CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219713Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	New Drug Application
Application Number(s)	219713
Priority or Standard	Priority
Submit Date(s)	10/23/2024
Received Date(s)	10/23/2024
PDUFA Goal Date	06/23/2025
Division/Office	DO2/OOD
Review Completion Date	See electronic stamp date
Established Name	Taletrectinib
(Proposed) Trade Name	IBTROZI
Pharmacologic Class	Kinase inhibitor
Code name	Taletrectinib (DS-6051b and AB-106)
Applicant	Nuvation Bio
Formulation(s)	Taletrectinib capsules: 200 mg
Dosing Regimen	600 mg orally once daily on an empty stomach (no food intake at least 2 hours before and 2 hours after taking taletrectinib)
Applicant Proposed Indication(s)/Population(s)	The treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC)
Recommendation on Regulatory Action	Traditional approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC)

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

CDRH=Center for Devices and Radiological Health

Glossary

AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLA	Biologics License Application
BOR or cBOR	(confirmed) best overall response
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
CR or cCR	(confirmed) complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DMF	Drug Master File
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
HNSTD	highest non-severely toxic dose
HR	hazard ratio
IAP	Intracranial Analysis Population
IC	intracranial
ICH	International Council for Harmonisation
ILD	interstitial lung disease
IRC	Independent Review Committee

ISE	integrated summary of efficacy
ISS	integrated summary of safety
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mDOR	median duration of response
mOS	median overall survival
mPFS	median progression-free survival
mRECIST	modified Response Evaluation Criteria in Solid Tumors
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	no-observed-adverse-effect level
NR	not reached
NSCLC	non-small cell lung cancer
OCE	Oncology Center of Excellence
ORR or cORR	(confirmed) objective response rate
OS	overall survival
OSEI	other safety events of interest
OSI	Office of Scientific Investigations
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
popPK	population pharmacokinetics
PPI	proton pump inhibitor
PR or cPR	(confirmed) partial response
PRO	patient-reported outcome
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategies
REP	Response Evaluable Population

REP2	Response Evaluable Population per Investigator Assessment
REP3	Response Evaluable Population with ≥14 Months of Follow-up
ROS1	c-ros oncogene 1
RTK	receptor tyrosine kinase
QD	once daily
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMQ	standardized MedDRA query
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTF	time to treatment failure
TTiP	time to intracranial progression
TTR	time to response
ULN	upper limit of normal
US	United States

1 Executive Summary

1.1. Product Introduction

Taletrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1 (ROS1). There are currently no FDA approved indications for taletrectinib.

The Applicant's proposed indication is for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC). The recommended dosage regimen is taletrectinib 600 mg orally once daily on an empty stomach (no food intake at least 2 hours before and 2 hours after taking taletrectinib).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

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

The recommendation for traditional approval is based on the results from two single-arm studies in patients with advanced *ROS1*-positive NSCLC and other solid tumors: Study AB-106-G208 (Study G208 or TRUST-II, NCT04919811) and Study AB-106-C203 (Study C203 or TRUST-I, NCT04395677). Study G208 was a global multi-regional study including clinical sites in the US, Canada, Europe and Asia. Study C203 was a single-country (China only) study. The statutory requirement for demonstration of substantial evidence of effectiveness is met based on the efficacy results from two adequate and well-controlled trials. The indication includes both patients who are ROS1 tyrosine kinase inhibitor (TKI) naïve and patients who have received one prior ROS1 TKI based on the evidence of effectiveness demonstrated in both populations. Additionally, responses were observed in subsets of patients with CNS metastases and in patients whose tumors had *ROS1* resistance mutations.

The primary evidence of effectiveness for this application is derived from data from Studies G208 (Cohorts 1 and 2) and C203. Patients with *ROS1*-positive NSCLC with or without prior chemotherapy who had received one prior ROS1 TKI or were ROS1 TKI-naïve and received at least one dose of taletrectinib 600 mg QD as the starting dose, as of a data cutoff (DCO) date of October 28, 2024, were included in the primary efficacy population. The primary objective was to determine the confirmed objective response rate (ORR) as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy outcome measures included duration of response (DOR) and confirmed intracranial objective response rate (IC-ORR) assessed by BICR per modified RECIST v1.1.

Given the differences in baseline demographics and follow-up durations between Study C203 and Study G208, which enrolled its first patient approximately 14 months after the first patient enrolled on Study C203, FDA determined it was not appropriate to present pooled efficacy results in the product label, particularly those dependent upon follow-up time such as DOR. Therefore, efficacy results are presented by individual study.

Among the 103 patients in Study C203 and 54 patients in Study G208 (157 patients in total) with NSCLC who were ROS1 TKI-naïve, the ORRs were 90% (95% CI: 83, 95) and 85% (95% CI: 73, 93), respectively. The median DOR was not reached (NR) (95% CI: 30.4 months, NR) in Study C203. The median DOR in Study G208 was also not reached; (b) (4)

In the TKI-naïve cohort, 72% of responders in Study C203 and 63% of responders in Study G208 had an observed DOR ≥ 12 months. In addition, 15 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 as assessed by BICR were observed in 11 patients.

Among the 66 patients in Study C203 and 47 patients in Study G208 (113 patients in total) with NSCLC who had received prior treatment with a ROS1 TKI, the ORRs were 52% (95% CI: 39, 64) and 62% (95% CI: 46, 75), respectively. The median DOR in Study C203 was 13.2 months (95% CI: 7.7, 24.9). (b) (4)

In the TKI-pretreated cohort, 74% of responders in Study C203 and 83% of responders in Study G208 had an observed DOR ≥ 6 months; 44% of responders in Study C203 and 45% of responders in Study G208 had a DOR ≥ 12 months. In addition, 24 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 as assessed by BICR were observed in 15 patients.

Among 32 patients in Studies G208 and C203 who had re-biopsied samples tested by next-generation sequencing (NGS) after progression on a prior ROS1 TKI, 15 had resistance mutations. Responses were observed in 8 of these 15 patients; all responding patients had tumors with solvent front mutation G2032R.

Additional supportive information derives from other products in the same class which are approved in the same indication as well as strong mechanistic evidence of *ROS1* alterations being molecular drivers of NSCLC. Repotrectinib, entrectinib and crizotinib were approved for the treatment of adult patients with metastatic NSCLC whose tumors are *ROS1*-positive based on robust and durable tumor response rates and taletrectinib has a mechanism of action similar to these approved therapies.

The magnitude and duration of responses observed with taletrectinib are considered to reflect clinically meaningful benefit in the indicated patient population; these results, coupled with the rarity of *ROS1*-positive NSCLC, render the conduct of a randomized trial challenging. The review team considers these results to be sufficient to establish clinical benefit in this genetically defined, rare subgroup of patients with *ROS1*-positive metastatic NSCLC. The submitted evidence meets the statutory evidentiary standard for traditional approval. Treatment with taletrectinib demonstrated a clinically meaningful and durable ORR among adult patients with locally advanced or metastatic *ROS1*-positive NSCLC who were ROS1 TKI-naïve and ROS1 TKI-pretreated. Subgroup analyses also indicated activity in CNS metastases and in patients with resistance mutations following prior ROS1 TKI therapy. Therefore, traditional approval is recommended for taletrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

There are more than 226,000 new cases of lung cancer annually in the United States, and lung cancer is the leading cause of cancer-related death accounting for approximately 124,000 deaths per year (SEER 2025). Non-small cell lung cancer (NSCLC) accounts for nearly 85% of lung cancer cases. *ROS1* rearrangement occurs in 1 to 2% of NSCLC and *ROS1* fusions have been identified as an actionable target (Rikova 2007). The clinicopathologic characteristics of patients with *ROS1*-positive NSCLC include median age at diagnosis of 50 years, higher incidence in patients of Asian race, and greater incidence in never-smokers compared to patients with NSCLC without *ROS1* fusions. Overall survival (OS) for patients with NSCLC at 5 years has been reported as 22% (SEER Zappa 2016); patients with *ROS1*-positive NSCLC had similar outcomes based on data in the era prior to the availability of ROS1-targeted therapy. ROS1-targeted therapy is recommended for the treatment of *ROS1*-positive NSCLC; approved therapies include crizotinib, entrectinib, and repotrectinib, which were all approved based on ORR and DOR results in single-arm trials. Notably, mechanisms for resistance to TKI therapy exist in patients with *ROS1*-positive NSCLC. Gainor et al. identified resistance mutations (G2032R [41%], D2033N [6%], and S1986F [6%]) in 53% of repeat biopsies from patients with *ROS1*-positive NSCLC who progressed on crizotinib (Gainor 2017). Data supporting the approvals of crizotinib and entrectinib did not include patients previously treated with a ROS1-targeted therapy. Data supporting the approval of repotrectinib included patients who had not received a ROS1-targeted therapy as well as patients who had been previously treated with a ROS1-targeted therapy.

Taletrectinib is an inhibitor of proto-oncogene tyrosine-protein kinase ROS1. There are currently no FDA approved indications for taletrectinib.

The primary evidence of effectiveness for this application is derived from data from patients with *ROS1*-positive NSCLC (including patients previously treated with a ROS1 TKI and those naïve to a ROS1 TKI) from two studies (Study AB-106-C203 [TRUST-I or Study C203] and Study AB-106-G208 [TRUST-II or Study G208]). The primary evidence supporting safety is based on safety data from five studies (Studies AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102 and DS6051-A-U101).

In Studies C203 and G208, patients with *ROS1*-positive NSCLC with or without prior chemotherapy who had received one prior ROS1 TKI or who were ROS1 TKI-naïve and received at least one dose of taletrectinib 600 mg QD as the starting dose, as of a data cutoff (DCO) date of October 28, 2024, were included in the primary efficacy population. The primary endpoint was confirmed objective response rate (ORR) as assessed by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Additional efficacy outcome measures included duration of response (DOR) and confirmed intracranial objective response rate (IC-ORR) assessed by BICR per modified RECIST v1.1.

Among the 103 patients in Study C203 and 54 patients in Study G208 (157 patients in total) with NSCLC who were ROS1 TKI-naïve, the ORRs were 90% (95% CI: 83, 95) and 85% (95% CI: 73, 93), respectively. The median DOR was not reached (NR) (95% CI: 30.4 months, NR) in Study C203. The median DOR in Study G208 was also not reached; (b) (4) In the TKI-naïve cohort, 72% of responders in Study C203 and 63% of responders in Study G208 had an observed DOR ≥ 12 months. In addition, 15 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 by BICR were observed in 11 patients.

Among the 66 patients in Study C203 and 47 patients in Study G208 (113 patients in total) with NSCLC who had received prior treatment with a ROS1 TKI, the ORRs were 52% (95% CI: 39, 64) and 62% (95% CI: 46, 75), respectively. The median DOR in Study C203 was 13.2 months (95% CI: 7.7, 24.9). (b) (4) In the TKI-pretreated cohort, 74% of responders in Study C203 and 83% of responders in Study G208 had an observed DOR ≥ 6 months; 44% of responders in Study C203 and 45% of responders in Study G208 had a DOR ≥ 12 months. In addition, 24 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 by BICR were observed in 15 patients.

Among 32 patients in Studies G208 and C203 who had re-biopsied samples tested by next-generation sequencing (NGS) after failure of a prior ROS1 TKI, 15 had resistance mutations. Responses were observed in 8 of these 15 patients; all responding patients had tumors with solvent front mutation G2032R.

Taletrectinib has an acceptable safety profile when assessed in the context of a life-threatening disease. The pooled safety population included 352 patients with *ROS1*-positive NSCLC (N=337) and other solid tumors (N=15) who received at least one dose of taletrectinib 600 mg QD. The *ROS1*-positive NSCLC 600 mg QD safety population included the 337 patients with *ROS1*-positive NSCLC who received at least one dose of taletrectinib 600 mg QD.

Among patients in the pooled safety population (n=352), serious adverse reactions occurred in 30% of patients. The most common (⩾20%) adverse reactions were diarrhea, nausea, vomiting, dizziness, rash, constipation, and fatigue. The most common (≥5%) Grade 3 or 4 laboratory abnormalities were increased ALT, increased AST, decreased neutrophils, and increased creatine phosphokinase.

Among patients with *ROS1*-positive NSCLC in the 600 mg QD safety population (n=337), serious adverse reactions occurred in 31% of patients. Serious adverse reactions occurring in ≥2% of patients included pneumonia (7%), pleural effusion (4.7%), and hepatotoxicity (2.4%). Fatal

adverse reactions occurred in 18 (5%) patients who received taletrectinib, including pneumonia (2.4%), multiple organ dysfunction syndrome (0.6%), hepatotoxicity (0.6%), cardiac arrest (0.6%), cardiac failure (0.3%), cardiopulmonary failure (0.3%), respiratory failure (0.3%), and death not otherwise specified (0.3%). Permanent discontinuation of taletrectinib was required in 7% of patients due to adverse reactions; adverse reactions resulting in permanent discontinuation in ≥2 patients were pneumonia, ILD, and hepatotoxicity. Dosage interruptions due to an adverse reaction occurred in 41% of patients; adverse reactions which required dosage interruption in ≥5% of patients included increased AST and increased ALT. Dose reductions due to an adverse reaction occurred in 29% of patients; adverse reactions that required dosage reductions in ≥5% of patients included increased ALT and increased AST. The most common adverse reactions (≥15%) were diarrhea (64%), nausea (47%), vomiting (43%), dizziness (22%), rash (22%), constipation (21%), fatigue (20%), QTc prolongation (19%), peripheral neuropathy (17%), decreased appetite (16%), cough (16%) and dysgeusia (15%). The most common (≥5%) Grade 3 or 4 laboratory abnormalities were increased ALT (13%), increased AST (10%), decreased neutrophils (5%), and increased creatine phosphokinase (5%).

Safety risks identified as significant and serious enough to warrant inclusion in the Warnings and Precautions section of labeling for taletrectinib are hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, QTc prolongation, hyperuricemia, myalgia with creatine phosphokinase elevation, skeletal fractures, and embryo-fetal toxicity. These safety concerns are adequately addressed in the Warnings and Precautions section and dose modification recommendations included in the product label. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Taletrectinib will be prescribed by oncologists who are familiar with monitoring, identifying, and managing the toxicities described in the USPI.

Although the safety profile of taletrectinib 600 mg QD is acceptable in the indicated population of patients with locally advanced or metastatic NSCLC in the context of the observed efficacy, preliminary evidence from a randomized dose optimization study suggests that a lower dose may provide similar efficacy results, particularly in patients with TKI-naïve disease, with an improved safety profile. Further, administration with food may result in improved tolerability. A multicenter trial to further characterize known serious risks with taletrectinib and evaluate the safety and activity of a lower daily dosage of 400 mg QD taken with standard meals in patients with advanced or metastatic *ROS1*-positive NSCLC who are TKI-naïve and patients who are TKI-pretreated with one prior ROS1 TKI will be conducted as a post-marketing requirement to further evaluate the optimal dose of taletrectinib.

Four post-marketing requirements (PMRs) and four post-marketing commitments (PMCs) will be included in the approval letter. PMRs were issued to address the requirements of the Pediatric Research Equity Act (PREA), to further evaluate the safety and activity of taletrectinib at the dosage of 400 mg QD, to evaluate the safety of the drug in patients with moderate or severe hepatic impairment, and to address the potential for drug-drug interactions (DDIs). PMCs were issued to provide a companion diagnostic (CDx) device for patient selection, to provide updated DOR results from patients in the efficacy populations included in the product label, to evaluate the effect of taletrectinib on the pharmacokinetics of

sensitive substrates of CYP3A and CYP1A2, and to evaluate the effect of H2-receptor antagonists on the exposure of taletrectinib.

The clinical review team determined that it is in the best interest of U.S. patients to approve taletrectinib before a CDx assay is available. Given the routine use of *ROS1* fusion testing in the community and the availability of FDA approved CDx *ROS1* fusion tests for use with other approved ROS1 TKIs, FDA considers there is limited risk of inappropriate selection of patients for taletrectinib treatment. Since an application for an in vitro CDx device was not submitted for contemporaneous approval with this NDA, the approved labeling will state that there is no FDA-approved test for selecting patients for treatment with taletrectinib. A PMC will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a CDx test to detect *ROS1* fusions for identifying patients who may benefit from taletrectinib.

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer exceeds 226,000 new cases annually in the United States, and nearly 85% of lung cancer cases are non-small cell lung cancer (NSCLC). (SEER 2025) • *ROS1* rearrangement occurs in 2% of NSCLC and *ROS1* fusions have been identified as an actionable target (Rikova 2007). • The clinicopathologic characteristics of patients with *ROS1*-positive NSCLC include a median age at diagnosis of 50 years, Asian race, and never-smokers.	Locally advanced *ROS1*-positive NSCLC is a life-threatening condition with poor survival.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Overall survival (OS) for patients with NSCLC at 5 years has been reported as 22% (SEER Zappa 2016); patients with *ROS1*-positive NSCLC have similar outcomes based on data in the era prior to the availability of ROS1-targeted therapy. Patients also experience disease and treatment sequelae such as respiratory, central nervous system (CNS), and hepatic complications. • In addition to poor long-term survival, there are resistance mechanisms to TKIs for *ROS1*-positive NSCLC; ROS1 resistance mutations include G2032R (41%), D2033N (6%), and S1986F (6%) (Gainer 2017).	
Current Treatment Options	• ROS1 TKI therapy is the current standard of care for the treatment of patients with advanced or metastatic *ROS1*-positive NSCLC (Marinelli D 2022). • Repotrectinib, entrectinib and crizotinib are approved for adult patients with metastatic *ROS1*-positive NSCLC. • The response rate included in the product labels for patients with advanced or metastatic *ROS1*-positive NSCLC who were ROS1 TKI naïve is 66% (95% CI: 51, 79) for crizotinib, 74% (95% CI: 64, 83) for entrectinib and 79% (95% CI: 68, 88) for repotrectinib. The response rate included in the product label for patients with advanced or metastatic *ROS1*-positive NSCLC who previously received ROS1 TKI was 38% (95% CI: 25, 52) for repotrectinib. Entrectinib and repotrectinib have shown activity against brain metastases in *ROS1*-positive NSCLC. Repotrectinib has demonstrated activity in patients with tumors with ROS1 resistance mutations. These therapies are associated with pulmonary, hepatic, and CNS toxicity.	While there are approved therapies for patients with advanced or metastatic *ROS1*-positive NSCLC, resistance mutations have been identified, and there is only one ROS1 TKI approved for patients previously treated with a ROS TKI. Additional therapeutic options, particularly if associated with some differences in toxicity profile, may provide improved access to effective therapies for patients with *ROS1*-positive NSCLC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The primary efficacy data supporting this application is derived from Studies G208 (Cohorts 1 and 2) and C203, single-arm trials in patients with locally advanced or metastatic *ROS1*-positive NSCLC with or without prior chemotherapy who had received one prior ROS1 TKI or were ROS1 TKI-naïve. • Among the 103 patients in Study C203 and 54 patients in Study G208 (157 patients in total) with NSCLC who were ROS1 TKI-naïve, the ORRs were 90% (95% CI: 83, 95) and 85% (95% CI: 73, 93), respectively. The median DOR was not reached (NR) (95% CI: 30.4 months, NR) in Study C203. The median DOR in Study G208 was also not reached: (b) (4) In the TKI-naïve cohort, 72% of responders in Study C203 and 63% of responders in Study G208 had an observed DOR ≥ 12 months. In addition, 15 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 as assessed by BICR were observed in 11 patients. • Among the 66 patients in Study C203 and 47 patients in Study G208 (113 patients in total) with NSCLC who had received prior treatment with a ROS1 TKI, the ORRs were 52% (95% CI: 39, 64) and 62% (95% CI: 46, 75), respectively. The median DOR in Study C203 was 13.2 months (95% CI: 7.7, 24.9). (b) (4) In the TKI-pretreated	The submitted evidence meets the statutory evidentiary standard for traditional approval. The durable ORR provides evidence of a clinically meaningful benefit of taletrectinib in patients with *ROS1*-positive NSCLC. A post-marketing commitment (PMC) will be issued to obtain a more precise estimation of the BICR-assessed ORR and DOR for the 139 responders in the response evaluable population of 157 ROS1 TKI-naïve patients and for the 63 responders in the response evaluable population of 113 ROS1 TKI-pretreated patients, after all responders have been followed for at least 18 months from the date of initial response.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cohort, 74% of responders in Study C203 and 83% of responders in Study G208 had an observed DOR ≥ 6 months; 44% of responders in Study C203 and 45% of responders in Study G208 had a DOR ≥ 12 months. In addition, 24 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 as assessed by BICR were observed in 15 patients. • Among 32 patients who had re-biopsied samples tested by next-generation sequencing after failure of a prior ROS1 TKI in Studies G208 and C203, 15 had resistance mutations. Responses were observed in 8 of these 15 patients; all responding patients had tumors with solvent front mutation G2032R.	
Risk and Risk Management	• The pooled safety population included 352 patients with solid tumors who received at least one dose of taletrectinib 600 mg QD. The *ROS1*-positive NSCLC 600 mg QD safety cohort included 337 patients with *ROS1*-positive NSCLC who received at least one dose taletrectinib 600 mg QD. • The Warnings and Precautions in the product label for taletrectinib are hepatotoxicity, ILD/pneumonitis, QTc prolongation, hyperuricemia, myalgia with CPK elevation, skeletal fractures, and embryo-fetal toxicity. • Among patients in the *ROS1*-positive NSCLC 600 mg QD safety analysis population (n=337), serious adverse reactions occurred in 31% of patients. • The most common (≥ 15%) adverse reactions were diarrhea (64%), nausea (46%), vomiting (43%), dizziness (22%), rash (22%),	Although taletrectinib can cause serious adverse reactions, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Taletrectinib will be prescribed by oncologists who are familiar with monitoring, identifying, and managing the toxicities described in the USPI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	constipation (21%), fatigue (20%), QTc prolongation (18%), peripheral neuropathy (17%), decreased appetite (17%), dysgeusia (16%), and cough (16%). • The most common (≥5%) Grade 3 or 4 laboratory abnormalities were increased ALT (13%), increased AST (10%), decreased neutrophils (6%), and increased creatinine phosphokinase (5%).	PMRs were issued to further evaluate the safety and efficacy of taletrectinib at the dosage of 400 mg QD, to evaluate the safety of the drug in patients with moderate or severe hepatic impairment and to address the potential for drug-drug interactions (DDIs). The clinical review team determined that it is in the best interest of U.S. patients to approve taletrectinib before a companion diagnostic assay is available. Since an application for an in vitro companion diagnostic device was not submitted for contemporaneous approval with this NDA, the approved labeling will state that there is no FDA-approved test for selecting patients for treatment with taletrectinib. A post-marketing commitment (PMC) will be issued for the Applicant to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a companion diagnostic test to detect *ROS1* fusions for identifying patients who may benefit from taletrectinib.

