Indication(s)	NDA 212725: Treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive NDA 212726: Treatment of adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive, (b) (4) metastatic solid tumors who have either progressed (b) (4) (b) (4)
Consultation Request Date	February 6, 2019
Summary Goal Date	June 14, 2019
Action Goal Date	August 10, 2019
PDUFA Date	August 18, 2019

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Clinical data pooled from three open-label trials (Studies RXDX-101-02, RXDX-101-01, and ALKA-372-001) were submitted to the Agency in support of the two New Drug Applications (NDAs) for entrectinib for two different indications as listed above. Four study sites and the Contract Research Organization (CRO) which performed Blinded Independent Radiologic Review (BICR) for the three trials were selected for clinical inspections. Detailed information about the inspection of these sites and the CRO is described in the Section III of this summary.

All the five inspections were conducted and completed in a timely manner with no refusals. The inspectional findings, as summarized below, verified the applicant's submitted clinical data with source documents at these study sites and the CRO facility. There was no evidence of underreporting of adverse events.

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.

Overall, based on the inspectional findings as described in this summary along with relevant documents contained in the available Establishment Inspection Reports, the OSI review team considers that the submitted clinical data from the four study sites and the CRO for Independent Review appear acceptable in support of the two NDAs for entrectinib.

II. BACKGROUND

Entrectinib is an inhibitor of tyrosine kinases, including NTRK, ROS1, and anaplastic lymphoma kinase (ALK). To support the proposed indications, the Applicant submitted clinical data, pooled by biomarker ROS1 or NTRK, from the three open-label trials as aforementioned. Across the three trials, Efficacy Evaluable Population for each biomarker-specified group [as of the data cutoff (5/31/2018) for analyses] is shown in the following table. Key efficacy measures for each pooled Efficacy Evaluable Population were objective response rate (ORR) and duration of response (DOR) as assessed by a Blinded Independent Central Review (BICR) per RECIST v1.1.

Evaluable Efficacy Population for Each Biomarker Group

Trial Name (Phase)	Number of Subjects in the ROS1 Group	Number of Subjects in the NTRK Group
RXDX-101-02 (Phase 2)	37	51
RXDX-101-01 (Phase 1)	7	2
ALKA-372-001 (Phase 1)	9	1
Total (Pooled)	53*	54**
*Including subjects with ROS1-positive metastatic NSCLC who had measurable disease at baseline (as assessed by the Investigator) and at least 12 months follow-up after the first dose of entrectinib. Subjects who received prior ROS1 inhibitor were excluded.		

**Including subjects with NTRK fusion-positive solid malignancies who had measurable metastatic disease at baseline (as assessed by the Investigator) and at least 6 months of follow up after the first dose of entrectinib. Subjects who received prior NTRK inhibitor were excluded.

The current two NDA submissions included clinical data collected from subjects enrolled from study initiation up to November 30, 2017. Biomarker status in tumor specimens (ROS1-positive or NTRK fusion-positive tumor) was determined by a nucleic acid-based test performed at a Clinical Laboratory Improvements Amendments (CLIA)-certified or equivalently accredited laboratory, prior to study entry. See detailed information about each listed trial (e.g., eligibility and enrollment) in the Clinical Study Report and the Clinical Review of the NDAs.

In the three trials, baseline tumor assessments were performed within 4 weeks prior to study entry. Tumor responses to entrectinib were evaluated at the end of every odd cycle (starting with Cycle 1), as clinically indicated, and at the End of Treatment. In RXDX-101-02 and RXDX-101-01, scans could be performed within ±7 days of the protocol-scheduled time points. At the discretion of the investigator, additional tumor assessments were allowed outside of the protocol-scheduled assessments.

The trial RXDX-101-02 (NCT02568267) was initiated in November 2015 and was conducted at 84 study sites in 15 countries including the United States. Of the 206 entrectinib-treated subjects, 37 in the ROS1 NSCLC group and 51 in the NTRK group met the criteria for inclusion in the Efficacy Evaluable Population as shown in the table above. The trial RXDX-101-01 (NCT02097810) was conducted in the United States, Spain, and South Korea, with the first patient enrolled in July 2014. As of the data cutoff date, seven subjects with NSCLC positive for ROS1 molecular alteration and two with NTRK fusion tumor were eligible for the respective Efficacy Evaluable Population. The trial ALKA-372-001 was the first-in-human, dose escalation trial of entrectinib, conducted in Italy. Of the 58 enrolled subjects, nine subjects with ROS1-positive NSCLC and 1 subject with NTRK tumor were found to be eligible for inclusion in the above Efficacy Evaluable Populations. Note that subjects with ALK-positive tumor were enrolled in the three trials but were not included in the current submitted analyses to support the two proposed indications.

The Review Division selected four investigator sites (shown below) and requested clinical inspections to verify the reported efficacy and safety findings in the NDAs. These sites, relative to other sites, were associated with a high number of study subjects and responders to treatment with entrectinib. The Review Division also requested a clinical inspection of the BICR facility because of the trial design and central determination of objective responses in study populations regardless of biomarker selection.

III. RESULTS (by inspected site):

Name of CI, Address; Site #	Protocol # and # of Subjects	Inspection Date	Classification
Doebele, Robert 1665 Aurora Court, MSF 70, Aurora, CO 80045 Study Site #19022	Protocol: RXDX-101-02 Enrolled: 9	Mar. 11-15 2019	NAI
Drilon, Alexander 31275 York Avenue New York, NY 10065 Study Site #19011	Protocol: RXDX-101-02 Enrolled: 10	Apr. 22-26, 2019	NAI
Chul Cho, Byoung 250 Seongsanro Seoul, 120-752 Korea Study Site #14001	Protocol: RXDX-101-02 Enrolled: 9	Apr. 22-26, 2019	NAI*
Lee, Jeeyun Samsung Medical Center 50 Irwon-Dong, Gangnam-gu Seoul, 135-710 Korea Study Site 013	Protocol: RXDX-101-01 Enrolled: 9	Apr. 29-30 & May 2-3, 2019	NAI*
(b) (4) Site: Independent Review Facility	Protocols: RXDX-101-02 RXDX-101-01 ALKA-372-001 Total 107 subjects in the Efficacy Evaluable Populations	(b) (4)	NAI
*Preliminary classification was based on preliminary communication with the field inspector; the EIR has not been received from the field and complete review of EIR is pending. Final classification occurs after the final OSI review of the EIR occurs.			

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations. Data is unreliable.

1. Dr. Robert Doebele: Study Site #19022

This study site was inspected as a data audit for the trial RXDX-101-02. There was no prior FDA inspection of this Investigator. The inspector found that nine of the eighty subjects screened for molecular testing had the protocol-required biomarkers, met the trial eligibility criteria, and enrolled in the trial prior to 11/20/2017. Of the nine subjects, six were positive for ROS1, one for NTRK fusion, and two for ALK alterations. At the time of the inspection, one subject with NTRK fusion positive tumor and four subjects with ROS1 positive NSCLC remained on entrectinib. Two subjects with ROS1+ NSCLC were discontinued (one due to death and one with disease progression). Source records of all the enrolled subjects were reviewed. These included informed consent documents, molecular screening results and eligibility documentation, progress notes for adverse event (AE) reporting, Investigator signed FDA Form 1572s, delegation of authority, financial disclosure, Institutional Review Board (IRB) approvals, and investigational product accountability. The inspection also reviewed the trial monitoring and related reports provided by the CRO (b) (4) before the site initiation and during the trial.

The inspection revealed no major regulatory violations or deficiencies. No FDA Form 483 was issued at the close-out. The reported data were verified, with no discrepancies noted between the source data and the line listings submitted to the NDAs. There was no evidence of unreported adverse events and SAEs. There were two inspectional findings discussed at the close-out meeting: 1) one screened subject who did not enroll in the trial was found to have incomplete informed consent documentation for molecular screening; 2) the Investigator did not update the Financial Disclosure Form (FDF) (b) (4) (b) (4) (b) (4) The Investigator acknowledged the issues and stated that he would take actions to prevent them from reoccurring in the future.

2. Dr. Alexander Drilon: Study Site #19011

This site was also inspected as a data audit for the trial RXDX-101-02. The first FDA inspection of this site was conducted in May 2018 for another NDA, and the final compliance classification was NAI. At the time of this inspection, the site screened 20 subjects whose tumor tested positive for the required molecular markers and enrolled 17 of them in the trial. The NDA cutoff dates for the two NDAs was 11/30/2017. Ten of the 17 subjects were enrolled prior to the NDA cutoff date and had their data listings submitted to the NDAs. Seven additional subjects were enrolled thereafter (December 2017 through September 2018), with no data listings for these subjects in the current submissions.