1.4. Patient Experience Data

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

x	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			**Section 8.1.3**
			x	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Lung cancer is the leading cause of cancer-related deaths, accounting for almost 25% of all cancer deaths in the United States (US) in 2021 (Siegel et al., 2021). Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for approximately 85% of all lung cancer patients, and can be further divided by histological subtypes, such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Approximately 70% to 80% of patients with NSCLC present with either locally advanced or metastatic disease at diagnosis. Advanced NSCLC remains a fatal, incurable disease with 5-year survival rate estimated to be <10% (American Cancer Society, 2024; NIH, 2024).

Receptor tyrosine kinases (RTKs) play important roles in many cellular signaling processes involved in cancer growth and development (Pacenta and Macy, 2018). Rearrangements or fusions of the RTK human c-ros oncogene 1 (*ROS1*) as tumorigenic genomic driver events have been identified in a variety of human malignancies including NSCLC (Zhu et al., 2015). *ROS1* is located on human chromosome 6 (6q22.1). Multiple partner genes can be rearranged with the *ROS1* gene resulting in and encoding unique constitutively active transmembrane tyrosine kinase receptors.

Approximately 1% to 2% of patients with NSCLC harbor a *ROS1* rearrangement (*ROS1*-positive, ROS1+), which is a rare molecular subtype of NSCLC driver genes. Clinically, *ROS1* rearrangement in NSCLC is associated with brain metastasis, particularly in the advanced setting, and poor prognosis (Bergethon et al., 2012). As with other common driver mutations, NSCLC patients harboring a *ROS1* rearrangement tend to have adenocarcinoma and are young, female, and more frequently nonsmokers (Chevallier et al., 2021).

The FDA's Assessment:
FDA agrees with the Applicant's analysis of *ROS1*-positive non-small cell lung cancer (NSCLC). The clinicopathologic characteristics of patients with *ROS1*-positive NSCLC include younger age at diagnosis (median age at diagnosis of 50 years of age), Asian race, and never-smokers. Overall survival (OS) for patients with NSCLC at 5 years was reported as 22% (SEER Zappa 2016); patients with *ROS1*-positive NSCLC had similar outcomes based on data in the era prior to the availability of ROS1-targeted therapy.

2.2. Analysis of Current Treatment Options Platinum-based chemotherapy was the standard treatment for ROS1+ NSCLC before targeted therapies (i.e., ROS1 tyrosine kinase inhibitors [TKIs]) were developed and approved for use. Currently, there are 3 ROS1 TKIs approved in the US for the treatment of locally advanced or metastatic ROS1+ NSCLC: crizotinib, approved in 2016 (XALKORI® (crizotinib), 2022); entrectinib, approved in 2019 (ROZLYTREK™ (entrectinib), 2024); and repotrectinib, approved in 2023 (AUGTYRO™ (repotrectinib), 2024).

A summary of the Food and Drug Administration (FDA)-approved treatment armamentarium is provided in **Table 1**.

Table 1. Applicant - Summary of Treatments Approved for ROS1-Positive NSCLC

Product (s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Crizotinib[a] XALKORI®	Adult patients with metastatic NSCLC whose tumors are ALK or ROS1+ as detected by an FDA-approved test	Initial US accelerated approval: 2011 US approval in ROS1+: 2016	Metastatic NSCLC: 250 mg PO twice daily	**PROFILE 1001** Multicenter, single-arm, open-label ORR by BICR (95% CI): 66% (51, 79) mDOR, months by BICR (95% CI): 18.3 (12.7, NR) IC-ORR by BICR (95% CI): NA	Hepatotoxicity, ILD/pneumonitis, QT interval prolongation, bradycardia, severe visual loss, gastrointestinal toxicity, and embryo-fetal toxicity
Entrectinib[b] ROZLYTREK®	Adult patients with ROS1+ metastatic NSCLC as detected by an FDA-approved test	Initial US approval: 2019	Recommended dosage for ROS1+ NSCLC: 600 mg PO once daily	**ALKA, STARTRK-1, STARTRK-2** Multicenter, single-arm, open-label cORR by BICR (95% CI): 74% (64, 83) Observed DOR, by BICR (%) ≥9 months, 75% ≥12 months, 57% ≥18 months, 38% IC-ORR (%, n/N): 70 (7/10)	Congestive heart failure, CNS effects, skeletal fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, visual disorders, and embryo-fetal toxicity

Product (s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Repotrectinib[c] AUGTYRO®	Adult patients with locally advanced or metastatic ROS1+ NSCLC	Initial US approval: 2023	Recommended dosage: 160 mg PO once daily for 14 days, then increase to 160 mg twice daily, with or without food	**TRIDENT-1** Multicenter, single-arm, open-label, multi-cohort cORR by BICR (95% CI) ROS1 TKI-naïve: 79% (68, 88) ROS1 TKI-pretreated: 38% (25, 52) mDOR (months) by BICR (95% CI) ROS1 TKI-naïve: 34.1 (25.6, NE) ROS1 TKI-pretreated: 14.8 (7.6, NE) Observed DOR, by BICR (%) ≥12 months, 70% (naïve) 48% (pretreated) IC-ORR by BICR (%, n/N): ROS1 TKI-naïve: 88% (7/8) ROS1 TKI-pretreated with no prior platinum-based chemotherapy: 42% (5/12)	CNS effects, ILD/pneumonitis, hepatotoxicity, myalgia with CPK elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity

Abbreviations: ALK, anaplastic lymphoma kinase; BICR, Blinded Independent Central Review; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; CPK, creatine phosphokinase; DOR, duration of response; FDA, Food and Drug Administration; IC-ORR, intracranial objective response rate; ILD, interstitial lung disease; mDOR, median duration of response; n, number of subjects in the category; N, number of subjects; NA, not applicable; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; ROS1, c-ros oncogene 1; SFM, solvent front mutation; TKI, tyrosine kinase inhibitor; US, United States.

[a] (XALKORI® (crizotinib), 2022)
[b] (ROZLYTREK™ (entrectinib), 2024)
[c] (AUGTYRO™ (repotrectinib), 2024)

The Applicant's Position:

Despite the currently available treatment options, there is still a clear unmet medical need for both ROS1 TKI treatment-naïve and ROS1 TKI-pretreated patients.

- A major limitation of crizotinib is the marginal penetration of the blood-brain barrier, resulting in limited central nervous system (CNS) activity and frequent CNS disease relapses.
- Compared to crizotinib, entrectinib has improved CNS penetration and activity. However, patients treated with entrectinib frequently experienced neurological adverse events (AEs) including dysgeusia (44%) and dizziness (38%) (ROZLYTREK™ (entrectinib), 2024).
- Of note, resistance to ROS1 TKIs invariably develops, limiting the clinical benefit of these agents and leading to disease relapse (Waliany and Lin, 2024). Neither crizotinib nor entrectinib has activity against resistance mutations, primarily G2032R. Median duration of response (mDOR) and progression-free survival (PFS) are less than 2 years for both drugs.
- Repotrectinib shows improved clinical efficacy. However, over 75% of patients (N=351) developed a wide range of treatment-emergent neurological AEs, including but not limited to dizziness (all grades: 64%), ataxia (all grades: 29%), dysgeusia (all grades: 50%), and peripheral neuropathy (all grades: 47%) (AUGTYRO™ (repotrectinib), 2023).

Ideally, a new agent would be highly potent against both wild-type ROS1 fusion protein and ROS1 on-target resistance mutations, with substantial activity on brain metastases, while maintaining a favorable safety profile, with fewer clinically important neurological AEs. Taletrectinib is expected to fulfill this profile and therefore provide a needed new treatment option for ROS1+ advanced NSCLC patients.

The FDA's Assessment:

FDA agrees with the Applicant's list of current treatment options for patients with *ROS1*-positive NSCLC.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Taletrectinib is currently not marketed or approved in the US or any other country or region.

Taletrectinib has an active Investigational New Drug Application (IND; 122347) in the US since January 2014. Taletrectinib was granted the following designations in the US:

- Breakthrough therapy designation was granted on 01 Aug 2022 for the treatment of adult patients with advanced or metastatic ROS1-positive NSCLC who are ROS1 TKI treatment naïve or previously treated with crizotinib.
- Orphan drug designation was granted on 16 Jul 2024 for the treatment of ROS1-positive, NTRK-positive, anaplastic lymphoma kinase (ALK)-positive, leukocyte receptor tyrosine kinase receptor-positive, activated Cdc42-associated kinase-positive, or discoidin domain receptor 1-positive NSCLC.

The FDA's Assessment:
FDA agrees with the Applicant's position. Taletrectinib is not currently approved in the United States for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of key regulatory interactions is provided in **Table 2**.

Table 2. Applicant - Key Regulatory Interactions for Taletrectinib With FDA

Interaction	Key Outcomes
EOP1 Interaction 18 Dec 2020	• The Agency indicated that, given the preliminary results observed in Phase 1 studies J102 and U101, the proposed Study AB-106-G208 would be supportive of a marketing application under the provisions of accelerated approval. • A CDx will be required for taletrectinib for use in NSCLC.
Initial Breakthrough Therapy Designation Interaction 24 Mar 2023	• AnHeart discussed and sought Agency's feedback on the diversity plan, planned regulatory interactions, proposed (b) (4) (b) (4) dosing strategy, and CDx development for taletrectinib.

Interaction	Key Outcomes
Type D Interaction (Written Responses) Clinical 25 Jul 2023	• The Sponsor sought feedback (b) (4) The Agency did not comment (b) (4) and determined that data from Study G208 (as primary study) and Study C203 (as supportive study) may be adequate to support traditional approval. • The Agency advised that dose/exposure-response (E-R) analyses for safety and efficacy should be submitted to better understand the relationships between dose/exposure, safety, and efficacy.
Type C Interaction (Written Responses) Clinical Pharmacology 28 Jul 2023	• The Agency provided guidance on the proposed plan to evaluate the DDI of taletrectinib related to CYP enzymes and transporters.
Type D Interaction (Written Responses) CMC 19 Sep 2023	• The Agency provided guidance on key elements of the proposed manufacturing process, specifically regarding bridging studies for capsule imprint requirements and the change of drug product packaging (b) (4) requirements.
Type B Interaction, Clinical 24 Oct 2023	• The Agency concluded that in general the proposed plan for key elements of the marketing application for taletrectinib for traditional approval is acceptable. • The Agency stated the Sponsor's plan to submit an NDA to seek traditional approval for taletrectinib for the treatment ROS1+ NSCLC based on pooled efficacy data from Studies G208 and C203 appeared reasonable. • The Agency recommended that the Sponsor include a dose-randomized cohort in Study G208 (randomized 1:1) with 20 participants per dose at 2 dose levels (Cohort 5). • The Agency agreed that the overall clinical pharmacology plan presented is acceptable and recommended that the Sponsor submit the hepatic impairment study plan/protocol to FDA for review prior to the planned NDA submission. (b) (4) • The Agency agreed that the proposed ISE plan is acceptable.

Interaction	Key Outcomes
Dosing Toolkit V1.0 (Seq. No. 0162) 19 Dec 2023	• The Sponsor accepted FDA invitation to participate in the Oncology Center of Excellence Oncology Dosing Toolkit pilot project to enhance communications relating to dosage optimization for taletrectinib (AB-106). • The Dosing Toolkit was updated to include preliminary results of Population PK and E-R analyses.
Type D Interaction (Written Responses) CMC 03 Jan 2024	• The Agency confirmed that the proposed regulatory starting materials are acceptable.
Proprietary Name Submission (Seq. No 0172) 16 Jan 2024	• The Sponsor submitted a proprietary name review request for IBTROZI. • The name was conditionally accepted by the Agency on 24 Apr 2024.
Type B (EOP) Interaction (Written Responses) 01 Mar 2024	• The Sponsor requested the Agency's feedback on the ISS and electronic datasets in support of the planned NDA for taletrectinib. Generally, the Agency was aligned with the Sponsor's proposals.
Type B (EOP) face-to-face Meeting 02 May 2024	• The Sponsor discussed and aligned with the Agency (b) (4)
Agreed iPSP 03 May 2024	• An agreed initial pediatric study plan was reached with the Agency.
Presubmission Interaction with CDRH 10 Jun 2024	• Foundation Medicine, in partnership with the Applicant, (b) (4) the tissue-based Foundation One CDx for use with taletrectinib.
Type B CMC Pre-NDA Interaction (Written Responses) 13 Jun 2024	• The Applicant aligned with the Agency on the drug substance specifications, dissolution data, the (b) (4) assessment, and stability package to support the planned NDA submission of taletrectinib for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC.
Type B Pre-NDA Multidisciplinary Interaction 26 Jun 2024	• The Applicant aligned with the Agency on an adequate nonclinical, clinical pharmacology, dose optimization, and data applicability package to support an initial NDA submission for taletrectinib as a treatment for adult patients with locally advanced or metastatic ROS1-positive NSCLC. In addition, the Applicant discussed with the Agency a (b) (4) (b) (4) CDx as a post-marketing commitment.

Abbreviations: CDRH, Center for Devices and Radiological Health; CDx, companion diagnostic; CMC, Chemistry, Manufacturing, and Controls; CYP, cytochrome P450; DDI, drug-drug interaction; EOP(1), end of Phase (1); E-R, exposure-response; FDA, Food and Drug Administration; IND, Investigational New Drug Application; iPSP, initial pediatric study plan; ISE, integrated summary of efficacy; ISS, integrated summary of safety; NDA, New Drug Application; NSCLC, non-small cell lung cancer; PK, pharmacokinetic(s); ROS1, c-ros oncogene 1; (b) (4) (b) (4)

The FDA's Assessment:

FDA agrees with the Applicant's timeline of events. The current NDA was submitted on October 23, 2024.

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

4.1. Office of Scientific Investigations (OSI)

Data from clinical Studies C203 and G208 were submitted to the Agency in support of NDA 219713 for taletrectinib for the treatment of adults with locally advanced or metastatic *ROS1*-positive NSCLC. Three clinical investigators, Drs. Caicun Zhou (site # 101/study C203), Yongchang Zhang (site # 122/study C203), and Haiyan Yang (site # 802/study G208), the study CRO (b) (4) and the imaging Contract Research Organization (CRO) (b) (4) were inspected.

Inspections of Drs. Zhou, Zhang, Yang, the CRO (b) (4) and the imaging CRO, (b) (4) (b) (4) did not find significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice, or regulatory compliance.

Based on these inspections, Studies C203 and G208 appear to have been conducted adequately by the study sponsor and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication. Refer to the clinical inspection summary from OSI uploaded in DARRTS on May 22, 2025 for full details.

4.2. Product Quality

The product quality review team has recommended approval. Please refer to the complete OPQ Review and Evaluation uploaded in DARRTS on April 28, 2025, for full details. Briefly, the review team determined that the Applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. Based on the submitted data, the Applicant proposed a retest period of 36 months when stored at or below 30°C in the proposed container system. All associated manufacturing, testing, packaging facilities were deemed acceptable.

4.3. Clinical Microbiology

There are no clinical microbiology issues that would preclude approval.

4.4. Devices and Companion Diagnostic Issues

In Studies G208 and C203, evidence of *ROS1* fusion(s) by a validated assay as performed in Clinical Laboratory Improvement Amendments (CLIA)-certified or locally equivalent diagnostic laboratories was required.

The development of a companion diagnostic (CDx) for the detection of *ROS1*-positive NSCLC is currently in progress, (b) (4) As FDA does not intend to

delay the approval of taletrectinib to permit contemporaneous approval with the CDx, and *ROS1* testing is currently standard of care, FDA will issue a post-marketing commitment to conduct an appropriate analytical and clinical validation study to support the development of an in vitro diagnostic device using clinical trial data that demonstrates that the device is essential to the safe and effective use of taletrectinib for the treatment of patients with advanced or metastatic *ROS1* positive NSCLC. FDA considers there to be limited risk of inappropriate patient selection of patients given the widespread and standard of care testing for *ROS1* fusions in patients with locally advanced or metastatic NSCLC and the availability of FDA approved CDx *ROS1* fusion tests for use with other approved ROS1 TKIs.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Taletrectinib is a small molecule inhibitor of tyrosine kinase ROS1. The established pharmacological class for taletrectinib is kinase inhibitor. ROS1 fusion proteins are oncogenic drivers in non-small cell lung cancer (NSCLC) driving tumorigenic potential through hyperactivation of downstream signaling pathways causing increased cellular proliferation (Chevallier et al., 2021).

Pharmacological assessment of taletrectinib showed inhibitory activity against human wild-type ROS1, ROS1 mutant kinases, and ROS1 fusion proteins with IC_{50} values ranging from 0.1 to 3.6 nM. Taletrectinib showed antiproliferative activity in cells harboring ROS1 alterations, including CD74-ROS1 and SLC34A2-ROS1 fusions without and with mutations. Some of these alterations included drug-resistant mutations to another ROS inhibitor. Taletrectinib decreased ROS1 phosphorylation in a NSCLC cell line expressing the SLC34A2-ROS1 fusion gene. In addition, taletrectinib decreased phosphorylation of ROS1 and its downstream signaling pathway partners AKT, ERK, MEK, and SHP2 in Ba/F3 cells with ROS1-CD74fusion or a $ROS1^{G2032R}$ mutation. Evaluation of antitumor activity was conducted in subcutaneous xenograft mouse models using Ba/F3 cells expressing ROS1 mutants/fusion proteins CD74-ROS1 and CD74-$ROS1^{G2032R}$ or NSCLC cells harboring the CD74-ROS1 gene fusion. Once daily oral administration of taletrectinib (10 to 100 mg/kg/day) led to significant tumor growth inhibition (13 to 95%) and decreased phosphorylation of ROS1 in tumor tissue. In an intracranial xenograft study in mice, taletrectinib (30 and 100 mg/kg/day orally once daily) had greater anticancer activity compared to controls in mice bearing patient-derived NSCLC tumors with the SDC4-ROS1 fusion, suggesting taletrectinib crossed the blood-brain-barrier (BBB).

Taletrectinib had higher inhibitory activity towards ROS1 compared to TrK proteins, ACK, DDR1, LTK, and ALK. Taletrectinib inhibited TrkA, TrkB, and TrkC with IC_{50} values that were below the unbound or total Cmax in humans, and 3-11 fold greater activity towards ROS1 when compared to TrK proteins in other assays. The inhibitory activity for ROS1 was >17 fold when compared to ACK, DDR1, LTK, and ALK.

Taletrectinib had no significant effects on cardiovascular function in monkeys; however, in vitro assays for hERG and $hNa_v1.5$ channels indicated a potential effect on QT prolongation. QT prolongation was noted as a treatment-emergent adverse event (TEAE; Grade ≥3) in patients treated with the recommended clinical dose of 600 mg once daily. Of note, in general toxicology studies in rats, myocardial necrosis and vacuolation were observed microscopically in the 28-day repeat-dose study and dose-dependent cardiomyopathy was reported in the 12-week repeat-dose study. Taletrectinib did not affect central nervous system (CNS) toxicity or respiratory toxicity in the 28-day and 12-week rat general toxicology studies. Taletrectinib was considered potentially

phototoxic in a neutral red uptake assay with a photo-irritation factor (PIF) of 26.6 and mean photo effect value (MPE) of 0.278. In addition, distribution to melanin containing tissues (skin and eyes) were noted in animals. Photosensitivity and skin reactions has been reported in patients.

Taletrectinib was distributed throughout rat tissues. There was notable distribution of taletrectinib to melanin-containing tissues of the eyeball and skin. Taletrectinib also accumulated in the choroid plexus region of the brain indicating the drug can cross the blood brain barrier. Protein binding analysis indicated that 92-97% of taletrectinib was protein bound in mouse, rat, cynomolgus monkey, and human plasma and showed dose-dependent potential saturation of plasma binding in rat, cynomolgus monkey, and human. After oral administration of taletrectinib at doses of 3, 10, 30, and 100 mg/kg to mice bearing CD74-ROS1^{G2032R} fusion gene-driven Ba/F3 tumors, the plasma and tumor concentrations increased with an increase in dose. Major elimination pathways for taletrectinib were through excretion in feces (~75%) and urine (~11%).

The Applicant evaluated the safety of taletrectinib administered orally once daily in 28-day and 12-week good laboratory practices (GLP)-compliant general toxicology studies using rats and cynomolgus monkeys. The oral route of administration is consistent with the intended clinical route of administration. Taletrectinib caused mortalities in rats at doses ≥100 mg/kg/day and monkeys at doses ≥60 mg/kg/day. The cause of death in the rats and monkeys was potentially due to gastrointestinal (GI) toxicity. Drug-related target organs in both species included lung, lymph nodes, kidney, GI tract, and pituitary. Of note, minimal to moderate vacuolation occurred in the choroid plexus in rats in both the 28-day and 12-week studies at the 100 mg/kg dose. Distribution studies identified the choroid plexus as a tissue with accumulation of taletrectinib. In addition, dose-dependent cardiomyopathy, and decreased cellularity with accumulation of foamy macrophages in the spleen was observed in the 12-week rat study. The liver was an additional target organ in the 12-week monkey study. Minimal to moderate inflammatory cell infiltration occurred in multiple organs in both rats and monkeys in the 12-week studies. Reproductive target organs included seminal vesicle and uterus with cervix in the rat. Clinical signs included dose-dependent salivation in the 12-week rat study and GI toxicity in the monkey study. Exposure range in the rats was 0.6- to 8-times compared to the human exposure at the recommended dose (AUC = 5396 to 76274 vs. 9375 ng*h/mL, respectively). Exposure in the monkey was approximately 0.6- to 7-times compared to the human exposure at the recommended dose (AUC = 5586 to 64084 vs. 9375 ng*h/mL, respectively).

Taletrectinib was negative for mutagenicity in in vitro bacterial reverse mutation (Ames) assays and additional mutagenicity tests, including 2 mammalian cell gene mutation assays and one in vivo gene mutation assay in rats. Taletrectinib was not clastogenic or aneugenic in the in vivo micronucleus study in rats in liver or bone marrow when administered orally up to 300 mg/kg. See **Section 5.5.2** for further information.

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

The Applicant conducted a fertility and early embryonic development study in rats with daily oral administration of taletrectinib at 4, 25, or 60 mg/kg to males or 4, 25, or 100 mg/kg to females. Because taletrectinib at 100 mg/kg resulted in mortality in males in the 4-week general toxicology study, in the current study, the highest dose tested in males was 60 mg/kg. Mating pairs were both treated with taletrectinib. Males were dosed for 83 consecutive days (10 weeks prior to mating and during mating period) while females were dosed for 34 consecutive days (2 weeks prior to mating, during mating period and up to gestation day 6). Taletrectinib had no adverse effects on the estrus cycle, fertility, or pregnancy rates of female rats. In males, sperm morphology abnormalities were found in all taletrectinib dose groups compared to vehicle control group. The Applicant did not specify what specific sperm morphological abnormalities were observed. Additionally, no malformations of the fetuses were observed when dams were treated up to gestation day 6.