The inspection reviewed the trial status for all 10 subjects and examined source records

against the submitted data listings. Of the eight subjects with ROS1 positive NSCLC, six were on entrectinib and two were discontinued (one due to withdrawal and one due to disease progression) at the data cutoff date One subject with an NTRK positive tumor discontinued due to disease progression. One subject with an ALK+ malignancy also discontinued entrectinib after progression of disease. Key subject source records which the inspector reviewed included informed consent, pathology and molecular test reports, eligibility documents, oncology history and progress notes, performance of study scans and submission to the BICR facility, radiology reports, Investigator's RECIST tumor response assessment forms, concomitant medications, dose modification forms, and test article accountability logs. The inspection also reviewed the signed Form 1572s, Financial Disclosure Forms, Study Personnel Signature-Delegation Form, study-specific training and monitoring records (e.g., Site Visit Log, data queries process and capture), IRB oversight and approvals, reporting of protocol deviations to the sponsor and/or IRB, and electronic record maintenance and signatures

The inspection revealed no objectionable observations in the conduct at this site. Comparison of the subjects' source documentation with the Applicant's data listings revealed no discrepancies. All AEs including SAEs were completely and accurately reported to the sponsor and, as necessary, to the IRB in a timely manner. There were no unreported protocol deviations.

3. Dr. Byoung Chul Cho: Study Site #14001

This foreign site was inspected as a data audit for the trial RXDX-101-02. There was no history of clinical inspections for the investigator. The EIR is not currently available. Based on the inspector's reported preliminary summary, this site enrolled total 14 subjects (as of the date of the inspection) which included nine subjects prior to the data cutoff date and five thereafter. Of the nine subjects, there were five with NSCLC positive for ROS1, one with tumor positive for NTRK fusion, and three with ALK+ tumor. All the records were audited.

The inspection revealed that at this site, the study was conducted overall in accordance with the protocol. No Form 483 was issued. The reported data listings and its sources were verifiable for the primary and secondary endpoints, with no discrepancies noted. There was no evidence of underreporting of adverse events. Of note, a few protocol deviations were identified, which were also reported by the sponsor's monitors. For instance, one subject took an extra-dose (600 mg) of entrectinib and one subject had scans outside the allowed time window.

4. Dr. Jeeyun Lee: Study Site #013

This foreign site was inspected as a data audit for the trial RXDX-101-01. There was no previous inspection history for the investigator. Currently, the EIR has not been received. Based on the Preliminary Summary provided by the inspector, this site screened 14 subjects and enrolled nine of them into the Dose Expansion Cohort (600 mg once daily) of this study. Four subjects had ROS1+ NSCLC and five had NTRK-

fusion tumor. As of the data cutoff date, three in the ROS1 group remained on study. The rest of subjects, including all the five in the NTRK group, discontinued study treatment due to disease progression.

The inspection revealed that the site overall conducted the study in accordance with the study protocol, with no significant deficiencies. No Form 483 was issued at the completion of the inspection. Source data for determination of objective response status were reported to be verifiable and consistent with the data listings submitted to the NDAs. There was no evidence of under-reporting of adverse events. A protocol deviation identified in the inspection was that a subject was allowed by the sponsor to continue entrectinib while receiving radiotherapy for a new brain lesion. The inspection verified that the Investigator signed a new Financial Disclosure with Roche/Genentech on August 27, 2018.

An amendment to this inspection summary will be issued if the EIRs for Drs. Cho and Lee contain substantial differences that affect the current assessments or conclusions.

5. CRO: (b) (4).

The CRO inspection was issued to evaluate the conduct of the BICR and verify the submitted efficacy data to the two NDAs. This CRO was last inspected in (b) (4) for another NDA, and the inspection was classified as NAI.

This inspection covered the BICR for the three trials and reviewed the CRO's history, organizational charts, standard operating procedures, and policies, CRO/sponsor work orders and agreements, review charters and related amendments, qualification of study sites for scans' acquisition and related quality control process (e.g., de-identification), qualification and training of independent reviewers and adjudicators, financial disclosures, data management plans and review reporting using the CRO's platform (b) (4). The inspection also focused on data verification by examining source data and reports as documented in the (b) (4) system. The examination reviewed the date of scans and related reporting of the best response status as of the data cutoff (5/31/2108) for analyses in the two NDAs. In addition, performance of the archived scan images that supported the reported response information were reviewed in multiple randomly selected subjects to assess whether the source scans submitted from study sites were maintained according to the Review Charter and related Agreement between the CRO and Sponsor for each trial.

The inspection revealed no major regulatory violations or deficiencies, with no Form 483 issued. There was no information about study subjects' molecular basket allocation (ROS1 or NTRK) found in the (b) (4) system or related subjects' response status, which is part of evidence demonstrating the blinded review regardless of biomarker groups. Source data and Independent Review reports in the (b) (4) system were randomly selected and reviewed for more than 20% of subjects in the Efficacy Evaluable Populations, with a primary focus on those who were reported to have a Complete Response or a durable Partial Response (e.g., duration of ≥12 months from the initial confirmed response to

disease progression or the data cutoff date). The response status for each reviewed subject was found to be consistent between the (b) (4) system and the data submitted to the FDA, except for one Subject (b) (6)). This subject had no best overall response status reported in the submitted dataset to the Agency; whereas in the (b) (4) system, the subject was found to have "No pathologic disease visualized" at the screening scan (b) (6)) and on-study scans (b) (6)) per the two adjudications endorsed in June and November of 2018. Based on the correspondence provided by the CRO, the adjudicated tumor status for this subject was included in the data transfer files that were conveyed to the current Sponsor Genentech on December 5, 2018. Regarding other subjects who had no best overall response information reported in the submitted NDA datasets, the CRO's documents showed either the submitted baseline scan(s) only or no submission of scan(s) from the respective study sites since these subjects discontinued study treatment before the first scheduled staging scan(s).

Given the identified Independent Review findings regarding Subject (b) (6), information inquiries from the OSI and DOP2 review teams were conveyed to the Applicant in order to better understand the reasons for continuation of study drug. Based on the Applicant's responses, this subject has continued study treatment with entrectinib, at the Investigator's discretion, for approximately twenty months following the Investigator-assessed disease progression in August 2017. However, the Study Protocol states "*At the discretion of the Investigator and with the Sponsor's approval, patients may continue treatment with entrectinib after BICR-confirmed disease progression if the patient is perceived to be deriving clinical benefit"*. For this subject, there were no Sponsor's and/or Investigator's requests for BICR confirmation of disease progression before the continuation of entrectinib, which was based on the Investigator-assessed disease progression. A teleconference was held with the Applicant on May 30, 2019. Based on the discussions, the Applicant has notified the Investigator of the BICR reports about this subject and acknowledged that the event should be categorized as a protocol deviation. The Applicant stated that there was not a specific protocol requirement that the sponsor or investigator should be notified of a BICR evaluation of "no pathologic disease" due to blinding review concerns.

The Applicant identified additional a total of 30 subjects who continued study treatment following Investigator-assessed disease progression without inquiries for the BICR confirmation of disease progression. There were additional 34 subjects who continued study treatment after Investigator-assessed disease progression had inquiries for BICR confirmation. Twenty-six of the 34 subjects had disease progression confirmed by BICR. To prevent similar protocol violations, the Applicant issued a Protocol Clarification letter to Investigators enrolling in the study and specified the need for BICR confirmation after Investigator-assessed disease progression.

Overall, the findings from this CRO inspection showed that the BICR was properly conducted for the pooled Evaluable Efficacy Populations from the three entrectinib trials and that the reported efficacy data submitted by the Applicant appear reliable in support of the two NDAs for the proposed indications.

PRIMARY REVIEW: {See appended electronic signature page}

Yang-min (Max) Ning, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Susan Thompson, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm. NDA 212725 and NDA 212726
Review Division /Division Director/P Keegan
Review Division /Cross Discipline Team Leaders/E Larkins; M Donoghue
Review Division /Project Manager/K Reece
Review Division/Medical Officers/L Marcus; S Marur
OSI/Office Director/D Burrow
OSI/DCCE/ Division Director/N Khin
OSI/DCCE/Branch Chief/K Ayalew
OSI/DCCE/Team Leader/S Thompson
OSI/DCCE/GCP Reviewer/YM Ning
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

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SUSAN D THOMPSON
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KASSA AYALEW
06/13/2019 09:30:27 AM

MEMORANDUM

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

Date of This Memorandum:	June 12, 2019
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 212725 and NDA 212726
Product Name and Strength:	Rozlytrek (entrectinib) Capsules, 100 mg and 200 mg
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	June 7, 2019
OSE RCM #:	2018-2756-1 and 2018-2760-1
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Rozlytrek (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant submitted revised container labels and carton labeling received on June 7, 2019 for Rozlytrek. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Little, C. Label and Labeling Review for Entrectinib (NDA 212725 and NDA 212726). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 04. RCM No.: 2018-2756 and 2018-2760.