GLP-compliant embryo-fetal development studies were conducted in pregnant rats and rabbits to assess the effect of taletrectinib on fetal development. After oral administration of taletrectinib to pregnant rats at doses of 10, 30, and 100 mg/kg daily during the period of organogenesis (Gestation Day 6-17) no maternal toxicity was observed. Pregnancy rates and the number of live fetuses in rats were not affected by taletrectinib. Abnormal dose-dependent ossification in the pelvic bone of fetuses occurred with taletrectinib, with 2.5 times higher incidences at 100 mg/kg (1.3 times the human exposure based on AUC at the recommended dose) compared to control. Daily administration of taletrectinib at doses of 15, 30, and 90 mg/kg/day to pregnant rabbits during the period of organogenesis (Gestation Day 6-19) resulted in dose-dependent maternal mortalities in all dose groups. Mortalities were due to liver and kidney toxicity that included hepatocellular vacuolar degeneration, hepatocellular necrosis, and renal degeneration/necrosis. Taletrectinib treatment resulted in increase in abortions and total pregnancy loss at doses ≥15 mg/kg/day (≥ 0.04 times the human exposure based on AUC at the recommended dose). Ventricular malformations in the fetuses were observed in the 30 mg/kg group, and thoracic vascular malformations were observed in 90 mg/kg group. In addition, one fetus in the 30 mg/kg group had undeveloped right ear and no development of eyes, nose, and mouth. The dose of 30 mg/kg is 0.1 times the human exposure based on AUC at the recommended dose.

Taletrectinib targeted Trk A, B, and C with activity comparable to the ROS1 targets. Therefore, beyond the animal findings in the embryo-fetal development study from taletrectinib and the known embryo-fetal teratogenicity of other Trk inhibitors, there are additional concerns about the use of taletrectinib during pregnancy due to the established role of Trk proteins in neuronal development (Tucker et al., 2001; Smeyne et al., 1994). Published reports of congenital somatic mutations in Trk proteins or their ligands suggest a relationship between deficient Trk signaling and development of schizophrenia, mood disorders, obesity, and peripheral sensory and motor disorders (Kranz et al., 2015; Otnaess et al., 2009; Knable, 1999; Lewis et al., 2005; Indo et al.,

1996; Yeo et al., 2004). While embryo-fetal development studies can detect malformations in brain structure, they are not designed to assess motor development or psychiatric function and though a pre- and postnatal development study may be capable of evaluating some of these endpoints, they are not typically required for a drug intended to treat patients with advanced cancer. Given the published literature on the importance of Trk signaling in neural development, including human syndromes, the limitations of the embryo-fetal development studies to assess the toxicities of particular concern following disruption of this pathway, and the available animal data, there is a potential for significant neurocognitive effects in children exposed to taletrectinib during prenatal development. Based on this data, additional information regarding the effect of Trk inhibition on embryo-fetal development was added to the label.

Because taletrectinib can cause fetal harm, the review team recommends an embryofetal toxicity warning. Based on FDA guidance, "Oncology Pharmaceutical: Reproductive Toxicity Testing and Labeling Recommendations," for embryofetal toxic drugs that are not genotoxic, the recommended duration of contraception for males and females is 3 weeks based on 5 half-lives of taletrectinib measured in patients ($T_{1/2}$ = 76.3 hours x 5 = 381.5 hours/ 24 hours = ~16 days rounded to 3 weeks).

The recommendation to lactating women treated with taletrectinib is to not breastfeed during treatment and for 3 weeks after the last dose based on 5 half-lives of taletrectinib measured in patients.

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

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Not applicable. This is the initial NDA for taletrectinib.

The FDA's Assessment:

FDA agrees. There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for taletrectinib.

5.3. Pharmacology

Primary pharmacology

In vitro studies

A mobility shift assay was conducted to investigate the inhibitory activities of taletrectinib against ROS1, NTRK1, NTRK2, and NTRK3. The adenosine 5'triphosphate (ATP) concentration in the assay was set at approximately the Michaelis constant value of each kinase. Taletrectinib inhibited the activity of each kinase in a concentration-dependent manner, with half maximal inhibitory concentrations (IC_{50}) of 0.207, 0.622, 2.276, and 0.980 nM, respectively, for ROS1, TRKA, TRKB, and TRKC. When an ATP concentration of 10 μM was used, taletrectinib inhibited ROS1, TRKA, TRKB, and TRKC kinase activity with IC_{50} values of 0.073, 1.26, 1.47, and 0.182 nM, respectively.

The inhibitory activity of taletrectinib on the proliferation of Ba/F3 cells driven by CD74-fused ROS1 (CD74-ROS1), $ROS1^{L1951R}$ (CD74-$ROS1^{L1951R}$), $ROS1^{L2026M}$ (CD74-$ROS1^{L2026M}$), $ROS1^{G2032R}$ (CD74-$ROS1^{G2032R}$), or $ROS1^{D2033N}$ (CD74-$ROS1^{D2033N}$) genes was evaluated. Cells were treated with taletrectinib at 0.153, 0.610, 2.44, 9.77, 39.1, 156, 625, 2500, or 10000 nM in triplicate and incubated for 3 days. ATP was quantified as a luminescent signal to determine the number of viable cells. Inhibition of proliferation of Ba/F3-CD74-ROS1, Ba/F3-CD74-$ROS1^{L1951R}$, Ba/F3-CD74-$ROS1^{L2026M}$, Ba/F3-CD74-$ROS1^{G2032R}$, and Ba/F3-CD74-$ROS1^{D2033N}$ cells was observed, with GI_{50} values of 0.7, 4.1, 3.5, 13.1, and 27.4 nM, respectively, while the GI_{50} value for parental Ba/F3 cells was determined to be 1396.7 nM (**Table 3**).

Table 3. Applicant - GI_{50} Values of Taletrectinib for Ba/F3 Cells Driven by CD74-Fused ROS1, $ROS1^{L1951R}$, $ROS1^{L2026M}$, $ROS1^{G2032R}$, or $ROS1^{D2033N}$ Gene and Parental Ba/F3 Cells

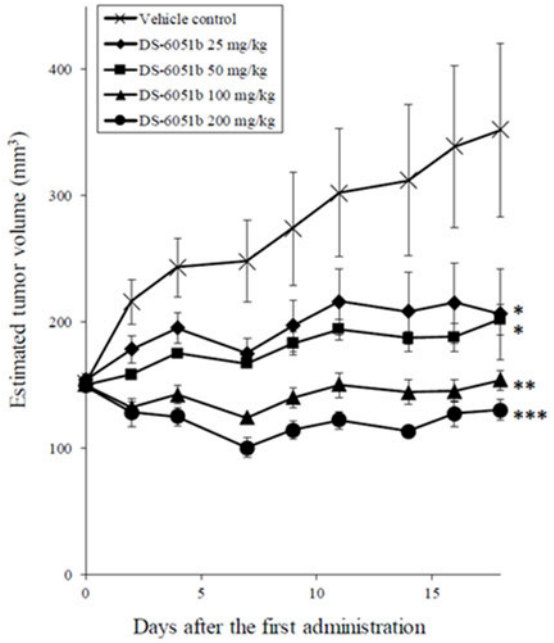
Cell line	GI_{50} (nM)
	Taletrectinib
Ba/F3-CD74-ROS1	0.7
Ba/F3-CD74-$ROS1^{L1951R}$	4.1
Ba/F3-CD74-$ROS1^{L2026M}$	3.5
Ba/F3-CD74-$ROS1^{G2032R}$	13.1
Ba/F3-CD74-$ROS1^{D2033N}$	27.4
Ba/F3	1396.7

Note: GI_{50}, half-maximal growth inhibitory concentration.

In vivo studies

The antitumor efficacy of taletrectinib was evaluated in a nude mouse (CAnN.Cg-Foxn1[nu]/CrlCrlj[Foxn1nu/Foxn1nu]) xenograft model of human U-118 MG cells, which harbor a FIG-ROS1 fusion gene. Five-week-old female nude mice were implanted subcutaneously with 5×10^6 cells/mouse. When the average estimated tumor volume reached over 100 mm^3, the mice (5/group) were orally administered taletrectinib (in 0.5% methyl cellulose [MC]) at 0 (vehicle), 25, 50, 100, or 200 mg/kg QD for 18 days and tumor growth inhibition was evaluated. The antitumor efficacy of taletrectinib is shown in **Figure 1**. The results indicate that taletrectinib has antitumor efficacy on ROS1-driven tumors in a dose-dependent manner.

Figure 1. Applicant - Antitumor Efficacy of Taletrectinib Against Xenograft U-118 MG Tumors

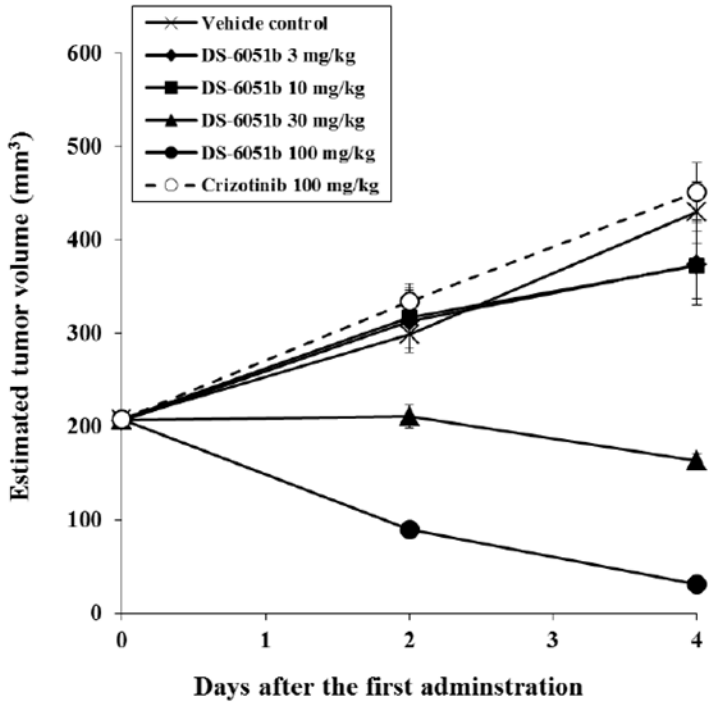


Abbreviation: DS-6051b, taletrectinib
Note: Each data point and bar represent the mean and standard error of the mean, respectively, of the estimated tumor volume of each group (n = 5, *p <0.05, **p <0.01, ***p <0.001, vs. vehicle control, parametric Dunnett's test using the data on Day 18).

The antitumor efficacy of taletrectinib was also evaluated in an allograft model of CD74-ROS1^{G2032R} fusion gene-driven Ba/F3 cells. The G2032R mutation in ROS1 has been reported to confer resistance to the ALK/ROS1 inhibitor crizotinib in ROS1-rearranged NSCLC. Ba/F3-CD74-ROS1^{G2032R} cells were transplanted subcutaneously into female nude mice (CAnN.Cg-Foxn1[nu]/CrlCrlj[Foxn1nu/Foxn1nu]) at 1×10^7 cells/mouse. When the average tumor volume was greater than 100 mm^3 (Day 0), groups of 6 mice were orally administered

taletrectinib at 0 (0.5% MC, vehicle control), 3, 10, 30, or 100 mg/kg, or crizotinib 100 mg/kg QD from Days 0 to 3. Tumor volumes were measured on Day 0, Day 2, and Day 4, and body weights measured from Day 0 to 4. Taletrectinib inhibited the tumor growth in a dose-dependent manner. The results showed that taletrectinib exerted antitumor activity on crizotinib-resistant ROS1 mutation-driven tumors (**Figure 2**).

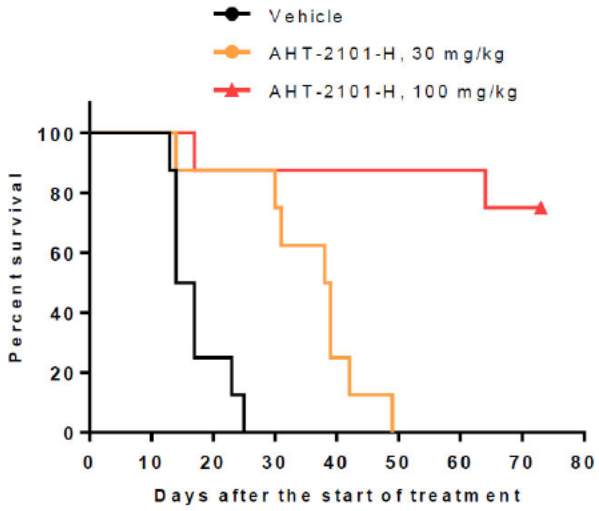
Figure 2. Applicant - Antitumor Efficacy of Taletrectinib and Crizotinib Against Allograft Ba/F3-CD74-ROS1^{G2032R} Tumors



Abbreviation: DS-6051b, taletrectinib
Note: Each data point and bar represent the mean and standard error of the mean of the estimated tumor volume of each group, respectively (n = 6).

The intracranial LU-01-0414 (an NSCLC patient-derived xenograft (PDX) model harboring the SDC4–ROS1 fusion) xenograft model in female BALB/c nude mice were used to evaluate the in vivo antitumor efficacy of taletrectinib. Taletrectinib was orally dosed at 30 mg/kg and 100 mg/kg (QD), respectively. The study results showed taletrectinib at 30 mg/kg and 100 mg/kg significantly prolonged median survival time with 38.5 days (increase in life span = 148.4%, $p<0.001$) and 73+ days (increase in life span >371.0%, $p<0.001$), respectively compared to control (**Figure 3**).

Figure 3. Applicant - The Effects of Taletrectinib on Survival Time of LU-01-0414 Tumor-Bearing BALB/C Nude Mice



Abbreviation: AHT-2101-H, taletrectinib

The FDA's Assessment:

FDA generally agrees with the Applicant's conclusions on the primary pharmacology of taletrectinib, with additional pertinent details below.

In vitro pharmacology

In an additional kinase profiling assay (Study #20220408-AHT-AL-KP-RV01), the Applicant evaluated the IC_{50} values for inhibition of ROS1 mutants or ROS1 fusions proteins by taletrectinib (**Table 4**).

Table 4. Inhibitory Activity of Taletrectinib Against ROS1 Mutant Kinases, ROS1 Fusion Proteins

Kinase	IC_{50} (nM)
$ROS1^{G2032R}$	0.2
$ROS1^{G2101A}$	0.2
$ROS1^{G2101C}$	3.6
ROS1-GOPC	0.1
ROS1-TPM3	0.06

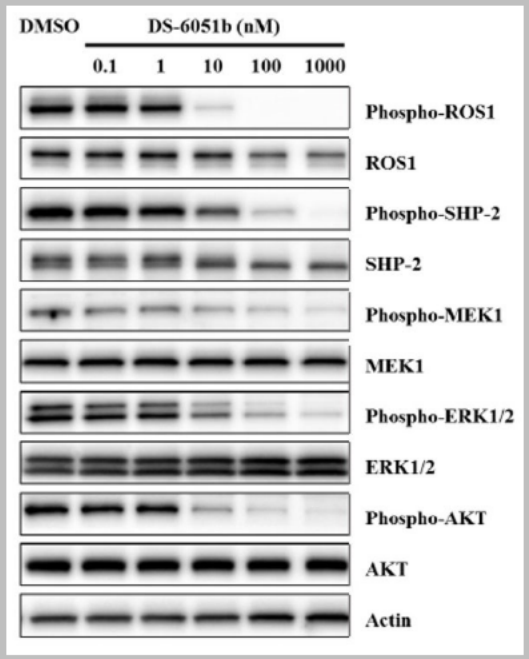
Taletrectinib also inhibited cell viability of Ba/F3 cells expressing SLC34A2-ROS1 fusion gene or SLC34A2-ROS1^{G2023R}, SLC34A2-ROS1^{L2026M}, and SLC34A2-ROS1^{D2033N} point mutations (Study# BKY202201), with IC_{50} values in the nanomolar range **Table 5**.

Table 5. Effects of Taletrectinib on Cell Viability for Parental Ba/F3 Cells Harboring ROS1 Fusion Gene Protein Without or With Point Mutations

Cell Line	IC_{50} (nM)
Ba/F3-CD74-ROS1	12.11
Ba/F3-SLC34A2-ROS1	10.10
Ba/F3-SLC34A2-ROS1^{G2032R}	143.41
Ba/F3-SLC34A2-ROS1^{L2026M}	18.99
Ba/F3-SLA34A2-ROS1^{D2033N}	117.88

Taletrectinib free base (DS-6051a) inhibited ROS1 phosphorylation in tumor cells in the non-small cell lung cancer cell line HCC78 expressing the SLC34A2-ROS1 fusion gene (not shown; Study# BD13-H0027-R04). Taletrectinib also inhibited ROS1 phosphorylation and downstream signaling pathway in Ba/F3 cells expressing CD74-ROS1 fusion gene (**Figure 4**) or ROS1^{G2032R} gene (Study# CQ16-H0024-R08).

Figure 4. Effects of Taletrectinib (DS-6051b) on ROS1 Phosphorylation and Its Downstream Signaling in Ba/F3-CD74-ROS1 Cells

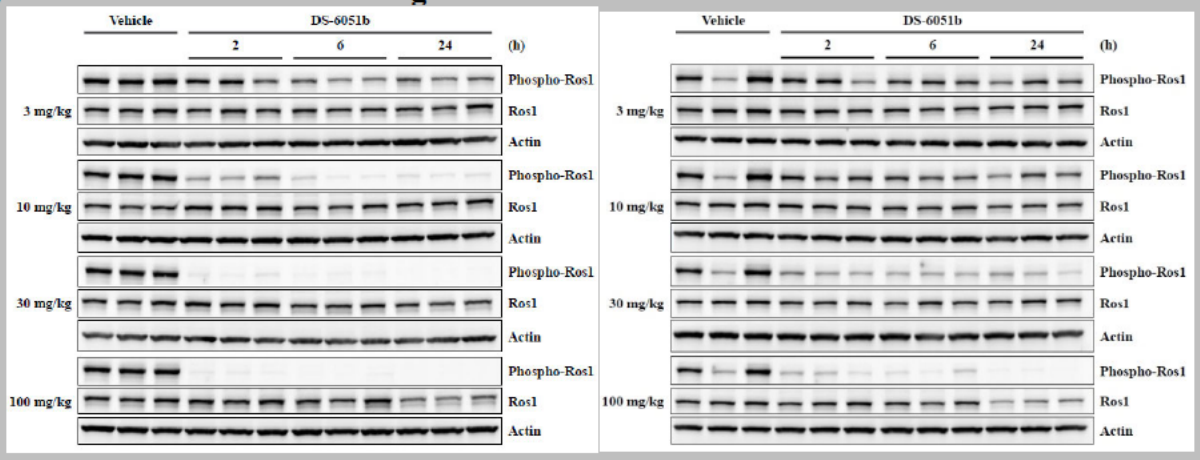


DS-6051b = taletrectinib.
(Excerpted from study CQ16-H0024-R08)

In Vivo Pharmacology

Single (Study# CQ16-H0024-R06) or repeat-dose (Study # CQ16-H0024-R07) oral administration of taletrectinib (DS-6051b) at 3, 10, 30, and 100 mg/kg in adult mice bearing subcutaneous Ba/F3-CD74-ROS1 or Ba/F3-CD74-ROS1^{G2032R} fusion tumors resulted in dose-dependent inhibition of ROS1 phosphorylation in both gene fusion-driven tumors with and without a point mutation (**Figure 5**).

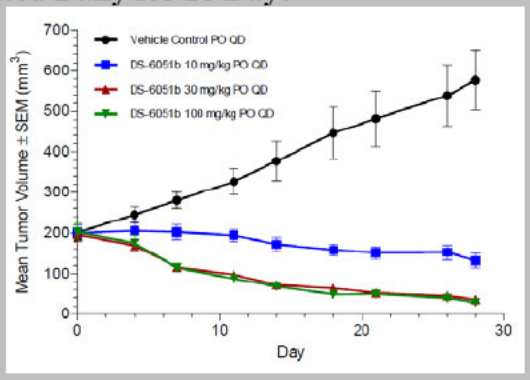
Figure 5. Inhibition of ROS1 Phosphorylation in Tumor Tissue From Mice Bearing Ba/F3-CD74-ROS1 (Left) and Ba/F3-CD74-ROS1^{G2032R} Fusion (Right) Gene-Driven Tumors at 2, 6, and 24 Hours Post Dose a Single Administration of Taletrectinib



DS-6051b = taletrectinib.
(Excerpted from study CQ16-H0024-R06)

Antitumor activity of taletrectinib was evaluated in the Champions TumorGraft® model, CTG-0848 (human non-small cell lung cancer [NSCLC]) tumors harboring the CD74-ROS1 fusion gene (Study # 1038-013). In mice implanted subcutaneously with CTG-0848 cells and treated with taletrectinib orally at doses of 10, 30, and 100 mg/kg daily for 28 days, the tumor growth inhibition (TGI) was 77, 94, and 95%, respectively (**Figure 6**). Additionally, 80 and 90% of mice in the 30 and 100 mg/kg groups showed partial responses. There were no mortalities and weight gain occurred in all groups.

Figure 6. Taletrectinib Had Antitumor Activity in ROS1 Gene Fusion Human NSCLC Tumor Bearing Mice Treated Daily for 28 Days



DS-6051b = taletrectinib. PO = orally. QD = once daily.
(Excerpted from study 1038-013)

Secondary Pharmacology

The Applicant's Position:

The kinase selectivity and inhibitory activity of taletrectinib was evaluated using an off-chip mobility shift assay using QuickScout Selectivity Profiling. The effect of taletrectinib at a concentration of 200 nM on 160 kinases was evaluated in the presence of 1 mM ATP and expressed as percent inhibition. In addition, the inhibitory effect of taletrectinib from 0.0003 to 10 µM on ACK, ALK, DDR1, DDR2, KIT, LTK, ROS1, NTRK1, NTRK2, NTRK3, and TXK was evaluated in the presence of 1 mM ATP, and the IC_{50} values were determined (**Table 6**).

Table 6. Applicant - IC_{50} Values of Taletrectinib Against Selected Kinases

Kinase	IC_{50} (nM)
ROS1	0.90
NTRK1	3.01
NTRK3	9.28
NTRK2	9.52
ACK	15.42
DDR1	24.72
LTK	25.41
ALK	32.51
TXK	183.18
DDR2	298.62
KIT	348.78

Abbreviations: ATP, adenosine 5′-triphosphate; IC_{50}, 50% viability (half-maximal) inhibitory concentration.

The FDA's Assessment:

FDA generally agrees with the Applicant's conclusion for secondary pharmacology of taletrectinib, with additional pertinent details below. Cmax of unbound taletrectinib was calculated by the FDA clinical and nonclinical team to be ~34 nM at the recommended dose of 600 mg orally once daily. Based on IC_{50} values presented by the Applicant in **Table 4**, taletrectinib has the potential to target NTRK1 (TRKA), NTRK2 (TRKB), NTRK3 (TRKC), ACK, DDR1, LTK and ALK at clinically relevant concentrations. Taletrectinib inhibited ROS1 with 3- to 11-fold greater activity compared to TRKA, TRKB, and TRKC and greater than 17-fold activity against all other kinases tested in kinase activity assays.

Safety Pharmacology

The Applicant's Position:

In vitro, taletrectinib inhibited hERG currents and $hNa_v1.5$ with IC_{50} values of 0.98 μM and 0.83 μM, respectively, indicating a potential effect on QT prolongation. However, in the telemetered monkey cardiovascular study, there were no effects on any electrocardiogram (ECG) parameters, including QTc at the highest non-severely toxic dose (HNSTD) of 100 mg/kg/day. Safety pharmacology studies in the rat further demonstrated the lack of effects on the CNS and respiratory system with administered taletrectinib doses up to 100 mg/kg/day (mean taletrectinib C_{max} of 634 ng/mL, equivalent to 1.56 μM).

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of the listed cardiovascular safety pharmacology findings on hERG and hNav1.5 current inhibition. In an in vivo cardiovascular safety study in cynomolgus monkeys, single administration of oral taletrectinib (DS-9051b) at doses of 10 and 30 mg/kg did not affect hemodynamic or ECG parameters, while a dose of 100 mg/kg led to minimal and transient increased QA interval of 9 msec noted 3 to 6 hours post dose suggesting decreased cardiac contractility. Considering this effect was transient and not accompanied by other cardiovascular changes it is unlikely adverse. There were no taletrectinib-related effects on cardiovascular function or histopathology in the monkey 12-week repeat-dose toxicology study; cardiovascular parameters were not measured in the 28-day monkey toxicology study. Of note, myocardial necrosis and vacuolation were observed microscopically at a dose of 100 mg/kg/day in the rat 28-day repeat-dose general toxicology study and dose-dependent cardiomyopathy was reported in the 12-week rat repeat-dose general toxicology study. FDA agrees that CNS and respiratory system safety pharmacology parameters measured in the 28-day repeat-dose general toxicology study in the rat demonstrated that taletrectinib had no effect when administered orally at doses up to 100 mg/kg/day; however, based on the mechanism of action (e.g., inhibiting Trk proteins), FDA cannot rule out the potential for taletrectinib to affect the CNS (see discussion in the Executive Summary).

5.4. ADME/PK

The Applicant's Position:

Absorption

The exposure of taletrectinib was studied in 14-, 28-, and 85-day repeat dose toxicity studies in rats and monkeys, and in reproductive and developmental toxicity studies in rats and rabbits. Toxicokinetic results in the rat (Day 1 only) and monkey (Day 1 and Day 14) attained from dose range-finding (DRF) studies, revealed a less than dose-proportional increase up to the highest dose level tested of 1000 mg/kg/day. This was also seen in the 28-day repeat dose toxicity study in the monkey where a dose-proportional or less than dose-proportional increase in exposure was noted. However, in the rat 28-day repeat dose toxicity study there was a greater than dose-proportional increase in exposure. In male and female rats administered 100 mg/kg/day for 28 days, there was an indication of taletrectinib accumulation, while in the monkeys, this was evident only in females administered 100 mg/kg/day. In the 85-day repeat dose study conducted in rats, accumulation of taletrectinib appeared to be associated with dose level. Further, the absorption of taletrectinib increased with the dose. In the 85-day repeat dose study in the monkeys, the overall level of taletrectinib exposure had a linear kinetic trend.

Distribution

The in vitro plasma protein binding study indicated that taletrectinib protein binding was high (90.7% to 97.2%) and similar across species tested (mouse, rat, monkey, and human). The results also showed a concentration-dependent binding of taletrectinib in human plasma (96.5% to 92.6%) in the concentration range of 100 to 10,000 ng/mL. Taletrectinib also exhibited a moderate partitioning into human erythrocytes. In quantitative whole-body autoradiography (QWBA) studies in rats, radioactivity was distributed to almost the entire body. In pigmented rats, the highest radioactivity concentrations in tissues were observed in the pituitary, followed by the spleen, liver, adrenal, and lung; taletrectinib and/or its metabolites showed a potential affinity for melanin.

Metabolism

Investigation of the in vitro metabolism of taletrectinib using recombinant human cytochrome P450 (CYP) enzymes and human liver microsomes (HLM) with CYP-selective chemical inhibitors, indicated that CYP3A4/5 was the major metabolic enzyme responsible for the metabolism of taletrectinib; CYP2C8 played a minor role and the contributions of other CYP isoforms were very limited. The metabolism of [^{14}C] taletrectinib was studied in vitro using rat, monkey and human cryopreserved hepatocytes. There were no unique metabolites observed in human hepatocytes, with the metabolites observed in both or at least one of the nonclinical species. In human plasma, taletrectinib and 9 metabolites were identified.

Excretion

In a rat study at a single oral 30 mg/kg dose of [^{14}C] taletrectinib, the highest radioactivity concentration was observed in the urine in the bladder at 4 hours (the ratio of radioactivity concentration in urine to that in the blood: Kb = 52.45). Following a single oral administration of unlabeled and [^{14}C] labeled taletrectinib (200 mg/5 μCi) in healthy subjects, 75.1% of radioactivity was excreted in feces (15.3% to dose in original) and 11.1% in urine (2.88% to dose in original), indicating that fecal excretion was the primary excretion route.

Drug–Drug Interactions (DDIs)

The in vitro inhibition studies indicated that there was a potential for taletrectinib to cause direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, with the lowest IC_{50} (0.38 μM) and K_i (0.46 μM) for CYP3A4. Taletrectinib did not show mechanism-based inhibition activity on CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 tested with midazolam, nifedipine, and testosterone. Taletrectinib was not considered to have induction potential up to 3.3 μM for CYP2B6 and up to 1.0 μM for CYP3A4, respectively. Taletrectinib may have induction potential for CYP1A2 at ≥0.33 μM. The in vitro study indicated that taletrectinib was only a substrate of P-gp, but not a substrate of other transporters. Taletrectinib inhibited P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K with the IC_{50} values of 2.29, 4.34, 4.71, 17.6, 15.4, 61.1, 18.0, 0.162, and 0.154 μM, respectively.

The FDA's Assessment:

FDA generally agrees with the Applicant's summaries of the ADME data, with additional notable findings described below. All the in vitro drug-drug interactions studies were reviewed by FDA's clinical pharmacology team (see **Section 6** for assessment).

Type of Study	Major Findings
Distribution	
Study AM13-H0075-R01: Qualitative Whole-body Autoradiography after a Single Oral Administration of [14C]DS-6051a to Male Albino Rats	After oral administration of [^{14}C]DS-6051a (1.2 mg/2mL/kg), rats were euthanized at 2, 6, 24, 72 and 168 hours post-dose and frozen bodies were embedded to create frozen blocks. Three kinds of whole-body sections were prepared: a section including the kidney, heart, and lung (renal plane),

Type of Study	Major Findings
Study B140170: Quantitative Whole-body and Brain Section Autoradiography after a Single Oral Administration of [14C]DS-6051a to Male Albino Rats	a section including the brain and spinal cord (mid-line plane), and a section including the adrenal cortex (adrenal plane). **Oral (Albino Rat)** • High levels of radioactivity were observed in the gastric and intestinal contents (due to oral administration), liver, and kidney at 2-, 6-, and 24-hours post-dose. Radioactivity in the liver and kidney • decreased by 72 hours, with slight radioactivity observed at 168 hours post-dose. • Mid-levels of radioactivity were observed in the heart, the mandibular gland, and choroid plexus. • Low levels of radioactivity were observed in the central nervous system (CNS) and testes. **Oral (Albino Rat)** • Quantification of radioactivity after a single oral administration at 30 mg/kg showed maximum concentrations at 4 to 8 hours after administration in most tissues. • Additional organs with radioactivity identified in the study were the Harderian gland, pituitary, skin, and spleen. **Oral (Pigmented Rat)** • After single oral administration of 30 mg/kg, radioactivity was noted in the pigmented tissue of the eyeball and skin with the maximum concentration in the eyeball reached at the period from 8 to 72 hours after administration. • In other tissues, distribution profiles of [^{14}C]DS-6051a in pigmented rats were similar to those in albino rats. • Except for the gastrointestinal contents, the highest tissue/blood concentration ratio at 8 hours after administration was observed in the spleen (31.91), liver (13.27), adrenal (29.88), and lung (22.04). • By 168 hours after administration, the radioactivity concentrations were only observed in the eyeball, pituitary, skin (pigmented), and testis with the eyeball having 8- to 41-fold higher radioactivity compared to the others.
Study B140171: Quantitative Whole-body Autoradiography and Radioactivity Concentration after a Single Oral Administration of	Investigators evaluated the brain distribution of taletrectinib free base (DS-6051a) following a single oral or 4-day repeated oral administration at 10 or 100 mg/kg in albino rats.

Type of Study	Major Findings
[14C]DS-6051a to Male Pigmented Rats **Study AM14-H0023-R01:** The brain concentration profile of DS-6051a following oral administration of DS-6051b	**Mean Concentration of Taletrectinib in Rat Plasma and Brain Homogenate**

10 mg/kg	Single				
Time (h)	Pre	2	6	24	48
Plasma (µg/mL)			0.05		0.03*
Brain homogenate (µg/g tissue)			0.07		BLOQ
10 mg/kg	**Daily**				
Time (h)	**Pre**	**2**	**6**	**24**	**48**
Plasma(µg/mL)			0.03		
Brain homogenate (µg/g tissue)			0.64		
100 mg/kg	**Single**				
Time (h)	**Pre**	**2**	**6**	**24**	**48**
Plasma(µg/mL)		0.16	0.19	0.11	0.03
Brain homogenate (µg/g tissue)		0.21	0.21	0.41	0.21
100 mg/kg	**Daily**				
Time (h)	**Pre**	**2**	**6**	**24**	**48**
Plasma(µg/mL)	0.69	0.71	0.55		
Brain homogenate (µg/g tissue)	0.82	1.26	1.21		

*Sample size was equal to one. BLOQ = below lower limit of quantification.

- The brain homogenate concentration was higher than plasma at all the time points tested. These findings show discrepancy with the qualitative autoradiography (Study AM13-H0075-R01) showing a low level of radioactivity detected in the central nervous system (CNS). Taletrectinib accumulated in choroid plexus in study AM13-H0075-R01, possibly contributing to overall higher radioactivity concentrations in the brain compared to the plasma, as the choroid plexus was not separated from the brain homogenate during sample preparation.

In vitro partitioning of taletrectinib (AB-106) in human blood

The Applicant determined the partitioning of taletrectinib in human blood, assessing the distribution of taletrectinib between plasma and erythrocytes.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Study 423090-20221012-BPR: Determination of the in vitro Partitioning of AB-106 in Human Blood</td><td>
Peak area ratio, Kb/p, Ke/p in whole blood sample taken at 60 minutes
<table>
<tr><th>Compound</th><th>Kb/p
Mean</th><th>Ke/p
Mean</th></tr>
<tr><td>Diclofenac, 1 µM</td><td>0.54</td><td>0.07</td></tr>
<tr><td>Chloroquine, 1 µM</td><td>4.09</td><td>7.26</td></tr>
<tr><td>Taletrectinib, 100 ng/ml</td><td>1.30</td><td>1.61</td></tr>
<tr><td>Taletrectinib, 300 ng/ml</td><td>1.29</td><td>1.59</td></tr>
<tr><td>Taletrectinib, 1000 ng/ml</td><td>1.44</td><td>1.90</td></tr>
</table>
Kb/p = Ratio of blood over plasma concentration. Ke/p = Ratio of erythrocytes over plasma concentration. Diclofenac and chloroquine served as controls.
Taletrectinib showed a moderate and non-concentration dependent partitioning into human erythrocytes.
</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

In the Good Laboratory Practice (GLP) 28-day repeat-dose rat toxicity and TK study with administered taletrectinib doses of 0, 10, 30 or 100 mg/kg/day, the STD_{10} for taletrectinib was estimated to be >100 mg/kg/day. In the pivotal 85-day repeat-dose rat toxicity and TK study with administered taletrectinib doses of 0, 20, 65 or 100 mg/kg/day, the STD_{10} for taletrectinib was not determined but was estimated to be >100 mg/kg/day. At the 100 mg/kg/day dose, the taletrectinib Day 85 sex combined mean C_{max} was 1,855.52 ng/mL and $AUC_{0\text{-}72h}$ was 62,588.16 ng•h/mL.

In the GLP 28-day repeat-dose monkey toxicity and TK study with administered taletrectinib doses of 0, 10, 30 or 100 mg/kg/day, the HNSTD was 100 mg/kg/day. In the pivotal GLP 85-day repeat-dose monkey toxicity and TK study with administered taletrectinib doses of 0, 10, 30, or 60/48 mg/kg/day. Initially, a dose of 60 mg/kg/day was the highest dose but was reduced to 48 mg/kg/day following deaths early in the study. The HNSTD for taletrectinib was 30 mg/kg/day with the sex combined mean C_{max} and $AUC_{0\text{-}24}$ values on Day 85 of 813.04 ng/mL and 13,941.54 ng•h/mL, respectively.

GLP-compliant 28-day and pivotal 85-day toxicity and TK studies in rats and monkeys confirmed that taletrectinib produced target organ toxicity that would be anticipated for a typical TKI. The safety concerns identified in these toxicology studies are considered to be either clinically monitorable (e.g., serum liver function tests [LFTs], cardiovascular effects) or reversible (degenerative and/or inflammatory changes in multiple organs).

Report VPT1473/2013: Taletrectinib: 28-Day Oral Repeat-Dose Toxicity Study in Crl:CD (SD) Rat with a 28-Day Treatment-Free Period

Module 4.2.3.2

								Test Article: Taletrectinib	
Species/Strain:		Rat/Sprague Dawley				**Report Number:** VPT1473/2013			
Initial Age:		8-9 weeks							
Date of First Dose:		22 May 2013							
Lot Number:		RS101 (b) (4)							
Duration of Dosing:		28 days				**GLP Compliance:**	Yes		
Duration of Post dose:		28 days							
Method of Administration:		Oral (gavage)							
Vehicle/Formulation:		0.5% (w/v) (b) (4) in sterile water for injections/suspension							
Special Features:		10/sex/group euthanized at the end of dosing and 5/sex/group assigned to 4 weeks treatment-free period as toxicology animals; 3/sex/group as toxicokinetic animals							
NOAEL:		NA							
STD_{10}:		100 mg/kg/day							
Repeat-Dose Toxicity									
Daily Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main Study + Recovery)		**M: 15 (10 + 5)**	**F: 15 (10 + 5)**	**M: 15 (10 + 5)**	**F: 15 (10 + 5)**	**M: 15 (10 + 5)**	**F: 15 (10 + 5)**	**M: 15 (10 + 5)**	**F: 15 (10 + 5)**
Number of TK Animals		**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 3**	**F: 3**
Toxicokinetics									
AUC_{0-24} (ng•h/mL)	Day 1	BLQ	BLQ	608 ± 172	833 ± 245	3730 ± 365	5360 ± 256	9620 ± 2060	12700 ± 2690
	Day 28	BLQ	BLQ	1330 ± 216	1110 ± 381	4820 ± 1040	6360 ± 1680	24900 ± 5220	26900 ± 2570

C_{max} (ng/mL)	Day 1	BLQ	BLQ	58.1 ± 10.8	94.6 ± 30.8	322 ± 38.7	585 ± 21.7	634 ± 35.7	770 ± 108
	Day 28	BLQ	BLQ	116 ± 6.68	115 ± 50.2	427 ± 62.7	596 ± 269	1270 ± 203	1390 ± 253
Key Findings: • A single mortality at the 100 mg/kg/day dose • Reductions in body weight gain and/or body weight loss, limited changes in clinical pathology parameters, and degenerative and/or inflammatory microscopic findings in numerous tissues were also noted at the 100 mg/kg/day dose									

Abbreviations: -, no noteworthy findings; AUC_{0-24}, area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; BLQ, below the lower limit of quantification; C_{max}, maximum plasma concentration; F, female; GLP, Good Laboratory Practice; M, male; NA, not applicable; NOAEL, no observed adverse-effect level; TK, toxicokinetic.

Report 2021009: 85-Day Repeated-Dose Toxicity Study of Taletrectinib by Oral Gavage in Sprague Dawley Rats with a 57-Day Treatment-Free Period

Module 4.2.3.2

Test Article: Taletrectinib

Species/Strain:	Rat/Sprague Dawley	**Report Number:** 2021009	
Initial Age:	5-6 weeks		
Date of First Dose:	24-25 February 2021 (M-F, respectively)		
Lot Number:	CPo124073-01-04-01-26-01		
Duration of Dosing:	85 days	**GLP Compliance:**	Yes
Duration of Post dose:	57 days		
Method of Administration:	Oral (gavage)		
Vehicle:	0.5% (b) (4)		
Special Features:	Body Temperature and Bone Marrow		
HNSTD	20 mg/kg		

Repeat-Dose Toxicity

Daily Dose (mg/kg/day)		**0 (Control)**		**20**		**65**		**100**	
Number of Animals (Main Study + Recovery)		**M: 15 (10 + 5)**	**F: 15 (10 + 5)**	**M: 15 (10 + 5)**	**F: 15 (10 + 5)**	**M: 15 (10 + 5)**	**F: 15 (10 + 5)**	**M: 15 (10 + 5)**	**F: 15 (10 + 5)**
Number of TK Animals		**M: 8**	**F: 8**	**M: 8**	**F: 8**	**M: 8**	**F: 8**	**M: 8**	**F: 8**
Toxicokinetics									
AUC_{0-24} (ng•h/mL)	Day 1	BLQ		1120.0614 ± 630.0076		5630.1245 ± 155.8073		8267.4582 ± 847.9228	
AUC_{0-72} (ng•h/mL)	Day 85	BLQ		5709.6847 ± 633.2093		37046.0343 ± 1167.6269		62588.1626 ± 2541.8905	
C_{max} (ng/mL)	Day 1	BLQ		159.8150 ± 51.8468		540.8898 ± 8.4414		720.4456 ± 7.7989	
	Day 85	BLQ		596.5271 ± 54.0203		1618.9918 ± 1.2731		1855.5155 ± 235.8848	

Key Findings:

- Changes were noted in the heart, liver, spleen, kidney, submaxillary, sublingual salivary gland, esophagus, seminal vesicles, uterus, pituitary, parathyroid, brain, mandibular and mesenteric lymph nodes (fully recovered following a 57-day recovery period)
- Granulomatous inflammation in the alveoli with crystal formation was observed in treated animals (the incidence, severity, and lack of recovery of this finding in animals administered 100 mg/kg/day were considered adverse)

Abbreviations: -, no noteworthy findings; /, not applicable; AUC_{0-24}, area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; AUC_{0-72}, area under the plasma concentration-time curve from the start of dosing (0 h) to 72 hours; BLQ, below the lower limit of quantification; C_{max}, maximum plasma concentration; F, female; GLP, Good Laboratory Practice; HNSTD, highest non-severely toxic dose; M, male; TK, toxicokinetic.

Report VPT1578/2013: Taletrectinib: 28-Day Oral Repeat-Dose Toxicity Study in Cynomolgus Monkey with a 28-Day Treatment-Free Period

Module 4.2.3.2

Test Article: Taletrectinib

Species/Strain:	Monkey/Cynomolgus	**Report Number:** VPT1578/2013	
Initial Age:	~ 2.5 years		
Date of First Dose:	28 June 2013		
Lot Number:	RS101		
Duration of Dosing:	28 days	**GLP Compliance:**	Yes
Duration of Post dose:	28 days		
Method of Administration:	Oral (gavage)		
Vehicle/Formulation:	0.5% (w/v) (b) (4) in sterile water for injections/suspension		
Special Features:	Electrocardiography		
HNSTD	100 mg/kg/day		

Repeat-Dose Toxicity

Daily Dose (mg/kg/day)		**0 (Control)**		**10**		**30**		**100**	
Number of Animals (Main study + Recovery)		**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**
Toxicokinetics									
$AUC_{0\text{-}t}$ (ng•h/mL)	Day 1	BLQ[a]	BLQ[a]	1930 ± 570	1560 ± 726	3560 ± 1260	6670 ± 1200	6560 ± 3290	4260 ± 1240
	Day 28	BLQ[a]	BLQ[a]	2130 ± 352	1880 ± 1 200	4220 ± 1200	6600 ± 2250	6590 ± 3300	10000 ± 2010
C_{max} (ng/mL)	Day 1	BLQ[a]	BLQ[a]	171 ± 84.8	123 ± 53.5	249 ± 92.1	455 ± 47.0	485 ± 239	324 ± 122
	Day 28	BLQ[a]	BLQ[a]	151 ± 32.4	138 ± 70.8	304 ± 125	463 ± 153	427 ± 247	601 ± 86.1

Key Findings:

- Drug related findings were noted primarily in animals administered 100 mg/kg/day, and to a lesser extent in animals administered 30 mg/kg/day
- Clinical pathology, microscopic findings noted at completion of dosing had fully recovered or demonstrated recovery following the dose free period

Abbreviations:-, no noteworthy findings; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from the start of dosing (0 h) to the last quantifiable time point (t); BLQ, below the lower limit of quantification; C_{max}, maximum plasma concentration; F, female; GLP, Good Laboratory Practice; HNSTD, highest nonseverely toxic dose; MC, methyl cellulose; M, male; NA, not applicable.