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/s/

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CHI-MING TU
06/12/2019 08:45:56 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 10, 2019

TO: Patricia Keegan, M.D.
Division Director
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of Ignyta, Inc., San Diego, CA

Inspection Summary

Per the request of OND/OHOP/DOP2 (**Attachment 1**), the Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of **Study RXDX-101-15** (**NDA 212725** and **NDA 212726**, Entrectinib) conducted at Ignyta, Inc., San Diego, CA.

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

Recommendation

Based on my review of the inspectional findings, I conclude the bioanalytical data from **Study RXDX-101-15** are reliable to support a regulatory decision.

Inspected Study

NDA 212725 and NDA 212726
Study Number: RXDX-101-15

Study Title: "A 2-Part, Open-Label, Randomized, 2-Period, Single-Dose Study to Assess the Relative Bioavailability of 2 Entrectinib Formulations Under Fasting Conditions and the Effect of Food on the Entrectinib F06 Formulation in Healthy Adult Male Subjects"

Bioanalytical Report Title: "Bioanalytical Report Determination of RXDX-101 and M5 in Human Plasma Samples from Protocol RXDX-101-15"

Sample Analysis Period: (b) (4)

Methodology: LC-MS/MS

Analytical Site: Ignyta, Inc.
4545 Towne Centre Court
San Diego, CA 92121

Scope of Inspection

OSIS scientist Yi g, Ph.D., Staff Fellow and ORA Investigator Mark W. Babbitt (b) (4) audited the analytical portion of the above study at Ignyta, Inc., San Diego, CA from (b) (4).

This was the site's first analytical BIMO BEQ inspection. The inspection included a thorough examination of study records, calibration records of laboratory equipment, method validation, sample analysis, and interviews with the site's management and staff.

During the inspection, we were informed that Ignyta was acquired by Roche, Ltd. in February 2018 and will eventually cease operation in August 2019. After the acquisition, all ongoing bioanalytical operations were transferred to other Roche facilities in the United States, UK, and Switzerland. In general, the last bioanalytical analysis was conducted at Ignyta in (b) (4) and the Bioanalytical Drug Development Department was permanently closed in October 2018. The laboratory equipment was auctioned off, and all study records were sent to (b) (4) (b) (4). The records of Study RXDX-101-15 were transferred from (b) (4) back to Ignyta during the inspection to accommodate the audit requests.

Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions and did not issue Form FDA 483 to Ignyta.

The bioanalytical report RXDX-101-15-BA mentioned that some carryover was observed in certain analytical runs. The assessment of carryover concluded that there is that no impact of carryover on the measured concentrations of study samples.

During the inspection, I specifically reviewed the 6 analytical runs that some blank and carryover samples showed responses >20% LLOQ. The site provided the carryover assessment for these runs and also a guideline on how they assessed carryover (**Attachment 2**). I reviewed the carryover assessment for all the runs mentioned above (see an example in **Attachment 3**), and I did not find any objectional condition.

OSIS Evaluation: Those samples either didn't reach the carryover threshold or reached the carryover threshold but were below the lower limit of quantitation. No measured concentrations originating from carryover exceeded 5% of C_{max} for the subjects. Therefore, the carryover observed in above analytical runs does not impact the study data reliability.

Conclusion

After review of the inspectional findings, I conclude that the concentration data from **Study RXDX-101-15** (**NDA 212725** and **NDA 212726**) are reliable.

Concentration data from studies using similar methods (LC conducted at Ignyta between the end of the audited study (b) (4) and the end of the current surveillance interval should b ed reliable without an inspection.

Yiyue Zhang, Ph.D.
Staff Fellow

Final Classification

Analytical Site

NAI – Ignyta, Inc., San Diego, CA (FEI#: 3013164026)

Attachments:

Attachment 1. Consult from OND/OHOP/DOP2
Attachment 2. Carryover assessment guideline
Attachment 3. Carryover assessment of sample analysis Run 21

cc:
OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/CDER-OSIS-BEQ@fda.hhs.gov
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/DBIMOII/Babbitt

Draft: YZ 06/07/2019
Edit: RCA 6/07/2019 AD 06/07/2019

ECMS: Cabinets/CDER OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/Ignyta, Inc., San Diego, CA

OSIS File #: BE 8372 (NDA 212725); 8373 (NDA 212726)
FACTS: 11908313

ATTACHMENT 1

OSIS Consult
Request for Biopharmaceutical Inspections

Date	1/29/2019		
Subject	Request for Biopharmaceutical Inspections (BE)		
Addressed to	Project Management Staff Office of Study Integrity and Surveillance CDER-OSIS-BEQ@fda.hhs.gov		
Consulting Office/Division	DOP2 - Division of Oncology Products (DOP2)		
Project Manager	Kelie Reece		
PEPFAR?	☐		
Application Type / Num / Sup Num	NDA	212725 & 212726	001
Priority Application?	☒		
Drug Product	Entrectinib		
Sponsor Name	Genentech, Inc.		
Sponsor Address	1 DNA Way, South San Francisco, CA 94080-4990		
US Agent (if applicable)	Click here to enter text.		
US Agent Address	Click here to enter text.		
Electronic Submission	☒		
GDUFA/PDUFA/BsUFA Goal	8/18/2019		
Action Goal Date	8/16/2019		
Requested Review Goal Date	5/10/2019		

Inspection Request Detail (Complete all applicable fields)	
Study #1	
Study Number	RXDX-101-15
Study Title	A 2-Part, Open-Label, Randomized, 2-Period, Single-Dose Study to Assess the Relative Bioavailability of 2 Entrectinib Formulations Under Fasting Conditions and the Effect of Food on the Entrectinib F06 Formulation in Healthy Adult Male Subjects
Study Type	In Vivo BE
Other:	Click here to enter text.
Site #1 Type	Clinical
Site #1 Name	Celerion Arizona
Select one:	Routine Inspection
Street	2420 West Baseline Road
City	Tempe
State	AZ
Country	USA
tel	+1 602 437 0097
fax	+1 602 437 3386
Investigator	Terry O'Reilly, MD; Jeffrey Pearl, MD

email	Terry.oreilly@celerion.com; jeffrey.pearl@celerion.com
Site #2 Type	Analytical
Site #2 Name	Ignyta, Inc.
Select one:	Routine Inspection
Street	4545 Towne Centre Ct.
City	San Diego
State	CA
Country	USA
tel	+1 858 255 5959
fax	+1 858 643 9295
Investigator	Jerry Cao, Ph.D.
email	jcao@ignyta.com
Site #3 Type	Choose an item.
Site #3 Name	
Select one:	Choose an item.
Street	
City	
State	Click here to enter text.
Country	Choose an item.
tel	
fax	
Investigator	Click here to enter text.
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Study Report: (location, eg., 5.3.1.2)	\\CDSESUB1\evsprod\NDA212726\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\rxdx-101-15
Validation Report: (eg., 5.3.1.2)	\\CDSESUB1\evsprod\NDA212726\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\1087327
Bioanalytical Report: (eg., 5.3.1.4)	\\CDSESUB1\evsprod\NDA212726\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\rxdx-101-15

(please include specific review concerns or items to be addressed during the inspection in the appendix below)

Inspection Request Detail (Complete all applicable fields)	
Study #2	
Study Number	Click here to enter text.
Study Title	Click here to enter text.
Study Type	Choose an item.
Other:	Click here to enter text.
Site #1 Type	Choose an item.

Site #1 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #2 Type	Choose an item.
Site #2 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #3 Type	Choose an item.
Site #3 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Study Report: (location, eg., 5.3.1.2)	Click here to add report link.
Validation Report: (eg., 5.3.1.2)	Click here to add report link.
Bioanalytical Report: (eg., 5.3.1.4)	Click here to add report link.
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	

Inspection Request Detail (Complete all applicable fields)	
Study #3	
Study Number	Click here to enter text.
Study Title	Click here to enter text.

Study Type	Choose an item.
Other:	Click here to enter text.
Site #1 Type	Choose an item.
Site #1 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #2 Type	Choose an item.
Site #2 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Site #3 Type	Choose an item.
Site #3 Name	Click here to enter text.
Select one:	Choose an item.
Street	Click here to enter text.
City	Click here to enter text.
State	Click here to enter text.
Country	Choose an item.
tel	Click here to enter text.
fax	Click here to enter text.
Investigator	Click here to enter text.
email	Click here to enter text.
Study Report: (location, eg., 5.3.1.2)	Click here to add report link.
Validation Report: (eg., 5.3.1.2)	Click here to add report link.
Bioanalytical Report: (eg., 5.3.1.4)	Click here to add report link.
(please include specific review concerns or items to be addressed during the inspection in the appendix below)	

I. Appendix

Specific Items To be Addressed During the Inspection
Study RXDX-101-15 was conducted to demonstrate bioequivalence (BE) between F2A gelatin capsule and the to-be-marketed F06 HPMC capsule formulations. Since the F06 formulation has not been used in any patients efficacy/safety studies, study RXDX-101-15 is considered a pivotal BE study to support the registration of F06 formulation. In addition to the PK aspects of the study, safety events should be reviewed. NDA 212715 EDR link: \\CDSESUB1\evsprod\NDA212715\0001 Proposed indication: Patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive Review timeline: Standard NDA 212726 EDR link: \\CDSESUB1\evsprod\NDA212716\0001 Proposed indication: Adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive, (b) (4) metastatic solid tumors who have either progressed (b) (4) (b) (4) Review timeline: Priority (The requested inspection timeline is based on the priority review.) Product/Dosage Forms: Entrectinib, capsules: 100 mg and 200 mg (both indications)

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KELIE M REECE
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ATTACHMENT 2

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ARINDAM DASGUPTA
06/10/2019 09:22:46 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: Tuesday, June 4, 2019

To: Kelie Reece
Regulatory Health Project Manger
Division of Oncology Products 2 (DOP2)
Office of Hematology and Oncology Products (OHOP)

From: Nazia Fatima
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for ROZLYTREK (entrectinib) capsules, for oral use

NDA: 212725 and 212726

Office of Prescription Drug Promotion (OPDP) has reviewed the proposed product labeling (PI) and Medication Guide (MG) for ROZLYTREK (entrectinib) capsules, for oral use as requested by Division of Oncology Products (DOP2) in the consult dated January 15, 2019.

OPDP's review of the proposed PI and MG is based on a proposed draft PI and draft MG sent by electronic mail on May 23, 2019 to OPDP (Nazia Fatima) from DOP2 (Kellie Reece). OPDP's comments on the proposed draft PI are attached. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed MG were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

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NAZIA FATIMA
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 30, 2019
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ROZLYTREK (entrectinib)
Dosage Form and Route:	Capsules, for oral use
Application Type/Number:	NDA 212725 NDA 212726
Applicant:	Genentech, Inc.

1 INTRODUCTION

On December 18, 2018, Genentech, Inc., submitted for the Agency's review two original New Drug Applications (NDA-212725 and NDA-212726) for ROZLYTREK (entrectinib) capsules, for oral use, for the proposed indication of use for the treatment of ROS1-positive metastatic non-small cell lung cancer (NSCLC) and use for the treatment of adult and pediatric patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive, (b) (4) metastatic solid tumors who have either progressed (b) (4) (b) (4). On March 29, 2019, Genentech, Inc., submitted a revised US Prescribing Information (USPI) and Patient Package Insert (PPI) providing updated labeling combining NDA 212725 and 212726 into one label.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on January 15, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ROZLYTREK (entrectinib) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft ROZLYTREK (entrectinib) PPI received on March 29, 2019 and received by DMPP on OPDP on May 17, 2019.
- Draft ROZLYTREK (entrectinib) Prescribing Information (PI) received on March 29, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 17, 2019.

3 REVIEW METHODS

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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/s/

SHAWNA L HUTCHINS
05/30/2019 11:42:53 AM

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Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 212725 / NDA 212726
Submission Number	001
Submission Date	12/18/2018
Date Consult Received	1/15/2019
Clinical Division	DOP2

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

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND 120500 dated 01/24/2017 in DARRTS;
- Sponsor's response to Information Request dated 02/21/2019 (NDA 212725 Submission 0016);
- Study 1091319 CQT study report (NDA 212725 Submission 0001);
- Study STARTRK-2 clinical study report (NDA 212725 Submission 0001);
- Proposed labels: NDA 212725, NDA 212726 (Submission 0001 in each application); and
- Highlights of clinical pharmacology and cardiac safety.

1 SUMMARY

No large QTc prolongation effect (i.e., >20 ms) of entrectinib was observed in our 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 by-time 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 $C_{trough,ss}$ (refer to Section 4.3) – see Table 1 for overall results. The data however did not support an exposure-response analysis because 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 ΔQTcF > 60 ms (Section 4.4).

Table 1: The Largest Mean Increase in QTcF by Time. Shown as Point Estimates and the 90% CIs (FDA Analysis)

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)

The sponsor provided an integrated assessment of QTc categorical outliers across all 4 studies (refer to Section 4.6). Across these studies, patients were exposed to a range of doses from 100 mg to 2600 mg/day. According to the sponsor's analysis, 11 of the 355 patients reported a maximum QTcF interval post-baseline >500 or maximum QTcF increase from baseline > 60 ms, as determined by single or triplicate measures. The number of patients with these outlier values does not match the numbers presented in section 5.2 of the label (see Section 2). The sponsor 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. It does not appear that this patient was included in the sponsor's categorical tables.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

- Nonclinical studies indicate a potential liability for QT prolongation. The hERG IC50 for entrectinib is 0.6 μM which provides a 86-fold multiple to unbound human mean $C_{max,ss}$ (0.007 μM). QTc prolongation was not seen after a high single dose in dogs (300 mg/kg/day) but after multiple dosing at dose levels as low as 15 mg/kg/day with calculated unbound Cmax of ~0.002 mM (300-fold below hERG IC50). The hERG IC50 for the major metabolite, M5, was 10.4 μM.
- Entrectinib exposure is increased 4- to 5-fold with CYP3A inhibition and the effects on the QTc interval at these exposures were not assessed.
- There are a few patients with sporadic QTc values exceeding 500 ms or with increases from baseline >60 ms. Without a control arm, it is difficult to determine whether the incidence of QT outliers reflect background rates of QTc prolongation in this patient population or if these outlier values are due to entrectinib exposure.
- Although Patient (b) (6) had QTc >500 ms and an increase from baseline >60ms, this patient was not included in the sponsor's outlier analysis. The reason for excluding this patient is not clear.
- The sponsor reports in the Summary of Clinical Safety and in Section 5.2 of the label that1 patient with syncope (unspecified grade of syncope) reported concurrent condition of QT prolongation (unspecified grade of QT prolongation). No additional information was provided about this patient. This patient was not described in the CSR for Study STARTRK-2 (RXDX-101-02).
- The sponsor is proposing Section 5.2 for QTc prolongation. We cannot confirm the numbers in Section 5.2, but they appear to be based on data collected in 4 clinical trials with entrectinib doses ranging from 100 mg to 2600 mg/day. We defer to the Division regarding whether Warnings and Precautions for QT interval prolongation is necessary for the intended dose of 600 mg/day.

2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 0001 under NDA (b) (4). Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Our edits are for suggestions only and that we defer final labeling decisions to the Division.

5.2 QT Interval Prolongation
(b) (4)
Based on the severity of QTc prolongation, withhold [Entrectinib] (b) (4) and resume at a reduced dose or permanently discontinue (b) (4).
Reviewer's comments:

(b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Entrectinib (RXDX-101) is a potent inhibitor of tyrosine kinases, NTRK1/2/3-transforming tyrosine kinase proteins (TrkA, TrkB, TrkC), proto-oncogene tyrosine-protein kinase 1 (ROS1), and anaplastic lymphoma kinase (ALK). It is being developed as an anti-cancer agent for the treatment of patients with tumors that harbor NTRK1/2/3, ROS1 or ALK gene rearrangements. The proposed therapeutic dose is 600 mg QD.

The QT-IRT reviewed the QT assessment proposal under IND 120500 (Previous QT-IRT review dated 01/24/2017 in DARRTS). The sponsor proposed to collect triplicate ECG at screening as well as approximately C_{max} (4 hours postdose) and C_{trough} with matching PK at 3 consecutive cycles of treatment (Cycles 1, 2, and 3) in a subgroup of US and Japan population in the registration-enabling, Phase 2 trial (Study STARTRK-2, RXDX-101-02). QT-IRT found the proposal acceptable and provided one recommendation, which was to ensure enrollment of adequate number of subjects in the QT sub-study. There were no major changes in the protocol, primary analysis, endpoint, or therapeutic dose since the review.

The sponsor's analysis used ECG data at screening as the baseline. The reviewer's analysis used ECG data collected at predose on Cycle 1 Day 1 as the baseline. See Section 4.2 for additional details.