Report 2021010: 85-Day Repeated-Dose Toxicity Study of Taletrectinib by Oral Gavage in Cynomolgus Monkeys with a 57-Day Treatment-Free Period

Module 4.2.3.2

								Test Article: Taletrectinib	
Species/Strain:	Monkey/Cynomolgus						**Report Number:** 2021010		
Initial Age:	3.4-4.9 years (M); 3.4-4.7 years (F)								
Date of First Dose:	30-31 March 2021 (M-F, respectively)								
Lot Number:	CPo124073-01-04-01-26-01								
Duration of Dosing:	85 days						**GLP Compliance:**	Yes	
Duration of Post dose:	57 days								
Method of Administration:	Oral (gavage)								
Vehicle:	0.5% (b) (4)								
Special Features:	Electrocardiography, Body Temperature, Blood Pressure, and Bone Marrow Smears								
HNSTD	30 mg/kg/day								
Repeat-Dose Toxicity									
Daily Dose (mg/kg/day)	**0 (Control)**		**10**		**30**		**48 or 60[a]**		
Number of Animals (Main Study + Recovery)	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	**M: 5 (3 + 2)**	**F: 5 (3 + 2)**	
Toxicokinetics[b]									
AUC_{0-24} (ng•h/mL)	Day 1	BLQ		2081.1777 ± 1357.4779		8905.6639 ± 4293.5446		14997.9955 ± 6368.6019	
	Day 85	BLQ		3424.2537 ± 687.2958		13941.5447 ± 5539.3493		20383.2963 ± 5624.4475	
C_{max} (ng/mL)	Day 1	BLQ		174.9510 ± 146.9667		649.1922 ± 469.1654		935.7534 ± 555.3960	
	Day 85	BLQ		245.9716 ± 71.0878		813.0412 ± 454.3595		1023.1941 ± 229.0009	

Key Findings:

- Early mortalities were observed in high-dose group males and females that led to dose reductions
- Taletrectinib related findings were noted in clinical pathology, coagulation, and in macroscopic and microscopic pathology parameters
- All findings presented demonstrated full recovery whereas distinct indications of recovery were noted in the stomach and mesenteric lymph nodes

Abbreviations: -, no noteworthy findings; AUC0-24, area under the plasma concentration-time curve from the start of dosing (0 h) to 24 hours; BLQ, below the lower limit of quantification; Cmax, maximum plasma concentration; GLP, Good Laboratory Practice; HNSTD, highest non-severely toxic dose; F, female; MC, methyl cellulose; M, male.

The FDA's Assessment:

FDA generally agrees with the Applicant's conclusions, with additional pertinent findings described below:

Study title/ number: A 12-week repeated-dose toxicity study of AB-106 by oral gavage in Sprague Dawley rats/ 2021009

- The target organs of toxicity were heart, lungs, spleen, lymph nodes, kidney (with corresponding urinalysis findings), esophagus, pituitary, adrenal, and brain (choroid plexus).
- Reproductive target organs included seminal vesicles, testes, epididymis, and uterus with cervix.

Observations and Results: changes from control

Parameters	Major findings
Mortality	No drug-related deaths. One female (65 mg/kg) found dead on Day 51 with multi-organ metastasis of malignant lymphoma including the heart, aorta, lung (with bronchi), liver, spleen, lymph nodes (mesenteric, mandibular, inguinal), kidney, ovary, oviduct, uterus, pituitary, harderian gland, breast, and the femur. Additionally, the gastrointestinal tract, thyroid gland (with parathyroid gland), and the sternum (bone marrow) showed various degrees of autolysis.
Clinical Signs	*Salivation-* considered test article related • 65 mg/kg - 8/15 females • 100 mg/kg - 2/15 males and 15/15 females
Body Weights	*100 mg/kg* -test-article induced decreased body weight gain **Males** • 26% decreased body weight vs. controls Day 85 (end of dosing) • 10% decreased body weight vs. controls Day 141 (end of recovery)

Females

- 16% decreased body weight vs. controls Day 85 (end of dosing)
- 14% decreased body weight vs. controls Day 141 (end of recovery)

Ophthalmoscopy

Unremarkable

Hematology

%-Change in Hematology Parameters from Vehicle-Treated Control Group in Rats Treated with Taletrectinib

Dose mg/kg	20		65		100	
sex	M	F	M	F	M	F
NEUT #	+26	-	-	+118	+88	+346
NEUT %	+14	+22	+35	+90	+99	+230
LYMPH #	-	-16	-27	-	-32	-16
LYMPH %	-	-	-10	-14	-26	-35
MONO #	+31	-	-	+73	+56	+173
MONO %	+17	+32	+29	+52	+71	+104
EOS #	+53	-	-24	-18	-41	-
EOS %	+40	+13	-	-17	-32	-21
PLT	-	-	+37	+42	+68	+71
APTT	-	-	-13	-11	-13	-15

Findings recovered or trended towards recovery by the end of the recovery period.

Clinical Chemistry

% Change in Clinical Chemistry from Vehicle-Treated Control Group in Rats Treated with Taletrectinib

Dose mg/kg	20		65		100	
sex	M	F	M	F	M	F
ALT	+23	-17	+28	+20	+44	+33
AST	-	-12	+80	+49	+113	+186
ALP	-	-	+13	+50	-	+61
TG	-	-29	-24	-11	-24	-
K	-	-	-	-	+12	-

Findings recovered or trended towards recovery by the end of the recovery period.

<table>
<tr><td>Urinalysis</td><td>Urinalysis findings correlate with histopathology findings in the kidney suggesting test article-related kidney injury. Findings recovered.
<u>65 mg/kg</u>
Increased protein: males and females
Increased specific gravity: males
Occult blood: males
Ketones: females
Leukocytes present: males and females
Urine creatinine; females
<u>100 mg/kg</u>
Increased protein: males
Occult blood: males
Ketone: males
Leukocytes present: males and females
Urine creatinine: females</td></tr>
<tr><td>Gross Pathology</td><td><u>100 mg/kg</u>
Mandibular lymph node-increased size; correlated with microscopic findings of mild active germinal center with increase of tingible body macrophages in the cortex and increased vacuolated macrophages in the paracortex/medulla.
Lung-gray plaque on surface (males only); correlated with microscopic findings of moderate accumulation of foamy macrophages/foamy materials in the alveoli.</td></tr>
<tr><td>Bone Marrow Smears</td><td>Unremarkable</td></tr>
<tr><td>Organ Weights</td><td>% Change in Absolute Organ Weights from Controls in Rats Treated with Taletrectinib
<table>
<tr><th>Dose mg/kg</th><th colspan="2">20</th><th colspan="2">65</th><th colspan="2">100</th></tr>
<tr><th>sex</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>Kidney</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>+18</td></tr>
<tr><td>Heart</td><td>-</td><td>-</td><td>-</td><td>+12</td><td>-</td><td>+12</td></tr>
<tr><td>Lung with bronchi</td><td>-</td><td>-</td><td>-</td><td>-</td><td>+40</td><td>+55</td></tr>
<tr><td>Liver</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-16</td><td>-</td></tr>
<tr><td>Adrenal gland</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-15</td><td>-</td></tr>
<tr><td>Epididymides</td><td>-11</td><td>na</td><td>-13</td><td>na</td><td>-10</td><td>na</td></tr>
</table>
na = not applicable. Lungs in males were still significantly increased in weight after recovery necropsy. All other findings recovered.</td></tr>
</table>

Histopathology

Adequate battery: Yes

Dose (mg/kg)		0		20		65		100	
Sex		M	F	M	F	M	F	M	F
# animals main /recovery		10/5	10/5	10/5	10/5	10/5	10/4	10/5	10/5
Heart									
Cardiomyopathy	Minimal	2,1	1	1,1	-	4,1	2	5,2	6
	Mild	-	-	-	-	-	-	3	2
Lungs with bronchi									
Accumulation of foamy macrophages/foamy materials, alveoli	Minimal	3,2	4	6,2	7,1	5,2	4	1,2	-,3
	Mild	-	-,1	-,1	-	1	6,1	4,1	3,1
	Moderate	-	-	-	-	-	-	2	7
	Marked	-	-	-	-	-	-	2	-
Hemorrhage, alveoli	Minimal	-	-	-	1	-	-	-	-
Inflammation, granulomatous, crystals, alveoli	Minimal	-	-	-,1	-	-	-	-,2	-,2
Osseous metaplasia	Minimal	-	-	-	-	-	-	-,1	-
Spleen									
Accumulation of foamy macrophages, marginal zone of white pulp/germinal center	Minimal	-	-	-	-	-	-	6	4
Pigment, red pulp/white pulp	Minimal	-	3	-	6,2	1	5	-	2,3
Congestion	Minimal	-	-	-	-	2	-	-	3
	Mild	-	-	-	-	-	-	-	2
Decreased cellularity, lymphocytes, white pulp	Minimal	-	-	-	-	-	-	2	1
	Mild	-	-	-	-	-	-	1	3
Lymph node, mandibular									
Increased vacuolated macrophages, paracortex / medulla	Minimal	-	-	-	-	-	-	1	2
	Mild	-	-	-	-	-	-,1	2,1	2,1
Erythrocytosis / phagocytosis	Minimal	-	-	1	1	1	3	1	-
Submaxillary gland									
Vacuolation, mucous acinar cells / ductal epithelium / granular duct	Minimal	-	-	2	-	3	3	3	2
	Mild	-	-	-	-	-	-	2	-
	Moderate	-	-	-	-	-	-	1	-
	Minimal	-	-	-	-,1	4	4	1,1	5

		Decreased secretion, granular duct	Mild	-	-	-	-	1	4	3	3
			Moderate	-	-	-	-	-	-	-	1
		Pancreas									
		Vacuolation, acinar epithelium, exocrine portion	Mild	-	-	-	-	1	-	-	-
		Atrophy, exocrine portion	Minimal	-	1	-	-	1	-	1	-
		Infiltration, inflammatory cells	Minimal	-	-	1	-	1	-	-	-
		Kidney									
		Vacuolation, glomerulus	Minimal	-	-	-	-	9	4	2	-
			Mild	-	-	-	-	-	5	7	10
		Vacuolation, renal tubules, cortex / Medulla	Minimal	-	-	-	-	6	6	3	1
			Mild	-	-	-	-	1	2	7	9
		Dilation, tubules	Minimal	-	-	-	-	-	-	-	1
			Mild	-	-	-	-	-	-	-	2
		Mineralization	Minimal	-	-	-	-	1	1	1	-
		Infarct	Minimal	-	-	-,1	1	-	-	-	1
		Scar, cortex	Minimal	-	-	-	-	1	-	-	-
		Dilation, pelvis	Minimal	-	-	-	-	-	1	-	-
		Urinary bladder									
		Accumulation of protein material	Minimal	-	-	-	-	1	-	-	-
		Infiltration, mononuclear cells, submucosa	Minimal	-	-	-,1	-	-	-	-	-
		Seminal vesicles									
		Vacuolation, acinar epithelium	Minimal	-	-	-	-	-	-	5	-
			Mild	-	-	-	-	-	-	1	-
		Testis									
		Atrophy/degeneration, tubular, bilateral	Mild	-	-	-	-	1	-	-,1	-
		Epididymis									
		Hyperplasia, interstitial cells, bilateral	Mild	-	-	-	-	1	-	-	-
		Reduced sperm, luminal, bilateral	Mild	-	-	-	-	1	-	-	-
		Esophagus									

		Infiltration, inflammatory cells, muscular layer	Minimal	1	-	-	-	1	2	3	1
		Degeneration of myocytes with inflammatory cell infiltrate, muscular layer	Minimal	-	-	-	-	-	-	6	6
			Mild	-	-	-	-	-	-	-	1
		Uterus with cervix									
		Vacuolation, endometrial glandular epithelium	Minimal	-	-	-	-	-	3	-	1
			Mild	-	-	-	-	-	-	-	8
		Parathyroid									
		Vacuolation, chief cell, bilateral	Minimal	-	-	-	-	-	-	-	1
		Infiltration, mononuclear cells	Minimal	-	-	-	1	-	-	-	-
		Adrenal gland									
		Vacuolation, increased, cortical	Minimal	1	3	3	-	1	-	4	2
			Mild	3	-	-	-	-	-	2	-
			Moderate	-	-	-	-	-	-	-	1
		Hemorrhage	Mild	-	-	-	-	-	-	-	1
		Pituitary									
		Vacuolation, pars distalis	Minimal	-	-	-	-	-	-	5	5
		Brain									
		Vacuolation, choroid plexus	Minimal	-	-	-	-	-	-	3	1

Study title/ number: A 12-Week Repeated-Dose Toxicity Study of AB-106 By Oral Gavage in Cynomolgus Monkeys/ 2021010

- The target organs of toxicity were the lungs, kidney, liver, pancreas, stomach, small intestine, thymus, lymph nodes, adrenal gland, and urinary bladder
- Reproductive organs of toxicity included testes and epididymis.

Methods – additional pertinent details:

Dose and frequency of dosing:	0, 10, 30, or 60/48* mg/kg daily for 12 weeks *60 mg/kg from Days 1-10 in males and Days 1-9 in females then reduced to 48 mg/kg due to toxicities
Age:	3-5 years / sexually mature

Observations and Results: changes from control

Parameters	Major findings
Mortality	*60 mg/kg* • 2 males (1 dead on Day 10, 1 dead on Day 2 30 minutes post second dose) and 1 female (found dead Day 10) o Cause of death in 1 male due to chronic incidental pulmonary infection not likely drug related and in the other male due to GI toxicity likely drug related o Cause of death in female not determined due to death in middle of night and autolysis of several organs making pathology difficult *30 mg/kg* • 1 male (found dead Day 19) o Displayed hypoactivity, quivering, moderate infiltration of inflammatory cells in subarachnoid/choroid plexus/meninges of brain was noticed and was considered to be cause of death
Clinical Signs	*30 mg/kg* • 1/5 males → red ruptured cyst, 2 pustules under arm, could not stand starting Days 70-86, no abnormality in vertebra lumbalis was detected, but no stimulus responses in legs, tail, and anal sphincter were seen, diagnosed with paralyzed lower limbs, displayed cold to touch and swollen abdomen on Days 84 to 86; unlikely drug related. • 1/5 females → mandibular fracture, unknown cause; unlikely drug related. • 2/5 females → loose/watery feces; drug related *60/48 mg/kg* • 1/5 males → diarrhea; drug related
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
Body Temp/ Blood Pressure	Unremarkable

<table>
<tr><td>Hematology</td><td>%-Change in Hematology Parameters from Vehicle-Treated Control Group on Day 86 in Monkeys Treated with Taletrectinib
<table>
<tr><th>Dose mg/kg</th><th>10</th><th>30</th><th>60/48</th></tr>
<tr><td>RBC</td><td>-11</td><td>-17</td><td>-19</td></tr>
<tr><td>HGB</td><td>-</td><td>-18</td><td>-22</td></tr>
<tr><td>HCT</td><td>-13</td><td>-17</td><td>-20</td></tr>
<tr><td>PT</td><td>-</td><td>-</td><td>+6</td></tr>
</table>
The Applicant combined values from males and females due to lack of differences in findings between males and females. Findings recovered or trended towards recovery by the end of the recovery period. Additional findings during at the end of the recovery period included an ~30% decrease in reticulocytes at the high dose.</td></tr>
<tr><td>Clinical Chemistry</td><td>% Change in Clinical Chemistry from Vehicle-Treated Control Group on Day 86 in Monkeys Treated with Taletrectinib
<table>
<tr><th>Dose mg/kg</th><th>10</th><th>30</th><th>60/48</th></tr>
<tr><td>ALT</td><td>-</td><td>-</td><td>+113</td></tr>
<tr><td>AST</td><td>-</td><td>-</td><td>+80</td></tr>
<tr><td>ALP</td><td>-</td><td>-42</td><td>-53</td></tr>
<tr><td>CK</td><td>-</td><td>+245</td><td>+344</td></tr>
</table>
The Applicant combined values from males and females due to lack of differences in findings between males and females. Findings recovered or trended towards recovery by the end of the recovery period.</td></tr>
<tr><td>Urinalysis</td><td>Urinary findings did not correlate with histopathology thus are unlikely related to toxicity
60/48 mg/kg

Increased protein: males and females
Increased color: males and females
Increased leukocytes: males and females
</td></tr>
<tr><td>Gross Pathology</td><td>Unremarkable</td></tr>
<tr><td>Bone Marrow Smears</td><td>Unremarkable</td></tr>
<tr><td>Organ Weights</td><td>60/48 mg/kg

Limited to increased thyroid/parathyroid absolute weights in combined male and females; +45% vs. controls; recovered
</td></tr>
</table>

Histopathology

Adequate battery: Yes

Dose (mg/kg)		0		10		30		60/48	
Sex		M	F	M	F	M	F	M	F
# animals main, recovery (early death)		3,2	3,2	3,2	3,2	3,1(1)	3,2	2,1(2)	2,2 (1)
Lungs with bronchi									
Accumulation of foamy macrophages, alveolus	Minimal	-	-	-,1	-,1	-	-	-	1
	Mild	-	-	-	-	-	-	-	1
Infiltration, inflammatory cells, capsule	Minimal	-	-	1	-	-,-(1)	1	1	-
Infiltration, bronchiole, mixed cells	Minimal	-	-	-	-	-	-	-	-,1
Hemorrhage, alveolus	Minimal	-	-	-	1	-	-	-	-
Edema with fibrinous exudation / hemorrhage	Mild					-,- (1)		-,-(1)	
Colon									
Necrosis materials, intraluminal, lamina propria	Minimal	-	-	-	-	-	1	-	-
Kidney									
Basophilia, tubules	Minimal	-	-	-,1	-	-	-	-	-,2
Mineralization	Minimal	-	-	-	-,1	-	-,1	-	-
Granulomatous inflammation	Minimal	-	-	-	-	-	1	-	-
Glomerulosclerosis	Minimal	-	-	-	-	-	1	-	-
Infiltration, mononuclear cells, cortex	Minimal	-	-	-	-	-	-	-,-(1)	-
Dilation, tubules, cortex/medulla	Mild	-	-	-	-	-	-	-,-(1)	-
Esophagus									
Infiltration, mononuclear cells, laminal propria/muscularis	Minimal	-	-	1	1	-	-	-,-(1)	1
Infiltration, inflammatory cells, muscularis	Minimal	-	-	-	-	-	-	-	-,1
Liver									
Necrosis/infiltrate, inflammatory cells, hepatocyte	Minimal	-	-	-	-	-	-	-,-(1)	1
	Mild	-	-	-	-	1	-	-	-
Vacuolation, hepatocyte	Mild	-	-	-	-	-	2	-	-
Pancreas									
Depletion of zymogen granules, exocrine portion	Minimal	-	-	-	-	-	-,1	1,-(1)	-,-(1)
Stomach									
Regeneration, glandular epithelium of fundic glands, lamina propria	Minimal	-	-	1,1	-,1	-	-	1,-(2)	-
	Mild	-	-	-	-	1	-	-	-
Infiltration, inflammatory cells, lamina propria	Minimal	-	-	-	1	1	-,1	-,-(1)	-
	Mild	-	-	-	-,1	-	-	-	-

Infiltration, eosinophils, perivascular/submucosa	Minimal	-	-	-	-	-	-	1	-
Duodenum										
Infiltration, foamy macrophages, lamina propria	Minimal	-	-	-	-	-	-	1	-
Erosion, epidermis	Mild	-	-	-	-	-	-	-,-(1)	-
Hemorrhage, mucosa	Mild	-	-	-	-	-	-	-,-(1)	-
Jejunum										
Infiltration, foamy macrophages, lamina propria	Minimal	-	-	-	-	-	1	-	-
	Mild	-	-	-	-	1	1	1	1
	Moderate	-	-	-	-	1	-	1	1
Erosion, epidermis	Mild	-	-	-	-	-	-	-,-(1)	-
Hemorrhage, mucosa	Mild	-	-	-	-	-	-	-,-(1)	-
Thymus										
Hemorrhage	Minimal	-	-	-	-,1	-	-	-	-,1
Decreased lymphocytes, cortex/medulla	Minimal	1	2	1	1	-	2	-	1
	Mild	-	-	-	-	-,-(1)	-	-,-(1)	1
	Moderate	-	-	-	-	2	-	-	-,-(1)
Infiltration, inflammatory cells, capsule / interstitial	Minimal	-	-	-	-	-,-(1)	-	-	-
Ileum										
Infiltration, foamy macrophages, lamina propria	Minimal	-	-	-	-	1	-	-	-
Cecum										
Necrosis material, intraluminal, lamina propria	Minimal	-	-	-	-	-	1	-	-
Lymph node, inguinal										
Active germinal center with increased tangible body macrophages, cortex	Minimal	-	-	-	-	1	1	1	-
Lymph node, para-lumbar										
Dilatation of subcapsular sinus, with infiltration of inflammatory cells	Mild	-	-	-	-	-,-(1)	-	-	-
Lymph node, mesenteric										
Histiocytosis, medullary sinus	Minimal	-	-	-	-	2,-(1)	2	1	2,1
	Mild	-	-	-	-	-	-	1,1	-,1
Decreased lymphocytes, cortex	Mild	-	-	-	-	-	-	-	-,-(1)
Erythrocytosis/phagocytosis	Minimal	-	-	-	-	-	-	-,-(1)	-
Lymph node, mandibular										

Granulomatous inflammation with necrosis	Moderate	-	-	-	-	1	-	-	-
Erythrocytosis/phagocytosis	Minimal	-,1	-,1	-	1	-	-	-,1	-,1
Increased vacuolated macrophages, paracortex	Mild	-	-	-	-	-,-(1)	-	-	-
Testes									
Atrophy, tubular, unilateral	Mild	-	-	1	-	-	-	-	-
Epididymis									
Round spermatids, luminal unilateral	Mild	-,1	-	1	-	-	-	-,-(1)	-
Mineralization	Minimal	-	-	-	-	1	-	-	-
Sciatic nerve									
Infiltration, mononuclear cells, unilateral	Minimal	-	-,1	-	-	1	-	-	-
Spinal cord, thoracic									
Necrosis with hemorrhage	Moderate	-	-	-	-	1	-	-	-
Brain									
Glial nodule	Minimal	-	-	-	-	1	-	-	-
Infiltration, inflammatory cells, subarachnoid/choroid plexus/meninges	Moderate	-	-	-	-	-,-(1)	-	-	-
Sternum with bone marrow									
Accumulation of lymphocytes	Minimal	-	-	-	-	-	-	-	1
Increased bone marrow cells	Minimal	-	-	-	-	-,-(1)	-	-	-
Prostate									
Infiltration, mononuclear cells	Minimal	-	-	-	-	-,-(1)	-	-	-
Adrenal gland									
Hypertrophy, fasciculata zona, cortex	Minimal	-	-	-	-	-,-(1)	-	-	-
	Mild	-	-	-	-	-	-	-,-(1)	-,-(1)
Urinary bladder									
Vacuolation, mucosal epithelium	Mild	-	-	-	-	-	-	-	-,-(1)

In 28-day GLP-complaint, repeat-dose toxicity studies in Sprague Dawley rats and cynomolgus monkeys, rats and monkeys were orally administered 10, 30, or 100 mg/kg/day taletrectinib (DS-6051b) for 28 days followed by a 28-day recovery period. Only one death occurred in either study, with one rat at the 100 mg/kg/day dose found dead on Day 19 without known cause of death. Major target organs of toxicity in rats included heart (minimal myocardial necrosis), kidney (apoptosis/single cell necrosis), liver (minimal hepatocyte hypertrophy), striated muscle (minimal to mild myofiber necrosis, regeneration), and lymphoid organs (lymphocyte depletion). Microscopic findings of vacuolation and foamy macrophages were observed in multiple tissues

including minimal to mild findings in the choroid plexus at the 100 mg/kg dose. In the high dose rats, retinal hyper-reflectivity was also noted in 4 out of 30 rats. Adverse effects were reversible by the end of recovery period except for microscopic findings in the heart (inflammation), liver (inflammation), thymus (hyperplasia), and skeletal muscle (myofiber regeneration). In monkeys, minimal to mild microscopic findings of inflammation and foamy macrophages were observed in the GI tract, prostate, skin, spinal cord, and sciatic nerve. Additional findings were noted in the thymus (atrophy), lymph nodes (erythrophagocytosis, foamy macrophages), and kidneys (basophilic casts, dilation, hyperplasia, vacuolation). There were minimal increases in liver enzymes, bilirubin, triglycerides, and creatine kinase in the 100 mg/kg dose group. Urinalysis showed significant increases in creatinine, glucose, and total protein, which were not fully recovered by the end of the non-dosing period.