3.2 SPONSOR'S RESULTS

The results are presented for the data collected in study STARTRK-2/RXDX-101-02: 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. Report No.1089936 and 1091319. November 2018

3.2.1 Central tendency analysis

Entrectinib excluded a 20 ms increase in QTc at the 600 mg dose level when ECGs were collected at times corresponding to steady state $C_{max,ss}$ and C_{trough}. The results of the reviewer's analysis are similar to the sponsor's results. Please see Section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable. The aim is to exclude large mean effect (i.e., >20 ms).

3.2.1.1.1 QT bias assessment

Not applicable.

3.2.2 Categorical Analysis

FDA reviewer reviewed the data from the ECG subset (113/206) of Phase 2 trial (Study STARTRK-2, RXDX-101-02). Among 113 subjects, 1 subject had QTcF > 500 ms and 4 subjects had ΔQTcF > 60 ms. Please see Section 4.4 for additional details.

In response to an IR issued by FDA, sponsor provided integrated categorical analysis of QTcF and ΔQTcF (see Section 4.6). Among 181 subjects with triplicate recordings, 2 subjects had QTcF > 500 ms and 8 subjects had ΔQTcF > 60 ms. Among 93 patients with singular ECG reading (with baseline and at least one valid post−baseline value), 3 patients (3.2%) had a maximum QTcF increased from baseline > 60 ms, and no patient had a maximum QTcF interval post baseline > 500 ms. The sponsor did not provide categorical analysis of other measurements (PR, QRS and HR).

3.2.3 Safety Analysis

None of the AEs leading to death were related to QTc prolongation or serious ventricular arrhythmia.

Overall, 81/206 (39.3%) patients reported at least one SAE of any grade. The most commonly reported SAEs by SOC (≥5% of patients) were respiratory, thoracic and mediastinal disorders (14.1%), infections and infestations (13.1%) and nervous system disorder (8.7%). Cardiac SAEs occurred in 4.4% patients and included pericardial effusions, cardiac failure congestive, cardio-respiratory arrest, acute right ventricular failure, cardiac failure cardiogenic shock and ventricular extrasystoles (narrative is below).

AEs leading to withdrawal of entrectinib were reported across a variety of SOCs with the most common (≥1% of patients) being respiratory thoracic and mediastinal disorders (2.4%), cardiac disorders (1.9%), infections and infestations (1.9%), gastrointestinal disorders (1.0%), and general disorders and administration site conditions (1.0%). The PTs associated with cardiac disorders include cardio-respiratory arrest (1.0%), cardiac failure congestive (0.5%), cardiogenic shock (0.5%) and pericardial effusion (0.5%).

Three patients (1.5%) had AE of electrocardiogram QT prolonged. Two events were Grade 1 and 1 event was Grade 3 in severity. The narrative for the patient with Grade 3 QT prolongation and Grade 1 ventricular extrasystoles is provided.

- Patient (b) (6) is 57-year-old male with metastatic non-small cell lung carcinoma and medical history of arrhythmia. On (b) (6) (Study Day 1), the patient received the first dose of treatment with entrectinib. Pre-dose ECG was normal with QTc interval 439 ms. Post treatment, two electrocardiograms performed as part of the protocol at 16:19 and 16:36 hours showed QTc interval 595 ms and 507 ms, respectively, and the patient was diagnosed with Grade 3 electrocardiogram QT

prolonged, and Grade 1 ventricular extrasystoles (ventricular arrhythmia with frequent premature ventricular contractions). The patient was asymptomatic, however, was hospitalized for safety monitoring due to ventricular extrasystoles. No treatment or intervention was reported for the events. The same day at 18:34 hours, a repeat ECG was normal with QTc interval 454 ms. The event of electrocardiogram QT prolonged was considered resolved on the same day. On (b) (6) (Study Day 2), his ECG showed normal sinus rhythm with QTc of 432 ms and, the event of ventricular extrasystoles was considered resolved. The same day, he was discharged from the hospital. Entrectinib was interrupted for 2 days due to the events of ventricular extrasystoles and electrocardiogram QT prolonged on (b) (6) (Study Day 2) and the dose of entrectinib was reduced to 400 mg due to electrocardiogram QT prolonged. On (b) (6) (Study Day 4), entrectinib was restarted. Post-treatment, the patient remained asymptomatic and an ECG was normal with QTc interval of 429 ms.

Reviewer's comment: *Although Patient (b) (6) had QTc >500 ms and an increase from baseline >60ms, this patient was not included in the sponsor's outlier analysis. The reason for excluding this patient is not clear. The AE profile and QT outlier analysis are not consistent with a drug that significantly prolongs the QTc interval at 600 mg/day dose. There are no AEs of torsade, sudden death, serious ventricular arrhythmia, and ventricular tachycardia.*

3.2.4 Exposure-Response Analysis

The sponsor conducted concentration-QTc analysis using data from 107 patients who had time-matched PK/ECG data in STARTRK-2 study. The sponsor used ECG data at screening as the baseline. ECG data from Cycle 1 Day 1 pre-dose was not included in the analysis. The White Paper model was used to assess the relationship between parent drug or metabolite (M5) vs ΔQTcF. The analysis did not suggest positive concentration-QTc relationships for entrectinib or M5.

The reviewer did not conduct a formal exposure-response analysis for reasons stated in Section 4.5.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases or decreases in heart rate (i.e., |mean| < 10 bpm) were observed (see Section 4.3.2).

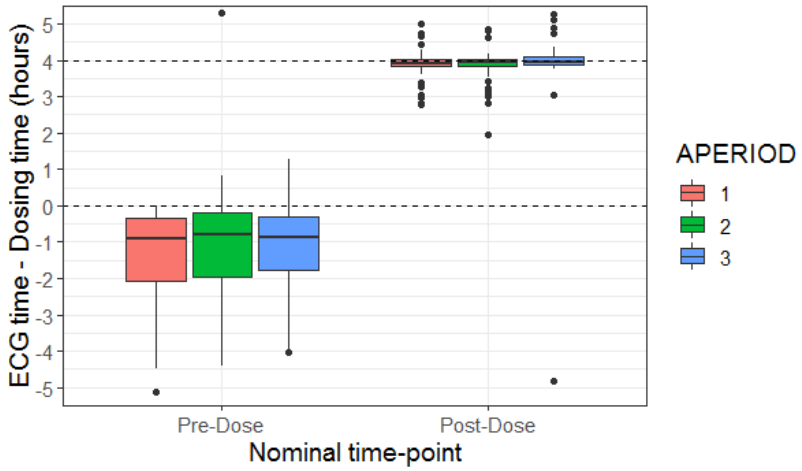
4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms from the ECG warehouse were reviewed. Overall ECG acquisition and interpretation in this study appears acceptable.

The sponsor used ECGs at screening as the baseline. These ECG data could be collected up to 30 days prior to the first dose. The reviewer examined the timing of ECG data collected at predose on Cycle 1 Day 1. It was shown that generally the predose samples were collected pre-dose and that the postdose samples were ~4 h as planned per protocol. Overall, ECG data collected predose on Cycle 1 Day 1 could be used as the baseline for QT assessment (Figure 1).

Figure 1. Distribution of ECG collection time relative to dosing.



4.2.2 QT bias assessment

Not applicable.

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

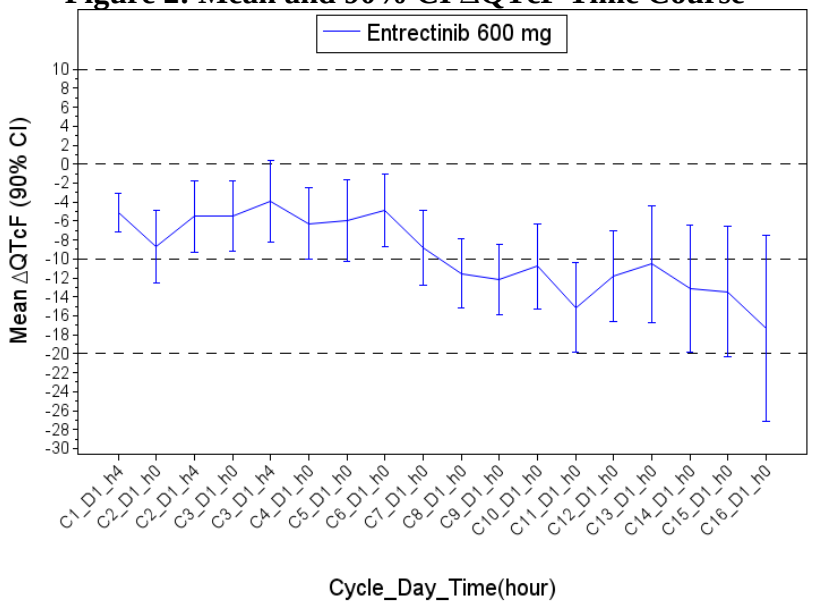
Table 2 presents the descriptive statistics (mean and 90% CI) for ΔQTcF ordered by period/cycle, cycle day and time point. We presented timepoints with at least 20 subjects.

Table 2: Descriptive Statistics for ΔQTcF

Cycle	DAY	Time	#Obs	#Subj	Mean	Lower 90% CL	Upper 90% CL
1	1	4	108	108	-5.13	-7.17	-3.09
2	1	0	87	87	-8.70	-12.50	-4.90
2	1	4	79	79	-5.53	-9.34	-1.73
3	1	0	88	88	-5.47	-9.22	-1.71
3	1	4	80	80	-3.93	-8.21	0.35
4	1	0	79	79	-6.30	-10.07	-2.53
5	1	0	73	73	-5.98	-10.27	-1.70
6	1	0	67	67	-4.89	-8.70	-1.07
7	1	0	66	65	-8.80	-12.78	-4.82
8	1	0	59	59	-11.54	-15.19	-7.89
9	1	0	49	49	-12.17	-15.87	-8.47
10	1	0	45	45	-10.79	-15.23	-6.34
11	1	0	42	42	-15.12	-19.86	-10.38
12	1	0	37	37	-11.82	-16.65	-6.99
13	1	0	34	34	-10.55	-16.72	-4.38
14	1	0	29	29	-13.11	-19.78	-6.45
15	1	0	29	29	-13.44	-20.29	-6.58
16	1	0	22	22	-17.33	-27.13	-7.54

Data is graphically presented in Figure 2.

Figure 2: Mean and 90% CI ΔQTcF Time Course



4.3.1.1 Assay sensitivity

Not applicable.

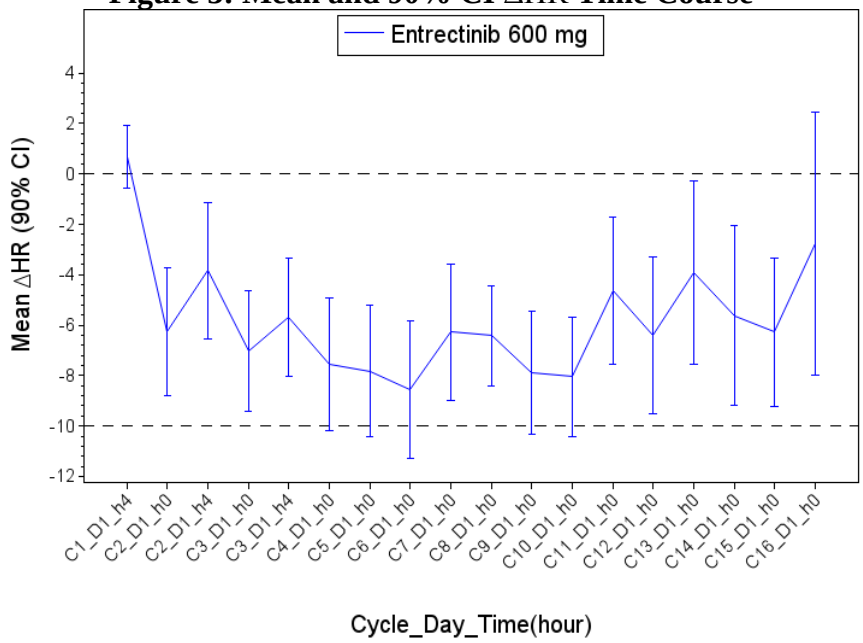
4.3.2 HR

Table 3 presents the descriptive statistics (mean and 90% CI) for ΔHR ordered by period/cycle, cycle day and time points. We presented timepoints with at least 20 subjects and data is also graphically presented in Figure 3.

Table 3: Descriptive Statistics for ΔHR

Cycle	DAY	Time	#Obs	#Subj	Mean	Lower 90% CL	Upper 90% CL
1	1	4	108	108	0.68	-0.56	1.92
2	1	0	87	87	-6.25	-8.81	-3.70
2	1	4	79	79	-3.84	-6.54	-1.13
3	1	0	88	88	-7.03	-9.43	-4.63
3	1	4	80	80	-5.70	-8.05	-3.36
4	1	0	79	79	-7.54	-10.17	-4.92
5	1	0	73	73	-7.82	-10.44	-5.19
6	1	0	67	67	-8.57	-11.31	-5.83
7	1	0	66	66	-6.28	-8.97	-3.58
8	1	0	59	59	-6.41	-8.41	-4.42
9	1	0	49	49	-7.87	-10.31	-5.43
10	1	0	45	45	-8.04	-10.40	-5.67
11	1	0	42	42	-4.63	-7.54	-1.71
12	1	0	37	37	-6.41	-9.52	-3.29
13	1	0	34	34	-3.90	-7.54	-0.26
14	1	0	29	29	-5.62	-9.19	-2.05
15	1	0	29	29	-6.26	-9.21	-3.32
16	1	0	22	22	-2.76	-7.97	2.45

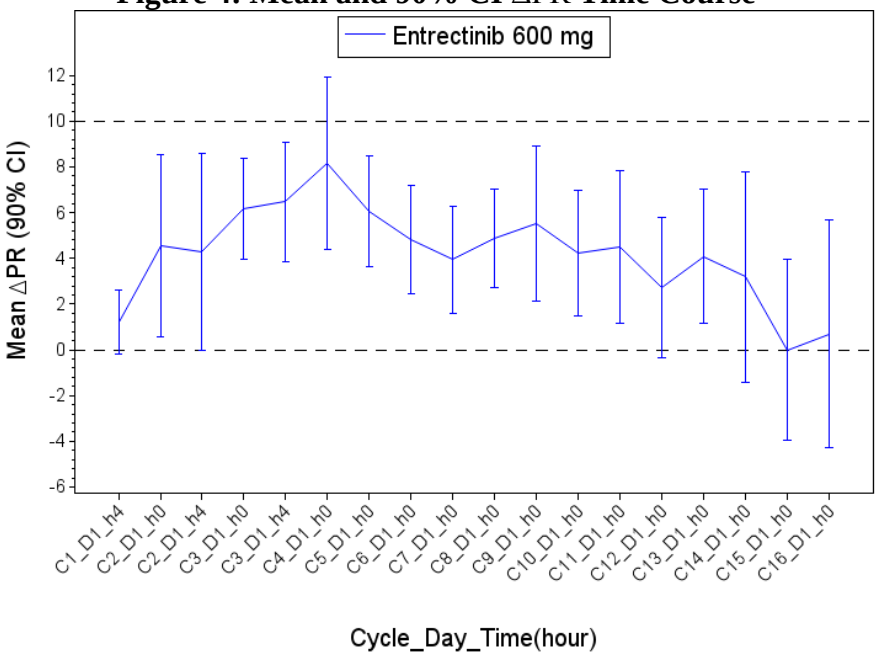
Figure 3: Mean and 90% CI ΔHR Time Course



4.3.3 PR

Figure 4 presents the descriptive statistics (mean and 90% CI) for ΔPR ordered by period/cycle, cycle day and time points. We presented timepoints with sample size of at least 20.

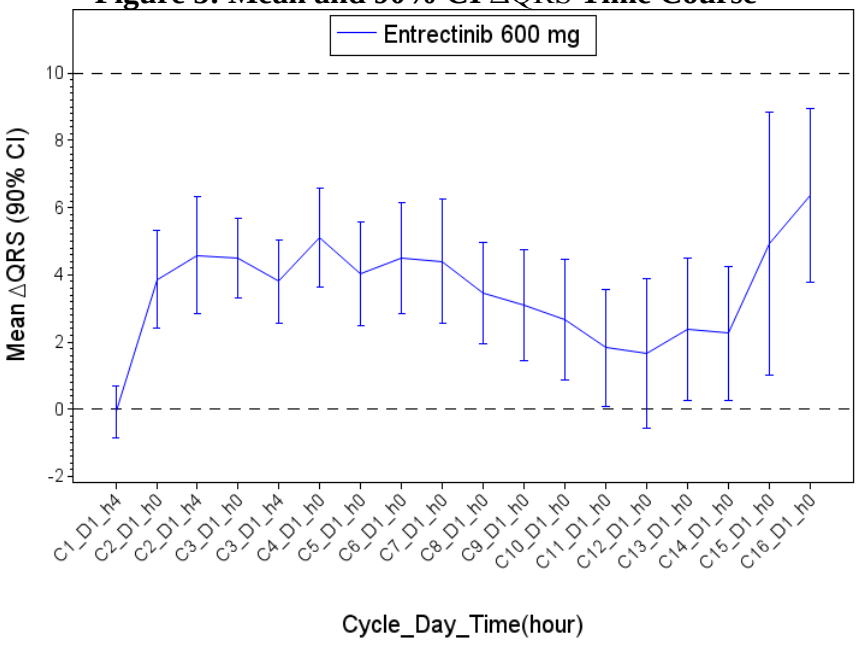
Figure 4: Mean and 90% CI ΔPR Time Course



4.3.4 QRS

Figure 5 presents the descriptive statistics (mean and 90% CI) for ΔQRS ordered by period/cycle, cycle day and time points. We presented timepoints with sample size of at least 20.