5.5.2. Genetic Toxicology

The Applicant's Position:

In a bacterial reverse mutation test, taletrectinib initially tested positive in the presence of metabolic activation in Ames tester strain TA98. However, when taletrectinib was retested in three additional bacterial reverse mutation studies conducted at 3 different GLP labs, test results with and without activation were found to be negative. In an in vitro chromosome aberration study, taletrectinib was predicted to have the potential to induce structural and numerical aberrations. However, subsequent results from two in vivo micronucleus studies assessing findings in the liver and bone marrow of rats were negative, indicating that taletrectinib-induced chromosome aberrations are not expected to occur in vivo. Overall, the risk for potential genotoxicity of taletrectinib is considered to be low.

To further evaluate the mutagenic potential of taletrectinib, the following have been initiated: quantitative structure-activity relationship, in vitro mammalian cell forward gene mutation (CHO/HPRT) assay, in vitro mammalian cell gene mutation test (L5178Y/$TK^{+/-}$ mouse lymphoma assay), and evaluation of in vivo Pig-A mutant frequency in male Sprague Dawley rats. Additional information will be provided during the NDA review.

Table 7. Applicant - In Vitro Studies

Study Number:	AN16-C0047-R01	95206-19-1043	946-0003-GT	BSU202301	AN16-C0048-R01
Study Title:	Bacterial Reverse Mutation Study of Taletrectinib	Taletrectinib: Bacterial Reverse Mutation Assay in Salmonella Typhimurium and Escherichia	Taletrectinib: Bacterial Reverse Mutation Assay	Taletrectinib: Bacterial Reverse Mutation Assay	Chromosome Aberration Study of Taletrectinib with Mammalian Cultured Cells

Study Number:	AN16-C0047-R01	95206-19-1043	946-0003-GT	BSU202301	AN16-C0048-R01
		Coli			
eCTD Location	4.2.3.3.1	4.2.3.3.1	4.2.3.3.1	4.2.3.3.1	4.2.3.3.1
Study Type	In vitro	In vitro	In vitro	In vitro	In vitro
Test System	S. typhimurium (TA98, TA100, TA1535, TA1537), E. coli (WP2 uvrA)	S. typhimurium (TA98, TA100, TA1535, TA1537), E. coli (WP2 uvrA)	S. typhimurium (TA98, TA100, TA1535, TA1537), E. coli (WP2 uvrA)	S. typhimurium (TA97a, TA98, TA100, TA102, TA1535)	CHL/IU
GLP Compliance	Yes	Yes	Yes	Yes	Yes
Test Validity	Yes	Yes	Yes	Yes	Yes
Evaluations	Reverse mutation in bacterial cells	Reverse mutation in bacterial cells	Reverse mutation in bacterial cells	Reverse mutation in bacterial cells	Forward mutation in mammalian cells
Findings	Dose-dependent increase in the number of revertant colonies for TA98 +S9	No genotoxic effects observed	No genotoxic effects	No genotoxic effects	A significant increase in structural aberrations with +S9 mix for 6 hours and in numerical aberrations with ± S9 mix for 6 hours.

Table 8. Applicant - In Vivo Studies

Study Number:	AN16-C0049-R01	AN16-C0050-R01
Study Title:	Micronucleus Study in Bone Marrow of Rats Treated Orally with Taletrectinib	Micronucleus Study of Taletrectinib in Rat Liver
eCTD Location	4.2.3.3.2	4.2.3.3.2
Study Type	In vivo	In vivo
Test System	Rat/Sprague Dawley	Rat/Sprague Dawley

GLP Compliance	Yes	Yes
Test Validity	Yes	Yes
Evaluations	Test for induction of bone marrow micronuclei	Test for induction of micronuclei in rat hepatocytes
Findings	No genotoxic effects observed	No genotoxic effects observed

The FDA's Assessment:

Data (presented by FDA) submitted at the 90-day NDA update:

Study type: In vitro Ames assay
Study title / study number: Bacterial Reverse Mutation Assay of DS-6051b /Study AN16-C0047-R01
Key drug-related adverse findings:

- Increased mean number of revertant colonies at concentrations ≥19.5 µg/plate in main test and ≥39.1 ug/plate in the dose-finding assay both with metabolic activation.
  - Findings showed concentration-dependency.
- Taletrectinib (lot#RS102) was considered positive for mutagenic activity under the conditions of this assay.

GLP compliance: Yes

Test system:	Test for induction of reverse mutation in bacterial cells (*Salmonella typhimurium* and *Escherichia coli* TA98, TA100, TA1535, TA1537, WP2 uvrA) using the plate incorporation method with or without metabolizing system (rat liver S9). DS-6051b (taletrectinib) tested at 2.44 to 313 µg/plate. Dimethyl sulfoxide (DMSO) served as the vehicle control.
Study validity:	Yes. Positive (2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, N-Methyl-N-nitro-N-nitrosoguanidine) and negative (DMSO) controls performed as expected.

Study type: In vitro AMES assay
Study title / study number: Bacterial Reverse Mutation Assay in Salmonella Typhimurium and Escherichia Coli/ Study 95206-19-1043
Key drug-related adverse findings:

- Cytotoxicity occurred at concentrations ≥ 75 µg/plate both in the presence and absence of S9 mix.
- Taletrectinib did not induce an increase in the mean number of revertant colonies in any tester strains used at any concentration tested in the presence or absence of metabolic activation.
- Taletrectinib (lot#CPo124073-01-04-01-26-01) was considered negative for mutagenic activity under the conditions of this assay.

GLP compliance: Yes

Test system:	Test for induction of reverse mutation in bacteria (*Salmonella typhimurium* and *Escherichia coli* TA98, TA100, TA1535, TA1537, WP2 uvrA) using the plate incorporation method with or without metabolizing system (β-naphthoflavone and phenobarbital induced rat liver S9). AB-106 (taletrectinib) tested at concentrations of 10, 20, 50, 100, 200, and 250 µg/plate for TA98, 5, 10, 20, 50, 75, and 100 µg/plate for TA1535 and TA1537, 10, 20, 50, 100, 150, and 200 µg/plate for TA100 in the presence of S9, 5, 10, 20, 50, 75, and 100 µg/plate for TA100 in the absence of S9, 10, 20, 50, 100, 200, and 300 µg/plate for WP2 uvrA.
Study validity:	Yes. Positive (2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, N-Methyl-N-nitro-N-nitrosoguanidine) and negative (DMSO) controls performed as expected.

Study type: In vitro AMES assays **Study title / study number:** AB-106: Bacterial Reverse Mutation Assay / Study 946-0003-GT **Key drug-related adverse findings:** • Cytotoxicity occurred at concentrations ≥ 50 µg/plate both in the presence and absence of S9 mix. • No precipitation occurred at any concentration. • Taletrectinib (lot#CPo124073-01-04-01-26-01) was considered negative for mutagenic activity under the conditions of this assay. **GLP compliance:** Yes	
Test system:	Test for induction of reverse mutation in bacteria (*Salmonella typhimurium* and *Escherichia coli* TA98, TA100, TA1535, TA1537, WP2 uvrA) using the plate incorporation method with or without metabolizing system (β-naphthoflavone and phenobarbital-induced rat liver S9). AB-106 (taletrectinib) tested at concentrations with S9 mix were 250, 200, 150, 100, 50, 25, 10, and 5 µg/plate; the dose levels tested with all tester strains without S9 mix were 250, 150, 100, 80, 50, 25, 10, and 5 µg/plate.
Study validity:	Yes. Positive (2-aminoanthracene, 2-nitrofluorene, sodium azide, acridine mutagen, methyl methane-sulfonate) and negative (DMSO) controls performed as expected.
Study type: In vitro AMES assays **Study title / study number:** AB-106 Bacterial Reverse Mutation Assay / Study BSU202301 **Key drug-related adverse findings:** • Cytotoxicity occurred at concentrations ≥320 µg/plate in the presence of S9 and at ≥128 µg/plate in the absence of S9. • Taletrectinib (lot#RS102*) was considered negative for mutagenic activity under the conditions of this assay. * Lot RS102 initially tested positive for mutagenicity in Study AN16-C0047-R01, while other lots tested negative, thus RS102 was tested again. **GLP compliance:** Yes	
Test system:	Test for induction of reverse mutation in bacteria (*Salmonella typhimurium* TA97a, TA98, TA100, TA102, TA1535) using the plate incorporation method with or without metabolizing system (β-naphthoflavone and phenobarbital-induced rat liver S9). AB-106 (taletrectinib) tested at concentrations ranging from 8.192 to 800 µg/plate.
Study validity:	Yes. Positive (dexon, sodium azide, 2-AF,) and negative (DMSO) controls performed as expected.
Study type: In vitro mammalian cell chromosomal aberration assay **Study title / study number:** Chromosome Aberration Study of DS-6051b with Mammalian Cultured Cells / Study AN16-C0048-R01 **Key drug-related adverse findings:** • Taletrectinib (lot#RS102) increased structural aberrations in the presence of S9 for 6 hours and numerical aberrations in the presence and absence of S9 for 6 hours. • Taletrectinib has the potential to induce structural and numerical aberrations. **GLP compliance:** Yes	
Test system:	Induction of chromosome aberrations in mammalian Chinese hamster cell line (CHL) was evaluated in cells treated with taletrectinib at 30, 40, and 45 µmol/L in the presence of S9 mix for 6 hours, at 8, 10, and 20 µmol/L in the absence of S9 mix for 6 hours, and 2, 4, and 6 µmol/L in the absence of S9 mix for 24 hours. For the continuous treatment, the cells were treated for 24

	hours, and for the short treatment, the cells were treated for 6 hours followed by an 18 hour recovery period.
Study validity:	Yes. Positive (mitomycin C and benzo[a]pyrene) and negative (DMSO) controls performed as expected.
Study type: In vivo rat bone marrow micronucleus assay **Study title / study number:** Micronucleus Study in Bone Marrow of Rats Treated Orally with DS-6051b/Study AN16-C0049-R01 **Key drug-related adverse findings:** • No notable clinical signs or mortality observed for any taletrectinib-treated animal. • Taletrectinib (Lot#RS102) did not increase micronucleated immature erythrocytes in treated rats. **GLP compliance:** Yes	
Test system:	Test for induction of micronuclei in immature erythrocytes of male Crl:CD(SD) rats; bone marrow cells were sampled 24 and 48 hours after a single oral administration of taletrectinib at doses of 0 (0.5 w/v% methylcellulose aqueous solution; vehicle), 30, 100, and 300 mg/kg.
Study validity:	Yes. Positive (20 mg/kg of cyclophosphamide monohydrate) and negative (vehicle) controls performed as expected.
Study type: In vivo rat liver micronucleus assay **Study title / study number:** Micronucleus Study of DS-6051b in Rat Liver/Study AN16-C0050-R01 **Key drug-related adverse findings:** • No notable clinical signs or mortality observed for any taletrectinib-treated animal. • Taletrectinib (lot#RS102) did not induce micronuclei rat hepatocytes at when administered orally at doses up to 300 mg/kg. **GLP compliance:** Yes	
Test system:	Test for induction of micronuclei in the liver of male Crl:CD(SD) rats by taletrectinib administered twice via oral gavage twice at 0 (0.5 w/v% methylcellulose aqueous solution; vehicle), 30, 100, and 300 mg/kg. The hepatocyte specimens were observed under a fluorescent microscope counting 4000 hepatocytes (HEPs) per animal to determine the incidence of micronucleated HEPs (MNHEPs).
Study validity:	Yes. Positive (diethylnitrosamine) and negative (vehicle) controls performed as expected.
Studies submitted at the 90-day NDA update	
Study type: In Vitro Mammalian Cell Forward Gene Mutation (Cho/Hprt) Assay **Study title / study number:** In Vitro Mammalian Cell Forward Gene Mutation (CHO/HPRT) Assay in Duplicate Cultures With AB-106/Study nbs-24-228 **Key drug-related adverse findings:** • No visible precipitate was observed at the beginning or end of the 5-hour treatment. • Taletrectinib (lot CPo124073-04-05C-03) did not increase mutant frequency at any concentration tested in the absence or presence of S9. • Taletrectinib was considered negative for induction of forward mutations at the HPRT locus of CHO cells. **GLP compliance:** Yes	
Test system :	Evaluated for the potential for taletrectinib to induce forward mutations at the hypoxanthineguanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells, in the absence and presence of rat S9, as assayed by colony growth in the presence of 6-thioguanine (TG resistance, TGr). Concentrations in the definitive mutagenicity assay were 0.5 to 13 µg/mL and 6 to 25 µg/mL in absence of S9 and presence of S9, respectively. DMSO served

	as the vehicle. Cultures treated at test article concentrations of 0.5, 5, 8 and 10 µg/mL in absence of S9 and 6, 9, 15, 20 and 25 µg/mL in presence of S9, were chosen for mutant selection based on cytotoxicity at higher concentrations.
Study validity :	Yes. The positive (ethyl methane sulfonate and benzo(a)pyrene) and negative (DMSO) controls performed as expected.

Study type: In Vitro Mammalian Cell Gene Mutation Mouse Lymphoma Assay
Study title / study number: In Vitro Mammalian Cell Gene Mutation Test (L5178Y/TK+/- Mouse Lymphoma Assay) With AB-106/Study nbs-24-229
Key drug-related adverse findings:

- No visible precipitate was observed at the beginning or at the end of treatment.
- Taletrectinib (lot CPo124073-04-05C-03) did not increase mutant frequency under any treatment condition.
- Taletrectinib was considered negative for the ability to induce forward mutations in mouse lymphoma cells in the presence and absence of metabolic activation.

GLP compliance: Yes

Test system :	Evaluated the ability of taletrectinib to induce forward mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in the presence and absence of S9. The taletrectinib concentrations chosen for the definitive mutagenicity assay were 1 to 7 µg/mL (4-hour treatment without S9), 5 to 11 µg/mL (4-hour treatment with S9), and 0.3 to 2.6 µg/mL (24-hour treatment without S9). DMSO served as the vehicle.
Study validity :	Yes. The positive (ethyl methane sulfonate and benzo(a)pyrene) and negative (DMSO) controls performed as expected.

Study type: In vivo PIG-A mutant in male SD rats
Study title / study number: Evaluation of PIG-A mutant frequency in male Sprague Dawley rats administered AB-106/Study nbs-24-230
Key drug-related adverse findings:

- No taletrectinib-related clinical signs or mortalities occurred
- Taletrectinib (lot CPo124073-04-05C-03) did not cause mutant RET or RBCs in treated rats.
- Taletrectinib was considered negative for mutagenicity under the conditions of this study.

GLP compliance: Yes

Test system :	Male rats were administered oral taletrectinib (25, 50, and 100 mg/kg/day) or vehicle for 28 days and blood samples collected on Day 29 to assess for Pig-a gene mutations in bone marrow erythrocytes, as measured in circulating immature red blood cells (reticulocytes; RET) in collected peripheral red blood cell (RBC) samples. Positive control animals were dosed with 20 mg/kg/day N-ethyl-N-nitrosourea (ENU) on Days 1-3.
Study validity :	Yes. The positive and negative controls performed as expected.

In consultation with the Genotoxicity Subcommittee, FDA concludes that taletrectinib is not genotoxic. The initial positive results in the bacterial reverse mutation (Ames) assay and the in vitro chromosome aberration assay with lot RS102 (99.5% purity) were likely due to a potential genotoxic impurity, (b) (4) rather than taletrectinib itself. This is not uncommon in early drug development and lot RS102 had high levels (b) (4) Levels of this impurity were reduced in subsequent lots (CPo 124073-01-04-01-26-01 and CP0124073-04-05C-03) tested in the genotoxicity studies, which were negative in multiple assays. These assays included

additional Ames testes conducted by different labs, 2 mammalian cell gene mutation assays (HPRT and mouse lymphoma) and in vivo Pig-A mutation assay in rats. Assessment by FDA computational Toxicology Consultation Service confirmed that taletrectinib was predicted to be non-mutagenic using (Q)SAR methodologies. In addition, taletrectinib did not induce micronuclei in vivo in rat liver or bone marrow when administered orally up to 300 mg/kg. Overall, the totality of the data suggests that taletrectinib is negative for mutagenicity and chromosomal damage.

5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies are not planned as taletrectinib is intended to treat patients with advanced cancer.

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not warranted for the current indication of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

In the rat fertility/early development reproductive toxicity study, the no-observed-adverse-effect level (NOAEL) relative to reproduction in males was 25 mg/kg/day, the NOAEL relative to reproduction in female rats was 100 mg/kg/day. In the rat embryo-fetal development study, the NOAEL for pregnant rats was 73.5 mg/kg/day, the NOAEL for embryo-fetal developmental toxicity in pregnant rats was 22.1 mg/kg/day. In the rabbit embryo-fetal development study, due to mortality/moribundity and abortions in pregnant rabbits at ≥15 mg/kg/day, the NOAEL for parental pregnant rabbits was <15 mg/kg/day. The NOAEL for embryo-fetal development in pregnant rabbits was 90 mg/kg/day.

Toxicity Study on Fertility and Early Embryonic Development Reproductive after Repeated Oral Gavage Administration of Taletrectinib in Sprague Dawley Rats (Seg I)

Report Number: 02049-20003

eCTD location: 4.2.3.5.1

Study type: fertility and early embryonic development

Key Drug-related Adverse Findings

- Reduced body weights were noted in males

GLP compliance: Yes

Methods

Dose and frequency of dosing:	M: 0, 4, 25, 60 mg/kg/day for 83 days[a] F: 0, 4, 25, 100 mg/kg/day for 21-34 days[b]
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (b) (4)
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	25 male and female per dose level
Age:	M: 8-9 weeks old F: 10-11 weeks old
Satellite groups:	N/A

[a] Dosing began 10 weeks prior to mating (Day 1) until the end of the mating period (Day 83).
[b] Dosing began 2 weeks prior to mating (Day 57) until GD 6.

Daily Dose (mg/kg/day)		**0 (Control)**	**4**	**25**	**60**
Males					
Number of Males		25	25	25	25
Number of TK Animals + Spare		8 + 1	8 + 1	8 + 1	8 + 1
Toxicokinetics					
AUC_{0-t} (ng•h/mL)	Day 1	BLQ	78.848	3019.603	6489.630
	Day 83	BLQ	239.099	3758.667	9599.867
C_{max} (ng/mL)	Day 1	BLQ	14.816	317.743	512.501
	Day 83	BLQ	24.814	289.328	584.198

Daily Dose (mg/kg/day)	**0 (Control)**	**4**	**25**	**100**
Females				
Number of Females	25	25	25	25
Number of TK Animals + Spare	8 + 1	8 + 1	8 + 1	8 + 1

Daily Dose (mg/kg/day)		0 (Control)	4	25	100
Females					
Toxicokinetics					
AUC_{0-t} (ng•h/mL)	Day 1 (GD -14)	BLQ	143.468	4506.170	10314.446
	Day 21-34 (GD 6)	BLQ	107.089	2745.008	12784.837
C_{max} (ng/mL)	Day 1 (GD -14)	BLQ	14.806	343.155	659.189
	Day 21-34 (GD 6)	BLQ	16.746	247.450	823.517

Effects on Embryo-Fetal Development Reproductive Study with Taletrectinib via Oral Administration in Sprague Dawley Rats (Seg II)

Report Number: 02049-20004

eCTD location: 4.2.3.5.2

Study type: embryo-fetal development

Key Drug-related Adverse Findings

- Taletrectinib-related fetal effects were limited to fetuses of females administered 73.5 mg/kg/day (high dose) of taletrectinib and manifested as abnormal ossification in the pelvic bone, which was significantly higher than that of controls, and considered adverse

GLP compliance: Yes

Methods

Dose and frequency of dosing:	F: 0, 7.35, 22.1, 73.5 mg/kg/day for 12 days (GD 6-17)
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (b) (4)
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	25 female per dose level
Age:	11-13 weeks old
Satellite groups:	N/A

Daily Dose (mg/kg/day)	0 (Control)	7.35	22.1	73.5
Dams/Dose				
Number of Females + Spare	20 + 5	20 + 5	20 + 5	20 + 5

Daily Dose (mg/kg/day)		**0 (Control)**	**7.35**	**22.1**	**73.5**
Dams/Dose					
Number of TK Animals + Spare		5 + 3	5 + 3	5 + 3	5 + 3
Toxicokinetics					
AUC_{0-t} (ng•h/mL)	First (GD 6)	BLQ	230.377	2848.627	7241.032
	Last (GD 17)	BLQ	568.310	3906.008	12339.190
C_{max} (ng/mL)	First (GD 6)	BLQ	27.168	243.338	546.312
	Last (GD 17)	BLQ	96.290	325.596	982.200
Number Pregnant		24/25	21/25	22/25	24/25
Number Died or Sacrificed Moribund		0	0	0	0

Embryo fetal Development Toxicity and Toxicokinetics Study of Taletrectinib by Oral Gavage in New Zealand Rabbits

Report Number: T2102034

eCTD location: 4.2.3.5.2

Study type: embryo-fetal development

Key Drug-related Adverse Findings:

- Death/moribundity and abortions in pregnant rabbits were identified when pregnant rabbits were administered 15, 30, or 90 mg/kg/day taletrectinib
- Microscopic changes were noted mainly in the liver, kidneys, spleen, and lung
- Decreased food consumption (and water consumption) during the dosing period was observed in pregnant rabbits administered 90 mg/kg/day, which recovered following drug withdrawal

GLP compliance: Yes

Methods

Dose and frequency of dosing:	F: 0, 15, 30, 90 mg/kg/day for 14 days (GD 6 to 19)
Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (b) (4)
Species/Strain:	Rabbit/ New Zealand
Number/Sex/Group:	24-34 female per dose level
Age:	~5 months

Satellite groups:	N/A

Daily Dose (mg/kg/day)		0 (Control)	15	30	90
Dams/Dose					
Number of Females		24	24	32	34
Number of TK Females (pregnant)		6 (3)	7 (3)	6 (4)	6 (3)
Toxicokinetics		2	3	4	5
AUC_{last} (ng•h/mL)	First (GD 6)	<LLOQ	214.80	507.50	2333.00
	Last (GD 19)	<LLOQ	374.67	915.75	4649.33
C_{max} (ng/mL)	First (GD 6)	<LLOQ	31.53	59.25	248.43
	Last (GD 19)	<LLOQ	66.37	163.98	445.67

Safety Margins

Table 9. Applicant - Comparison of Pharmacokinetic Parameters for Taletrectinib Across Nonclinical Species at the NOAEL and HNSTD (or STD_{10}) With Human Participants at 600 mg (Once Daily)

Species	Rat		Rat (Pregnant)	Rabbit (Pregnant)	Human
Study Duration	**Fertility**		**EFD**	**EFD**	**-**
	Male	**Female**	**Female**	**Female**	**-**
HNSTD (mg/kg/day)	-	-	-	-	600 mg
NOAEL (mg/kg/day)	25	100	73.5[e]	<15	-
C_{max} (ng/mL)	289.328[b]	823.517[b]	982.200[c]	66.37[d]	668
Margin of Exposure[a]	0.4	1.2	1.5	0.1	-
$AUC_{0\text{-}24h}$ (ng·h/mL)	3758.667[b]	12784.837[b]	12339.190[c]	374.67[d]	13100 (AUC_{tau})

Margin of Exposure[a]	0.3	1.0	0.9	0.03	-

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum concentration; EFD, embryo-fetal development; HNSTD, highest non-severely toxic dose; NOAEL, no observed adverse effect level; STD_{10}, severely toxic dose in 10% of the animals
Source: Module 2.6.6 and Report Nos. 02049-20003 (Rat fertility), 02049-20004 (Rat EFD), T2102034 (Rabbit EFD). Pharmacokinetic data represent repeat-dose exposure at the end of the dosing period. The pharmacokinetic data for human subjects are from Clinical Trial DS-6051-A-J102 (Section 9.2.1.2 in clinical study report) based on exposure at 600 mg QD.

[a] The margin of exposure was determined as the ratio of exposure (AUC or C_{max} of Taletrectinib) in animals to the exposure in humans.
[b] The last dosing day was at GD6 for female rats and Day 83 for male rats.
[c] The last dosing day was at GD17 for female rats.
[d] The last dosing day was at GD19 for female rabbits and the data $AUC_{0\text{-}24h}$ was presented.
[e] The dose levels used by salt form was 100 mg/kg, corresponding to 73.5 mg/kg in free form of taletrectinib, see Report No.02049-20004 (Section 7.1.2).

Table 10. Applicant - Comparison of Pharmacokinetic Parameters for Taletrectinib Across Nonclinical Species at the Highest Dose Tested and Human Pharmacokinetic Values at 600 mg (Once Daily)

Species	**Rat**		**Rat (Pregnant)**	**Rabbit (Pregnant)**	**Human**
Study Duration	**Fertility**		**EFD**	**EFD**	**-**
	Male	**Female**	**Female**	**Female**	**-**
High dose (mg/kg/day)	60	100	73.5[e]	90	600 mg
C_{max} (ng/mL)	584.198[b]	823.517[b]	982.200[c]	445.67[d]	668
Margin of Exposure[a]	0.9	1.2	1.5	0.7	-
$AUC_{0\text{-}24h}$ (ng·h/mL)	9599.867[b]	12784.837[b]	12339.190[c]	4649.33[d]	13100 (AUC_{tau})
Margin of Exposure[a]	0.7	1.0	0.9	0.4	-

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum concentration; EFD, embryo-fetal development.
Source: Module 2.6.6 and Report Nos. 02049-20003 (Rat fertility), 02049-20004 (Rat EFD), T2102034 (Rabbit EFD). Pharmacokinetic data represent repeat-dose exposure at the end of the dosing period. The pharmacokinetic data for human subjects are from Clinical Trial DS-6051-A-J102 (Section 9.2.1.2 in clinical study report) based on exposure at 600 mg QD.

[a] The margin of exposure was determined as the ratio of exposure (AUC or C_{max} of Taletrectinib) in animals to the exposure in humans.
[b] The last dosing day was at GD6 for female rats and Day 83 for male rats.
[c] The last dosing day was at GD17 for female rats.
[d] The last dosing day was at GD19 for female rabbits and the data $AUC_{0\text{-}24h}$ was presented.
[e] The dose levels used by salt form was 100 mg/kg, corresponding to 73.5 mg/kg in free form of taletrectinib, see Report No.02049-20004 (Section 7.1.2).

The FDA's Assessment:

FDA generally agrees with the Applicant's data summaries. In the rat embryo-fetal development (EFD) study report (Study #02049-20004) and the Applicant's Position above, the Applicant's refers to taletrectinib doses of 7.35, 22.1, 73.5 mg/kg/day, which are the free form concentrations of taletrectinib corresponding to 10, 30, and 100 mg/kg/day of the salt form, taletrectinib adipate, respectively. In contrast, all other toxicology study reports, including the rat fertility and the rabbit embryofetal development studies, report doses exclusively in the salt form, omitting the free form doses. For consistency, FDA discusses data using the salt form concentrations. Below are additional pertinent findings not discussed by the Applicant.

Study title / number: Toxicity Study on Fertility and Early Embryonic Development Reproductive after Repeated Oral Gavage Administration of AB-106 in Sprague Dawley Rats (Seg I)/ 02049-20003

Key Study Findings

- Sperm morphological abnormalities occurred in males in all dose groups: 3.4% at 4 mg/kg, 2.5% at 25 mg/kg, and 4.0% at 60 mg/kg, which were 2.31, 1.71, and 2.72 times higher than those in the vehicle control group; however, these did not influence mating performance and fertility.

Observations and Results

Parameters	Major findings
Mortality	There were no mortalities
Clinical Signs	Unremarkable
Body Weights and Feed Consumption	• Body weight decreases in males in low and the high dose group by 4.8 and 8.5% respectively compared to vehicle control and in pregnant females in the high-dose group by 3.2% on GD 12 compared with the vehicle control group in the same period • Pregnant females in all dose groups showed significantly increased food consumption.

<table>
<tr><td>Necropsy Findings: Gross/Histopathology</td><td>One female in the middle dose group showed mild infiltration of inflammatory cell in the left cornea and minimal degeneration of the left lens.</td></tr>
<tr><td>Organ weights</td><td>No taletrectinib -related effects. Statistically significant increases noted in testis and epididymis organ weights relative to body weight were most likely due to the reduced body weight before necropsy in males.</td></tr>
<tr><td>Mating Rate and Pregnancy Rate and Fertility Rate</td><td>No taletrectinib-related effects on mating rate, pregnancy rate, or fertility rate.</td></tr>
<tr><td>Sperm analysis</td><td>Sperm morphological abnormalities were found in all treatment groups: 3.4% at 4 mg/kg, 2.5% at 25 mg/kg, and 4.0% at 60 mg/kg, which were 2.31, 1.71, and 2.72 times higher than vehicle control group.
No abnormal changes in sperm motility and number were found in any dose group.</td></tr>
<tr><td>Estrous cycle analysis</td><td>No adverse effects of taletrectinib on the estrus cycle.</td></tr>
<tr><td>Necropsy Findings: Cesarean Section Data</td><td>Cesarean Section Data
<table>
<tr><th>mg/kg/day</th><th>0</th><th>4</th><th>25</th><th>100</th></tr>
<tr><td>Pregnancy index (%)</td><td>96.0</td><td>84.0</td><td>88.0</td><td>96.0</td></tr>
<tr><td>Number pregnant</td><td>24</td><td>21</td><td>22</td><td>24</td></tr>
<tr><td>Number not pregnant</td><td>1</td><td>4</td><td>3</td><td>1</td></tr>
<tr><td>Number of live fetuses</td><td>12.54</td><td>13.00</td><td>11.73</td><td>11.92</td></tr>
<tr><td>Number of dead embryos</td><td>0.00</td><td>0.00</td><td>0.00</td><td>0.00</td></tr>
<tr><td>Gravid uterine weight (g)</td><td>3.12</td><td>3.30</td><td>3.25</td><td>3.26</td></tr>
<tr><td>Mean corpora lutea</td><td>14.08</td><td>14.52</td><td>13.64</td><td>13.83</td></tr>
<tr><td>Mean implantation sites</td><td>13.67</td><td>13.76</td><td>12.86</td><td>12.96</td></tr>
<tr><td>Mean Total early resorptions</td><td>1.13</td><td>0.76</td><td>1.14</td><td>1.04</td></tr>
</table>
The Applicant did not provided data on pre- and post-implantation loss, late resorptions, and mean litter size.</td></tr>
</table>

The summary of TK parameters of taletrectinib

Dosing time	Dose	Sex	Tmax (h)	Cmax (ng/ml)	AUC(0-t) h*ng/mL
First Dosing[a]	4	M	4.250	14.816	78.848
	25	M	3.750	317.743	3019.603
	60	M	3.500	512.501	6489.630
	4	F	6.000	14.806	143.468
	25	F	4.750	343.155	4506.170
	100	F	5.714	659.189	10314.446
Last Dosing[a]	4	M	4.250	24.814	239.099
	25	M	4.000	289.328	3758.667
	60	M	6.750	584.198	9599.867
	4	F	4.250	16.746	107.089
	25	F	3.250	247.450	2745.008
	100	F	1.571	823.517	12784.837

[a] Note: Date of first dosing: (Male rats) Day 1; (Female rats) Day 57; Date of last dosing: (Male rats) Day 83; (Female rats) GD6.

Study title / number: Effects on Embryo-Fetal Development Reproductive Study with AB-106 via Oral Administration in Sprague Dawley Rats (SegII) / 02049-20004

Key Study Findings:

- Skeletal malformations including stubby cervical vertebra and short rib rupture, deficiency, displacement, and fusion were detected at doses ≥10 mg/kg/day. No dose response relationship was observed.

Observations and Results

Parameters	Major findings
Mortality	There were no maternal deaths
Clinical Signs	Unremarkable
Body Weights and Feed Consumption	Unremarkable
Necropsy Findings: Maternal, Gross	Unremarkable

Necropsy Findings: Cesarean Section Data	Decreased mean fetal weight in 100 mg/kg/day group likely due to larger litter size

Cesarean Section Data

mg/kg/day	0	10	30	100
Pregnancy index (%)	N/D	N/D	N/D	N/D
Number pregnant	20	20	20	20
Number not pregnant	-	-	-	-
Mean number of live fetuses per dam	13	14	14.4	15.3
Dead fetuses (early stage)	0	0	0	0
Dead fetuses (late stage)	0	0	0	0
Gravid uterine weight (g)	76.95	81.33	83.58	83.91
Mean corpora lutea	15.9	16.4	16.9	17.6
Mean implantation sites	14.4	15	16	16.2
Mean % pre-implantation loss	0	0	0	0
Mean % post-implantation loss	1.4	1	0.9	1
Total litter size	260	280	287	305
Male/female ratio	1.02 (131/129)	0.89 (132/148)	0.94 (139/148)	1.09 (159/146)
Mean fetal weight (g)	3.82	3.78	3.75	3.44*

* P<0.05, compared with the vehicle control group

N/D not determined

Skeletal Malformations

Dose (mg/kg/day)	0	10	30	100
# of Fetuses/Litters Examined	134/20	145/20	147/19	157/20
Total # of Fetuses with Malformations	7/134 (5%)	32/145 (22%)	3/147 (2%)	20/157 (13%)
Occipital bone				
Insufficient junction between ossified sides	2/134		1/147	4/157
Two ossified sides not connected				5/157
Thoracic Vertebra				
Split/rupture	1/134	1/145	2/147	2/157
Ribs				
Short/Missing	3/134	31/145		9/157
Displacement	1/134			

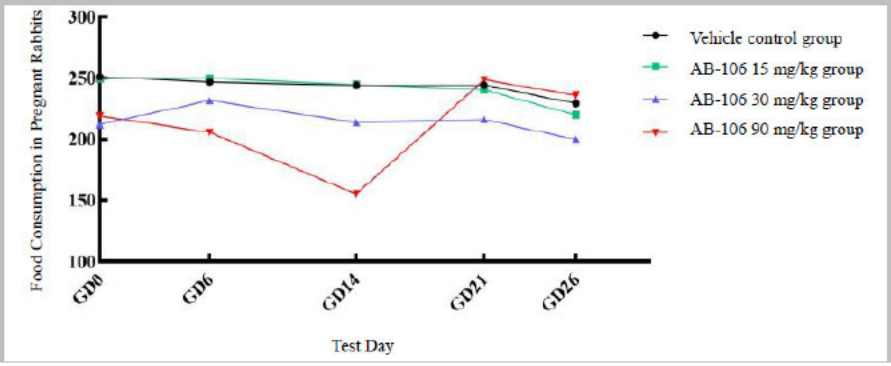
Skeletal malformations incidences observed in taletrectinib-treated rats were outside of the range of historical controls.

Study title / number: Embryo-fetal Development Toxicity and Toxicokinetics Study of AB-106 by Oral Gavage in New Zealand Rabbits/ T2102034

Key Study Findings:

- Dose-dependent increase in abortions rate and total pregnancy loss rate
- External, visceral, and skeletal malformations were noted in taletrectinib treated animals at the mid and high dose
- One fetus (Parental Animal No.: 3F034) in taletrectinib at 30 mg/kg group had undeveloped right ear and no development of eyes, nose, and mouth

Parameters	Major findings
Mortality	A total of 21 rabbits in the main study group and 3 rabbits in the TK groups were found dead /moribund: • 2 pregnant rabbits in the vehicle control group • 1 pregnant rabbit in the taletrectinib low dose (15 mg/kg) group • 2 pregnant rabbits in the taletrectinib mid dose group (30 mg/kg) • 5 non-pregnant rabbits and 11 pregnant rabbits in the taletrectinib high dose group (90 mg/kg) Taletrectinib-related mortality/moribundity (mainly due to liver and kidney toxicity): • 1 pregnant rabbit in the low dose group on GD20 after body weight loss on GD19 and abortion on GD20; found moribund • 1 pregnant rabbit in the mid dose group on GD21 after body weight loss on GD19 and abortion on GD21; found moribund • 11 pregnant rabbits in the high dose group GD11-18 all with body weight loss. The applicant attributed death of two animals to lung dysfunction not related to taletrectinib; however, we cannot rule out that these death were not drug-related, considering that this occurred at the high dose, taletrectinib distributes to the lung and that lung was identified as a target organ in the general toxicology studies.

Parameters	Major findings
Clinical Signs	*15 mg/kg:* • 1 pregnant rabbit aborted (moribund afterwards) on GD20 • 1 pregnant rabbit developed a transient cough on GD24 *30 mg/kg:* • 4 pregnant rabbits aborted from GD21 to GD25 (one of which was moribund) • Moderate alopecia (right hindlimb or upper nasal cavity and submandibular) was observed in 2 pregnant rabbits from GD10 to GD28 • 1 pregnant rabbit had soft stools on GD17 and increased ocular discharge from GD17 to GD28 • 1 pregnant rabbit occasionally had decreased food and drinking water from GD9 • 1 pregnant rabbit had swelling of the left forelimb from GD23 to GD28 *90 mg/kg:* • 1 pregnant rabbit had moderate alopecia (external ear margin, cheek, eyelid) from GD7 to GD13 • 1 pregnant rabbit showed decreased food and drinking from GD15 to GD19, recovered after drug withdrawal • 1 pregnant rabbit developed left forelimb swelling from GD24 to GD27
Body Weights and Feed Consumption	At 90 mg/kg, food consumption of pregnant rabbits was significantly lower than vehicle control group ($P \leq 0.05$) on GD6 and GD14; it returned to the control level after GD21. **Food Consumption in Pregnant Rabbits** 

Parameters	Major findings

Necropsy Findings: Maternal, Gross, Histopathology

Gross pathology was unremarkable.

Histopathology findings in Dead/Moribund animals

		Dose mg/kg/day	0	15	30	90
		Number of animals examined	2	1	2	16
Kidneys	Tubular dilation	Min		1		1
		Mild				1
		Mod				
		Severe				1
	Vacuolar degeneration/necrosis, tubular epithelium	Min		1		3
		Mild				1
	Protein casts	Min		1		
		Mild				
	Mineralization, tubular	Min				1
	Necrosis with calcification, tubular	Mod				1
		Severe				
	Increased cellular debris in lumen	Min				
		Mild				1
Liver	Vacuolar degeneration of hepatocytes	Min				
		Mild		1		
		Mod				2
		Severe				7
	Necrosis	Min				
		Mild				3
		Mod				1
	Inflammatory cell infiltration, portal area	Min				
		Mild		1		

Necropsy Findings: Cesarean Section Data

Cesarean Section Data

mg/kg/day	0	15	30	90
Pregnancy index (%)	67%	79%	50%	56%

Parameters	Major findings			
Number of successfully mated animals	24	24	32	34
Number pregnant GD6	16	19	16	19
Number necropsied GD28	22	23	27	11
Number pregnant on GD28	16	19	15	10
Number not pregnant on GD28	6	4	12	1
Dead/moribund pregnant animals	2	1	2	11
Early deliveries (# of animals)	0	0	0	2
Abortions (# of animals)	0	1	4	5
Mean number of live fetuses per litter	8	7	7	8
Number of still birth (# of rabbits)	0	0	1	0
Total dead fetuses	0	8	9	2
# of rabbits with dead fetuses	0	2	1	2
% of rabbits with dead fetuses	0	5	7	10
Mean litter size	8	7	8	8
Gravid uterine weight (g)	497.63	450.30	413.35	484.78
Mean corpora lutea	10	9	9	12
Mean implantation sites	9	8	8	9
Mean % post-implantation loss	2.5	5.6	24.6	6.7
Total number of resorptions per dose group	0	1	2	1
# pregnant rabbits with resorptions	2	3	5	3
% of animals with resorptions	13	16	33	30
Total loss rate (%)	13	21	29	23
Mean male and female fetal weight (g)	41	42	42	42

Fetal Malformations

Dose (mg/kg/day)	0	30	90
# of Litters Examined	16	13	10
External malformation rate (% of Litters)	0	8	0
No ear, eye, nose, or mouth development (# of litters)	0	1	0
Total viscera (fixed/fresh) malformation rate (%)	0	8	10
# of Litters with visceral malformation	0	1	1

Parameters	Major findings		
Ventricular malformation rate (%)	0	4	0
Thoracic vascular malformation rate (%)	0	0	2
Skeletal malformation Rate (%)	6	23	0
# of Litters with skeletal malformation	1	3	0
Thoracic vertebra separation rate (%)	1	2	0
Missing tympanic ring of skull	0	4	0
Skull ossicle missing	0	4	0
Missing skull, anterior skull	0	4	0
Skull lacrimal bone absent	0	4	0
Skull and nasal bone missing	0	4	0
Skull maxillary missing	0	4	0
Absence of skull vomer	0	4	0
Missing skull and palate	0	4	0
Incidence of visceral and skeletal malformations in rabbits treated with taletrectinib were outside of the range of historical controls.			

Toxicokinetic Parameters in Rats

Dose mg/kg/day	15	30	90
Gestational Day 6			
T_{max} (hr)	1.00 ± 0.87	3.25 ± 1.50	3.17 ± 4.19
C_{max} (ng/mL)	31.53 ± 19.56	59.25 ± 32.10	248.43 ± 197.53
$AUC_{(0-24)}$ (ng*hr/mL)	214.80 ± 154.69	507.50 ± 268.02	2333.00 ± 1745.58
Gestational Day 19			
T_{max} (hr)	1.00 ± 0.00	0.88 ± 0.25	1.67 ± 0.58
C_{max} (ng/mL)	66.37 ± 34.40	163.98 ± 99.33	445.67 ± 59.23
$AUC_{(0-24)}$ (ng*hr/mL)	374.67 ± 169.62	915.75 ± 563.46	4649.33 ± 786.55

5.5.5. Other Toxicology Studies

The Applicant's Position:

An in vitro assessment of taletrectinib for phototoxicity conducted in the absence and presence of ultraviolet irradiation demonstrated the potential for phototoxic effects based on standard phototoxicity indexes.

Study Title: BALB/C 3T3 CELL PHOTOTOXICITY ASSAY (NEUTRAL RED UPTAKE)						
eCTD Location: 4.2.3.7.7						
GLP compliance: Yes						
Study Number	**Type of Study**	**Test Article**	**Species/ Strain**	**Duration of Dosing**	**Doses (µg/mL)**	**Key Findings**
95860	In vitro phototoxicity	Taletrectinib	BALB/c 3T3 Cells	1 hour	+UVA; 0.00671, 0.0134, 0.0269, 0.0537, 0.107, 0.215, 0.430 and 0.859 µg/mL -UVA; 0.859, 1.72, 3.44, 6.88, 13.8, 27.5, 55.0 and 110 µg/mL	The PIF was 26.6 and the MPF was 0.278. Since MPE > 0.15 predicts phototoxicity, on the basis of the results obtained, it is concluded that taletrectinib is potentially phototoxic under these experimental conditions.

Abbreviations: MPE, mean photo effect; NA, not applicable; PIF, photo irritation factor; UVA, ultraviolet A.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the phototoxicity assay for taletrectinib. A concentration-dependent decrease in neutral red uptake was reported in the presence and absence of UVA with IC_{50} values of 0.186 and 4.95 µg/ml, respectively. The calculated photo-irritation factor (PIF) was 26.6 and the mean photo effect value (MPE) was 0.278. In accordance with OECD guidelines, taletrectinib is potentially phototoxic since the PIF score was > 5 and the MPE value was > 0.15.

X X

Primary Reviewer Primary Reviewer

X

Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking regular approval of taletrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC). The proposed recommended dosage is taletrectinib 600 mg administered orally once daily (QD) on an empty stomach (no food intake at least 2 hours before and 2 hours after taking taletrectinib).

The clinical pharmacology review has addressed the following key review issues:

Dosage Acceptability: Although the proposed recommended dosage of taletrectinib 600 mg QD is considered reasonable, it should be further optimized with regard to food intake supported by the following findings: (a) this dosage was associated with high rates of Grade ≥3 serious adverse events, (b) a standard meal increased taletrectinib exposure and improved its gastrointestinal tolerability, and (c) a lower dosage of 400 mg QD showed comparable overall response rate in patients who are naïve to prior ROS1 TKIs and a lower incidence of Grade ≥3 AEs, based on analysis of data in the dosage randomization cohort (Cohort 5) of Study G208. In addition, the flat exposure-response (E-R) relationship for efficacy and the positive E-R trend for safety (Grade ≥3 TEAEs, AEs leading to dose modification, and Grade ≥3 AST/ALT elevation) further support that a lower dosage may preserve efficacy while reducing toxicities. A postmarketing requirement (PMR) study will be issued to evaluate the safety and activity of taletrectinib 400 mg QD taken with standard meals in the targeted patient population.