Figure 5: Mean and 90% CI ΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

This categorical analysis is based on a subset of ECG data (n=113). Because of missingness, some of the categories have total number of subjects less than 113.

4.4.1 QTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms and greater than 500 ms. There were two subjects who experienced QTcF above 480 ms.

Table 4: Categorical Analysis for QTcF

	Total (N)		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms		Value>500	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Entrectinib 600 mg	111	1226	103 (92.8%)	1205 (98.3%)	6 (5.4%)	19 (1.5%)	1 (0.9%)	1 (0.1%)	1 (0.9%)	1 (0.1%)

Note: Two subjects had missing values for QTcF

Note: *Two subjects had missing values for QTcF.*

lists the categorical analysis results for ΔQTcF. There were 4 subjects with ΔQTcF greater than 60 ms.

Table 5: Categorical Analysis of ΔQTcF

	Total (N)		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Entrectinib 600 mg	111	1219	93 (83.8%)	1166 (95.7%)	14 (12.6%)	49 (4.0%)	4 (3.6%)	4 (0.3%)

Note: Two subjects had missing values for QTcF.

4.4.2 PR

The outlier analysis results for PR are presented in Table 6. There were 22 subjects who experienced PR interval greater than 200 ms. Four subjects had PR>200 ms and an increase >25% from baseline.

Table 6: Categorical Analysis for PR

	Total (N)		Value<=200 ms		200 ms<Value<=220 ms		Value>220 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Entrectinib 600 mg	112	1217	90 (80.4%)	1133 (93.1%)	18 (16.1%)	67 (5.5%)	4 (3.6%)	17 (1.4%)

Note: One subject had missing values for PR.

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 7. There were 26 subjects who experienced QRS interval greater than 110 ms.

Table 7: Categorical Analysis for QRS

	Total (N)		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Entrectinib 600 mg	113	1234	58 (51.3%)	864 (70.0%)	29 (25.7%)	222 (18.0%)	26 (23.0%)	148 (12.0%)

4.4.4 HR

The outlier analysis results for HR are presented in Table 8. There were 16 subjects who experienced HR greater than 100 bpm.

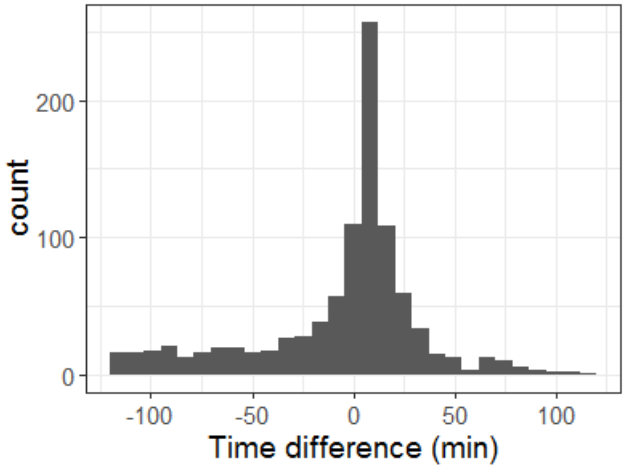
Table 8: Categorical Analysis for HR

	Total (N)		Value<=100 bpm		Value>100 bpm	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Entrectinib 600 mg	113	1234	97 (85.8%)	1210 (98.1%)	16 (14.2%)	24 (1.9%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The reviewer did not conduct a concentration-QTc analysis. There is only one dose level in the study. The PK/ECG sampling schedule is very sparse (i.e., C_{max} and C_{trough} only). The ratio of $C_{max,ss}/C_{max,first}$ and $C_{max,ss}/C_{min,ss}$ are both around 2-fold for the parent drug and the metabolite. The limited dose level and the sparse PK/ECG sampling schedule does not provide a wide exposure range to support concentration-QTc analysis. In addition, the sparse PK/ECG sampling schedule does not support an evaluation of potential delayed effect or to support the use of direct effect model. Lastly, it is desirable that ECG data is collected close to PK sampling and before PK data collection. In this study, close to 40% ECG data were collected after PK collection and only a small portion of ECG data were collected within 15 min before PK sampling (Figure 6). Note that approximately ~38% ECG samples were collected at 4 hr postdose. ~85% of these samples were collected within 15 min around PK sampling and ~65% of these samples were collected within 15 min before PK sampling. These data were acceptable for characterizing drug effect around Tmax using descriptive statistics.

Figure 6. Time difference between PK sampling time and ECG collection time. Positive values indicate ECG data collected before PK.



In exploratory analysis where a linear mixed effect model was applied to PK/ECG data (in the full dataset or in subsets where the absolute time difference is less than 15 min or 30 min), the reviewer obtained similar conclusions as the sponsor (i.e. a lack of positive concentration-QTc relationships and a lack of small effect when the parent drug or metabolite concentration was used as the exposure covariate).

4.5.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

Four clinical studies contributed to the integrated safety population (N=355). Across these studies, patients were exposed to a range of doses from 100 mg to 2600 mg/day.

Of the 355 patients, 181 patients had triplicate ECG recordings and 95 patients had single ECG recordings.

- In the 181 patients with triplicate ECGs readings, 2 patients (1.1%) had a maximum QTcF interval post baseline > 500 ms, 8 patients (4.4%) had a maximum QTcF increased from baseline > 60 ms, and 2 patients (1.1%) had a maximum QTcF interval post baseline > 500 ms and a maximum QTcF increased from baseline > 60 ms.
- In the 93 patients with singular ECG reading (with baseline and at least one valid post−baseline value), 3 patients (3.2%) had a maximum QTcF increased from baseline > 60 ms, and no patient had a maximum QTcF interval post baseline > 500 ms.

In total, 11 of the 355 patients reported a maximum QTcF interval post-baseline >500 or maximum QTcF increase from baseline > 60 ms, as determined by single or triplicate measures.

Narratives for the 2 patients with a maximum QTcF interval post baseline > 500 ms and a maximum QTcF increased from baseline > 60 ms are presented.

- A 59-year-old, female patient (patient ID: (b) (6)) from STARTRK-1 study had a baseline QTcF of 426 ms and experienced a post baseline QTcF interval of 501.6 ms (QTcF interval post-baseline > 500 ms, and maximum QTcF increase from baseline > 60 ms) at study day 485 (Cycle 17 day 28). The

patient has no relevant cardiac history. The patient was on metoclopramide and ondansetron (concomitant medications with QT prolongation potential) briefly at study day 1. At the time of the QTcF finding, the patient had no clinically relevant cardiac AE reported and her potassium or magnesium levels were within normal range. Entrectinib dose was not changed and the patient remained on entrectinib treatment.

- A 52 year-old-female patient (patient ID: (b) (6)) from STARTRK-2 study had a baseline QTcF of 408 ms. On study day 65 (end of treatment visit), the patient reported a QTcF of 545.3 ms (QTcF interval post-baseline > 500 ms, and maximum QTcF increase from baseline > 60 ms). The patient had a medical history of sinus tachycardia. At the time of the QTcF finding, the patient had no clinically relevant cardiac AE reported. The patient was not on concomitant medication that is known to prolong QT prior to the event. Her magnesium and potassium levels were within normal range at the time of the QTcF finding. End of treatment was noted to be on the same day.

Table 9: Categorical Outlier Analysis in Pooled Safety Population

Triplicate/Single ECGs Parameter	ALKA (N=57)	ST-01 (N=76)	ST-02 (N=206)	ST-NG (N=16)	Total (N=355)
Triplicate ECGs					
Maximum QTcF Interval Post Baseline (<=480 vs. >480 msec)*					
n$	0	76	105	0	181
<=480	0	75 (98.7%)	103 (98.1%)	0	178 (98.3%)
>480	0	1 (1.3%)	2 (1.9%)	0	3 (1.7%)
Maximum QTcF Interval Post Baseline (<=500 vs. >500 msec)					
n$	0	76	105	0	181
<=500	0	75 (98.7%)	104 (99.0%)	0	179 (98.9%)
>500	0	1 (1.3%)	1 (1.0%)	0	2 (1.1%)
Maximum QTcF Increase from Baseline (<=30 vs. > 30 msec)					
n#	0	76	105	0	181
<=30	0	66 (86.8%)	87 (82.9%)	0	153 (84.5%)
>30	0	10 (13.2%)	18 (17.1%)	0	28 (15.5%)
Maximum QTcF Increase from Baseline (<=60 vs. > 60 msec)					
n#	0	76	105	0	181
<=60	0	72 (94.7%)	101 (96.2%)	0	173 (95.6%)
>60	0	4 (5.3%)	4 (3.8%)	0	8 (4.4%)

Triplicate/Single ECGs Parameter	ALKA (N=57)	ST-01 (N=76)	ST-02 (N=206)	ST-NG (N=16)	Total (N=355)
Triplicate ECGs					
Maximum QTcF Interval Post Baseline and Increase from Baseline (msec)					
n#	0	76	105	0	181
Max. Int. > 500, Increase > 60	0	1 (1.3%)	1 (1.0%)	0	2 (1.1%)
Other	0	75 (98.7%)	104 (99.0%)	0	179 (98.9%)
Singular ECGs					
Maximum QTcF Interval Post Baseline (<=480 vs. >480 msec)*					
n$	0	0	94	1	95
<=480	0	0	93 (98.9%)	0	93 (97.9%)
>480	0	0	1 (1.1%)	1 (100.0%)	2 (2.1%)
Maximum QTcF Interval Post Baseline (<=500 vs. >500 msec)					
n$	0	0	94	1	95
<=500	0	0	94 (100.0%)	1 (100.0%)	95 (100.0%)
>500	0	0	0	0	0
Maximum QTcF Increase from Baseline (<=30 vs. > 30 msec)					
n#	0	0	92	1	93
<=30	0	0	75 (81.5%)	1 (100.0%)	76 (81.7%)
>30	0	0	17 (18.5%)	0	17 (18.3%)

Triplicate/Single ECGs Parameter	ALKA (N=57)	ST-01 (N=76)	ST-02 (N=206)	ST-NG (N=16)	Total (N=355)
Singular ECGs					
Maximum QTcF Increase from Baseline (<=60 vs. > 60 msec)					
n#	0	0	92	1	93
<=60	0	0	89 (96.7%)	1 (100.0%)	90 (96.8%)
>60	0	0	3 (3.3%)	0	3 (3.2%)
Maximum QTcF Interval Post Baseline and Increase from Baseline (msec)					
n#	0	0	92	1	93
Max. Int. > 500, Increase > 60	0	0	0	0	0
Other	0	0	92 (100.0%)	1 (100.0%)	93 (100.0%)

Baseline is the patient's last observation prior to initiation of study drug.
An average of the triplicate is taken.
In case multiple observations are available within a post baseline visit, the worst value is reported.
* The maximum QTcF interval post baseline is taken into account, even if a patient has no baseline QRcF value available.
$ Number of patients with at least one valid post-baseline value.
# Number of patients with baseline and at least one valid post-baseline value.

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LABEL AND LABELING REVIEW
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Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	April 4, 2019
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 212725 and NDA 212726
Product Name and Strength:	Entrectinib Capsules, 100 mg and 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Genentech, Inc.
FDA Received Date:	December 18, 2018 and March 29, 2019
OSE RCM #:	2018-2756 and 2018-2760
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of these NDAs, this review evaluates the proposed entrectinib prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of materials submitted found the proposed entrectinib PI, container labels, and carton labeling may be improved to promote safe use of this product.

We note the recommended dose of entrectinib for pediatric patients (b) (4) (b) (4). We also note Table 1: Dosing for Pediatric Patients in the PI, provides the daily dose for pediatric patients with a BSA (b) (4). It is unclear if all pediatric patients for which dosing is provided will be able to follow the recommended administration process (i.e., swallow capsules whole). (b) (4) (b) (4) (b) (4) however, we are concerned that providing dosing information (i.e., BSA and corresponding recommended dose) for pediatric patients (b) (4) (b) (4) may lead to administration errors (b) (4) (b) (4) (b) (4). Therefore, we recommend to only include dosage information for the pediatric patients who can swallow capsules whole (i.e. only provide BSA

values that reasonably reflect pediatric patients who should have the ability to swallow capsules whole).

Upon evaluation of the proposed PI, container labels, and carton labeling, we noted the product storage statement, [redacted]. We were concerned that including the word "below" [redacted] could lead to product storage errors [redacted], so we contacted CMC via email communication on February 13, 2019 regarding the acceptability of the proposed product storage statement. Subsequently, CMC sent an Information Request (IR) to Genentech on February 16, 2019 requesting justification for the proposed product storage statement. On February 27, 2019 in response to the CMC IR, Genentech proposed to revise the product storage statement to "Store below 30°C (86°F)" to avoid confusion [redacted] and stated that the proposed product is stable at temperature ranges below USP controlled room temperature.[a] Given Genentech stated the proposed product is stable at temperature ranges below USP controlled room temperature, we defer to CMC on the final determination of the product storage statement.

4 CONCLUSION & RECOMMENDATIONS

The entrectinib PI, container labels and carton labeling can be revised to promote safe use of this product as described in Section 4.1 and Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Dosage and Administration Section

[redacted]

b. In Section 2.3,

[a] Genentech, Inc. Responses to FDA Request for Information NDA 212725. San Francisco (CA): Genentech, Inc.; 2019 FEB 27. Available from: \\cdsesub1\evsprod\nda212725\0015\m1\us\20190227-resp-fda-req.pdf

[b] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2019 APR 01]. Available from: https://www.ismp.org/recommendations/error-prone-abbreviations-list.

i. we recommend to only include dosage information for the pediatric patients who can swallow capsules whole by only providing BSA values that reasonably reflect pediatric patients who should have the ability to swallow capsules whole in Table 1.

ii. revise the statement (b) (4) (b) (4) to "Do not open, crush, chew, or dissolve the capsules." to minimize administration errors.

c. (b) (4)

2. Patient Counseling Information

a. Under "Administration" revise (b) (4) to "...swallow capsules whole..." for clarity and to be consistent with language in Section 2.(b) (4) that reads "Swallow capsules whole".

B. General Comments

1. We note entrectinib capsules should be swallowed whole (i.e., should not be opened or dissolved). Since NTRK fusion-positive solid tumors are present in young pediatric patients who cannot swallow capsules whole, we ask the Review Team to consider if Genentech should be asked to develop a formulation post-approval, if approved, to address this medical need.

4.2 RECOMMENDATIONS FOR GENENTECH, INC.

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

A. General Comments (Container labels & Carton Labeling)

1. Ensure the font color of the proprietary name (b) (4) and the color used to highlight the 200 mg strength (b) (4) appear in unique, non-overlapping colors. The use of the same (b) (4) color font for both the proprietary name and to highlight the 200 mg strength minimizes the difference between the strengths, which may lead to wrong strength selection errors.

2. The similarity of the product code numbers in the NDC number has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (b) (4). Revise the product code in the NDC numbers to ensure that the middle 3 digits are different between the strengths. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their font size

in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXXX-XXX-XX.c

3. As presented, the NDC package codes for the 30-count bottle and the 90-count bottle are identical (b) (4). Revise the package code in the NDC numbers to ensure that the last 2 digits are different between the package sizes.
4. Revise (b) (4) to "See prescribing information."
5. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Labels (100 mg)

1. We note two barcodes in close proximity to each other on the 100 mg container label. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence of multiple barcodes is confusing to the healthcare providers.[d] Therefore, we recommend relocating one of the barcodes to a different location.

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[d] Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Entrectinib received on March 29, 2019 from Genentech, Inc.

Table 2. Relevant Product Information for Entrectinib	
Initial Approval Date	N/A
Active Ingredient	Entrectinib
Indication	• For the treatment of patients with metastatic non-small cell lung cancer (NSCLC) that is ROS1-positive. • For the treatment of adult and pediatric 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.
Route of Administration	Oral
Dosage Form	Capsules
Strength	100 mg and 200 mg
Dose and Frequency	<u>Recommended Dosage in Adult Patients</u> 600 mg orally once daily with or without food (b) (4)
How Supplied	100 mg: HDPE bottles of 30 capsules 200 mg: HDPE bottles of 90 capsules
Storage	Store below 30°C (86°F)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Entrectinib labels and labeling submitted by Genentech, Inc.

- Container labels received on December 18, 2018
- Carton labeling received on December 18, 2018
- Prescribing Information (Image not shown) received on March 29, 2019

G.2 Label and Labeling Images

Container labels

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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