Specific populations: Population PK analyses found no clinically meaningful effects on the PK of taletrectinib for the following covariates age (18 to 80 years), sex, race (22% White, 5% Black), mild and moderate renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (per NCI-ODWG). FDA's independent analysis identified that Asian patients (66%) with a relatively lower weight distribution, are associated with a 30% increase in exposure (AUC) compared to White patients, which likely attributed to an observed higher rate of Grade ≥3 ALT/AST increase in Asian patients. However, specific instructions for this subgroup are not considered necessary due to the similarity in AE profiles between Asian and White patients and proportion of dose reductions related to hepatotoxicity (the main clinically relevant safety concern), especially with frequent AST/ALT monitoring as proposed in the labeling (i.e., every 2 weeks during the first 2 months of treatment, and then monthly thereafter as clinically indicated with more frequent testing in patients who develop transaminase elevations).

Hepatic Impairment: Patients with hepatic impairment may have serious risk of increased exposure to taletrectinib as taletrectinib is eliminated primarily through hepatic metabolism. The pharmacokinetics (PK) and safety of taletrectinib in patients with moderate or severe hepatic impairment have not been evaluated. A PMR will be issued for a study to evaluate the potential

serious risk of increased drug exposure and determine an appropriate dosage of taletrectinib in patients with moderate to severe hepatic impairment.

Drug-drug interactions (DDIs):

Taletrectinib is a substrate of CYP3A. Clinical DDI studies were conducted with itraconazole (P-gp and strong CYP3A inhibitor), rifampin (P-gp and strong CYP3A inducer), and PBPK modeling was used to predict the effect of moderate CYP3A4 inhibitors and inducers.The labeling recommends avoid of concomitant use of strong and moderate CYP3A inhibitors and inducers based on the observed and predicted large magnitude of changes in taletrectinib exposures and only one available dosage strength of 200 mg.

Taletrectinib displays pH-dependent aqueous solubility. Taletrectinib Cmax decreased by 65% and AUC by 40% following concomitant administration of daily omeprazole (a proton pump inhibitor [PPI]) which may reduce the effectiveness of taletrectinib. The labeling recommends avoidance of concomitant use with PPIs and H2-receptor antagonists. A PMC will be issued for a study to assess if staggered dosing approach for H2-receptor antagonists can mitigate the decrease in drug exposure to allow for taking H2-receptor antagonists while on taletrectinib treatment.

Based on the results of in vitro DDI studies, the following additional PMR/PMC studies will be included in the approval letter: (1) to assess the effect of taletrectinib as an inhibitor on the PK of sensitive substrates of CYP3A, CYP2D6, BCRP, OATP1B1, and OATP1B3, and (2) to assess the effects of taletrectinib as an inducer on the PK of substrates of CYP3A and CYP1A2.

QTc Interval Prolongation: The observed largest mean increase in the QTc interval was 12.8 msec (upper confidence interval of 15.4 msec) at steady state Cmax after administration of 600 mg QD. Taletrectinib prolongs the QTc interval in a concentration-dependent manner. Significant prolongation of the QTc interval may occur when taletrectinib is taken with food, strong and moderate CYP3A4 inhibitors, and/or drugs with a known potential to prolong QTc. The potential risk for QTc interval prolongation and the relevant recommendations for drug interaction and safety monitoring are described in the label.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 219713. The NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized in **Table 11**. Clinical pharmacology PMRs and PMCs are summarized in **Table 12**.

Table 11. Key Clinical Pharmacology Review Issues, Recommendations, and Comments

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal evidence of effectiveness	The primary evidence of effectiveness comes from two Phase 2 single-arm studies, AB-106-G208 and AB-106-C203, conducted in patients with locally advanced or metastatic *ROS1*-positiveNSCLC. The primary endpoint of overall response rate (ORR) was 89% (95% CI: 83, 93) in ROS1 TKI naïve patients and 56% (95% CI: 46, 65) in patients with one prior ROS1 TKI. The intracranial ORR was 77% (95% CI: 50, 93) in ROS1 TKI naïve patients and 66% (95% CI: 47, 81) in patients with one prior ROS1 TKI. See **Section 8.1.2** for details. Note that a flat E-R relationship for efficacy was observed across the dose range of 400 mg to 600 mg QD with a small portion of data from 400 mg dose level. Positive E-R relationships were identified for various safety endpoints, including Grade≥3 TEAEs, AE leading to dose modification, and Grade≥3 AST/ALT elevation.
General dosing instructions	The recommended dosage is taletrectinib 600 mg QD administered on an empty stomach (i.e., no food intake at least 2 hours before and 2 hours after taking the drug). Given that the proposed recommended dosage could be optimized with regard to food intake, a PMR study is to be issued for further dosage optimization.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Renal impairment: Per population PK analysis, no dosage modification is recommended in patients with mild and moderate renal impairment (eGFR 30 to < 90 mL/min). The effect of severe renal impairment on taletrectinib exposure is not expected to be clinically meaningful due to the minimal involvement of renal elimination (approximately 11% of total dose with < 5% as the parent drug) in taletrectinib clearance. • Hepatic impairment: Per population PK analysis, no dosage modification is recommended in patients with mild hepatic impairment (per NCI-ODWG). The PK and safety of taletrectinib in patients with moderate or severe hepatic impairment have not been evaluated. A PMR study will be issued for a hepatic impairment study to evaluate the potential serious risk of increased drug exposure and determine an appropriate dosage of taletrectinib in patients with moderate or severe hepatic impairment.

	• Race and ethnicity: The patients who received taletrectinib in the pivotal studies C203 and G208 included Asian (229/273, 84%), White (28/273, 10%) and others (16/273, 6%). Per population PK analysis, a 30% increase in taletrectinib exposure (AUC) was observed in Asian patients compared to White patients, which is associated with a higher incidence of increased liver enzymes and subsequent a higher proportion of dose reduction in Asian patients. No clinically significant differences in PK were observed between White and Black patients. • *ROS1* fusion partner and *ROS1* secondary TKI resistance mutations: data suggest that taletrectinib has clinical activity in ROS1 TKI-naïve and ROS1 TKI-pretreated patients with tumors carrying *ROS1* fusions with various partners. Limited data suggest that taletrectinib has clinical activity in TKI-pretreated patients with tumors carrying the G2032R TKI resistance mutation in *ROS1*.
DDI	CYP3A is the primary CYP450 enzyme involved in taletrectinib metabolism. Taletrectinib Cmax increased by 1.8-fold and AUC by 3.3-fold following concomitant administration of itraconazole (P-gp and strong CYP3A inhibitor) 200 mg daily. Taletrectinib Cmax decreased by 42% and AUC by 86% following concomitant administration of rifampin (P-gp and strong CYP3A inducer) 600 mg daily. The PBPK approach was used to simulate the effects of moderate CYP3A4 inhibitors and inducers on the PK of taletrectinib and predicted that a moderate CYP3A inhibitor increases taletrectinib AUC up to 2.6-fold and Cmax up to 1.5-fold, and concomitant use with a moderate CYP3A inducer is predicted to reduce taletrectinib AUC by 66% and its Cmax by 40%. Taletrectinib displayed pH-dependent aqueous solubility. Taletrectinib Cmax decreased by 65% and AUC by 40% following concomitant administration of omeprazole (a PPI) 40 mg daily. Based on the above clinically meaningful DDI effects and limitation with only one available dose strength of 200 mg, the

	review team agrees with the proposed labeling recommendations to avoid concomitant use with strong and moderate CYP3A inhibitors and inducers, PPIs, and H2 receptor antagonists. The review team recommends using the staggered dosing approach for locally acting antacids. The following PMR and PMC studies will be issued to conduct clinical DDI studies to assess the potential inhibitory effects of taletrectinib on CYP3A, CYP2D6, BCRP, and OATP1B1 (under PMR), the induction effects of taletrectinib on CYP3A and CYP1A2, and the impact of H2-receptor antagonists on the exposure of taletrectinib (both under PMCs).
QTc	Taletrectinib prolongs the QTc interval in a concentration-dependent manner. The observed largest mean increase in the QTc interval was 12.8 msec (upper confidence interval of 15.4 msec) at steady state Cmax after administration of 600 mg QD. At plasma concentrations achieved with administration of 600 mg QD with high-fat food, the predicted increase in the QTc interval is 20.5 (16.3, 24.7) msec. Refer to FDA's QT-IRT analysis (Reference ID: 5545184) for details. Given the potential risk for QTc interval prolongation, FDA recommends 1) avoidance of concomitant use of taletrectinib with other drug(s) with a known potential to prolong the QTc interval, 2) adjustment of the frequency of monitoring as recommended in the labeling if concomitant use cannot be avoided, and 3) withholding taletrectinib if the QTc interval is >480 msec or the change from baseline is >60 msec. It is also described in the labeling that significant prolongation of the QTc interval may occur as a consequence of exposure increase following concomitant use with strong and moderate CYP3A inhibitors.
Labeling	FDA labeling revisions per regulations and FDA guidance were provided. Overall, the proposed labeling language in the Clinical Pharmacology pertinent sections are generally acceptable upon the Applicant's agreement to the FDA revisions.

Table 12. Post-Marketing Requirements and Commitments

PMR/PMC	Rationale	PMR/PMC language
PMR #1 Dosage optimization	1) High rates of Grade 3 or greater AEs at the proposed dosage of 600 mg QD. 2) Improved safety profile with 400 mg QD as suggested by limited clinical data. 3) Food intake has the potential to improve GI tolerability.	Conduct a multicenter trial to further characterize known serious risks with taletrectinib including severe hepatotoxicity, interstitial lung disease, other serious adverse reactions, and the risk of gastrointestinal toxicity, by evaluating the safety, activity, and pharmacokinetics of taletrectinib 400 mg daily taken with standard meals, in patients with advanced or metastatic *ROS1* positive non-small cell lung cancer who are naïve to prior ROS1 tyrosine kinase inhibitors (TKIs) and in patients who have received one prior ROS1 TKI. Include an adequate number of patients from each subgroup (i.e., ROS1 TKI-naïve and previously treated with ROS1 TKI).
PMR #2 Hepatic impairment	The PK and safety of taletrectinib in patients with moderate and severe hepatic impairment have not been evaluated. Given the hepatic elimination pathway of taletrectinib and the positive E-R relationship for safety, a hepatic impairment study is warranted.	Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dosage of taletrectinib in patients with moderate and severe hepatic impairment.
PMR #3 DDI	In vitro studies showed that taletrectinib inhibited CYP3A, CYP2D6, BCRP, OATP1B1, and OATP1B3. The potential inhibitory effects of taletrectinib may increase plasma concentrations of substrate drugs, and thus increase the incidence and severity of serious adverse reactions.	Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A, CYP2D6, BCRP, OATP1B1, and OATP1B3 (b) (4) (b) (4) and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP and transporter substrates.

PMR/PMC	Rationale	PMR/PMC language
PMC #1 DDI	In vitro studies showed that taletrectinib induces CYP3A and CYP1A2. The potential induction effects of taletrectinib may decrease plasma concentrations of substrate drugs, which may reduce the efficacy of the substrate drugs.	Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A and CYP1A2 in healthy subjects and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP substrates.
PMC #2 DDI	Concomitant use of a PPI decreased taletrectinib exposure, which may reduce the effectiveness of taletrectinib. To potentially expand the use of acid-reducing agents (e.g., H2 receptor antagonists) in the targeted patient population, a clinical study will be recommended to assess the magnitude of decreased drug exposure with staggered administration of H2-receptor antagonists.	Conduct a clinical trial to evaluate if staggered administration of an H2-receptor antagonist decreases the exposure of taletrectinib and to inform instructions for taking taletrectinib with H2-receptor antagonists.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Taletrectinib has been investigated in 10 clinical studies and in more than 400 participants to date. This includes 5 Phase 1 healthy volunteer studies to investigate drug-drug interactions, mass balance, and food effect; 2 completed Phase 1 studies in locally advanced or metastatic participants with cancer; and 3 Phase 2 studies in adult participants with ROS1+ NSCLC and in solid tumors with NTRK fusion genes.

In participants with cancer, the geometric mean (CV%) of taletrectinib steady state peak concentration (C_{max}) is 476.3 (36.5%) ng/mL and the area under the time concentration curve (AUC_{tau}) is 9649 (35.8%) ng•h/mL following the recommended 600 mg once daily (QD) dosage. Taletrectinib C_{max} and AUC increase approximately proportional to dose over the range of 50 to 1200 mg QD. Steady state is achieved within 7 days of daily administration of 600 mg. Accumulation ratios after 600 mg QD dosing were approximately 3.3 to 4.5 based on area under the concentration-time curve overdosing interval tau (AUCτ).

Absorption

Peak taletrectinib concentration occurred at approximately 2 to 6 hours following a single oral dose of 600 mg. High-fat, high-calorie meals increase taletrectinib AUC_{inf} and C_{max} by approximately 50% and standard low-fat, low-calorie meals increase taletrectinib AUC_{24} and C_{max} by approximately 24% and 45%, respectively. Plasma taletrectinib C_{max} and AUC_{inf} were decreased by 65% and 40% when co-administered with omeprazole.

Distribution

The estimated apparent volume of distribution (V_{ss}/F) was 9820 L.

Taletrectinib plasma protein binding in vitro was concentration-dependent and decreased with increasing taletrectinib concentrations (from 96.5% at 100 ng/mL to 92.6% at 10,000 ng/mL). The blood-to-plasma ratio was 1.29 to 1.44 in vitro.

Metabolism

Taletrectinib is primarily eliminated by CYP450 and non-CYP450 (i.e., sulfation and acetylation) metabolism. CYP3A and, to a lesser extent, CYP2C8 and CYP2C9 are the CYP450 enzymes involved in taletrectinib metabolism. Hydroxylation via CYP P450 3A4 is the primary route of metabolism, with sulfation, dealkylation, and N-acetylation as notable additional metabolic pathways; sulfate conjugates are the major circulating metabolites.

Elimination

The taletrectinib effective half-life is approximately 66 h for patients with cancer.

The geometric mean (CV%) apparent oral clearance (CL/F) was 63.4 L/h (35.8%) in patients with cancer following 600 mg daily oral dose of IBTROZI.

Excretion

Following a single oral 200 mg dose of radiolabeled taletrectinib, 11.1% (<5% as unchanged) was recovered in urine and 75.1% in feces.

The Applicant's Position:

Overall, the clinical pharmacology profile of taletrectinib is considered supportive of the proposed marketed dose of 600 mg QD in adult patients with ROS1+ NSCLC.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of clinical pharmacology data.

FDA agrees that the proposed taletrectinib dosage of 600 mg QD is approvable for the targeted indication. However, FDA does not agree that the proposed dosage is optimized with regard to food intake. See **Section 6.2.2** for details on the FDA's position and recommendation for further dosage optimization of taletrectinib.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data and the Applicant's Position:

The proposed dosing regimen for taletrectinib is 600 mg QD without food (at least 2 hours before or 2 hours after food intake) until disease progression or unacceptable toxicity.

The 600 mg QD dose was selected as the RP2D for the Phase 2 studies based on:

- The maximum tolerated doses established in 2 early clinical studies.
  - 800 mg QD in Caucasian participants in Study DS6051-A-U101.
  - 600 mg QD in Asian participants in Study DS6051-A-J102.
- Free plasma concentration-time profiles and C_{trough} at steady state that were mostly above the IC_{90} values against both ROS1 and the key ROS1 mutation (i.e., G2032R).
  - Previous work with other ROS1 inhibitors indicated that a high percentage of inhibition may be necessary to achieve optimal antitumor activity for ROS1+ tumors.
  - Doses less than 600 mg were considered potentially insufficient, as it is expected that with a lower dose (e.g., 400 mg), over 30% of participants will achieve a steady-state concentration below the IC_{90} for ROS1 on-target resistant mutations, primarily the ROS1 G2032R mutant.
  - From a pharmacological perspective, participants with brain metastasis would benefit from higher dose to overcome the blood-brain barrier.

The 600 mg QD regimen demonstrated a favorable benefit-risk ratio in 2 pivotal studies. The efficacy and safety results from the pooled studies AB-106-C203 and AB-106-G208 supported the selection of 600 mg QD as an effective and safe dose for treating ROS1+ participants with NSCLC.

From a clinical pharmacology perspective, an E-R analysis evaluated the relationship between taletrectinib exposure and select measures of response. No significant E-R relationship was identified for 2 efficacy endpoints (objective response and tumor size shrinkage) and 3 safety endpoints (serious AEs [SAEs], Grade ≥2 GI AEs, and Grade ≥3 alanine aminotransferase [ALT]/aspartate aminotransferase [AST] AEs).

The 600 mg QD dose provides exposures within the efficacious range, and higher taletrectinib doses are unlikely to offer improved efficacy. Body weight and race were identified as covariates that help explain the variability in taletrectinib pharmacokinetics (PK). The exposure range achieved with the 600 mg QD dosing regimen appears to be appropriate across diverse participant populations. This dosage is suitable for patients with varying body weights, including those with higher body weight who may experience lower drug exposure and therefore require a sufficiently high dose. Additionally, the dosage is appropriate for patients of different racial backgrounds, eliminating the need for dose adjustments based on these factors.

Although a slight E-R trend was observed for treatment-emergent AEs (TEAEs) leading to dose modifications and Grade ≥3 TEAEs, this does not justify recommending a lower dosage. The observed trend is sufficiently shallow, such that a decrease in exposure of 166 ng/mL (corresponding to a reduction from 600 mg QD to 400 mg QD) would not significantly reduce the rate of dose modifications and Grade ≥3 TEAEs. However, a lower dose may risk compromising efficacy for patients with resistant mutations or brain metastases.

The FDA's Assessment:

Taletrectinib QD dosing regimens of 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg, and a BID regimen of 400 mg were explored in the first-in-human (FIH) trial, Study DS6051-A-U101, which established an MTD of 800 mg QD in White patients. A lower MTD of 600 mg QD was determined in Asian patients in Study DS6051-A-J102 evaluating 400 mg, 600 mg, and 800 mg QD.

Although a positive E-R relationship for efficacy was not found, the dosage of 600 mg QD was selected for further investigation, as the Ctrough at steady state following this dosage was predicted to be more likely above the IC90 values against both ROS1 and the key ROS1 mutation (i.e., G2032R), i.e., 94% versus 68% at a lower dosage of 400 mg QD.

Based on the efficacy and safety results obtained from the pivotal trials Studies G208 and C203, FDA agrees that the favorable benefit-risk profile observed in these two studies support the proposed taletrectinib dosage of 600 mg QD in adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.

However, FDA does not agree that the proposed dosage is optimized due to the following reasons:

1) **Potential for similar efficacy and improved safety at a lower dosage**

   The dosage randomization cohort (Cohort 5) in Study G208 evaluated a lower dosage of 400 mg QD (n=25) and 600 mg QD (n=23). Limited data from Cohort 5 suggest 400 mg QD may achieve comparable efficacy as that of 600 mg QD, while improving the safety profile, in the targeted patient population. The ORR and the dosages used in patients with ROS 1 positive NSCLC across different cohorts in Studies C203 and G208 are summarized in **Table 13**.

Table 13. Summary of ORR in Studies C203 and G208

Study #	C203		G208						
Cohort #	**1**	**2**	**1**	**2**	**3**	**5**	**5**	**5**	**5**
Dosage (mg, QD)	**600**	**600**	**600**	**600**	**600**	**400**	**600**	**400**	**600**
Prior lines of ROS1 TKI	0	1	0	1	≥ 2	0	0	1-≥3[#]	1-≥3[#]
Sample size (n)	106	66	54	47	35	10	10	15	13
Median Follow-up (months)	36	30	16	16	12	5	5	5	5
ORR (%)	**91**	**52**	**85**	**62**	**19**	**88**	**90***	**17**	**46***
95% CI	(83, 95)	(39, 64)	(73, 94)	(46, 75)	(7, 37)	(47,100)	(56, 100)	(2, 48)	(17, 77)
CR (%)	5	0	5.6	11	0	0	0	0	0
PR (%)	86	52	80	51	19	88	90	17	45

Source: FDA generated the table based on safety data in AB-106-G208 – Report Body and AB-106-G208 Cohort 5 Analysis Report (Module 5.3.5.2)
[#] The proportion of patients receiving ≥ 2 prior lines of ROS 1 TKIs was 60% in 400 mg dose group and 31% in the 600 mg dose group.
* Unconfirmed PRs are included.

In the dose randomization Cohort 5 of Study G208, the ORR (including unconfirmed PRs) in ROS1 TKI-naïve patients was comparable between 400 mg QD (88%) and 600 mg QD (90%), which are similar to the ORR (85%-91%) obtained in the same patient population in the primary efficacy population for the NDA. The lower ORR observed at 400 mg QD (ORR of 17% versus 46% at 600 mg QD) in pre-treated patients is difficult to interpret, given a higher proportion of heavily pre-treated (≥ 2 prior lines of ROS 1 TKI treatment) patients in the 400 mg dose group (60% versus 31% in the 600 mg group). The ORR in patients with ≥2 prior lines of ROS1 TKI was determined to be 19% in Cohort 3 of Study G208.

The safety profiles of the two dose levels obtained from the dosage randomization cohort are summarized in **Table 14** and **Table 15**.

Table 14. Summary of TEAEs in the Dosage Randomization Cohort (Cohort 5, Study G208)

Category	400 mg QD N=25	600 mg QD N=23	Overall N=48
Any TEAEs	23 (92%)	22 (96%)	45 (94%)
Any Grade ≥3 TEAEs	5 (20%)	10 (43%)	15 (31%)
Any SAEs	2 (8%)	5 (22%)	7 (15%)
Any TEAEs leading to treatment interruption	4 (16%)	10 (44%)	14 (29%)
Any TEAEs leading to dose reduction	4 (16%)	7 (30%)	11 (23%)
Any TEAEs leading to discontinuation	0	1 (4%)	1 (2%)
Any TEAEs leading to death	0	1 (4%)	1 (2%)

Source: Module 5.3.5.2, AB-106-G208 Cohort 5 Analysis Report

Table 15. Incidence of Gastrointestinal Disorders Occurring in ≥10% of Patients in Cohort 5 of Study G208

Gastrointestinal disorders	400 mg QD N=25, n (%)	600 mg QD N=23, n (%)	Overall N=48, n (%)
Diarrhea	**10 (40%)**	**17 (74%)**	27 (56%)
Nausea	12 (48%)	11 (48%)	23 (48%)
Vomiting	**6 (24%)**	**10 (44%)**	16 (33%)
Constipation	5 (20%)	3 (13%)	8 (17%)
Abdominal pain	3 (12%)	2 (9%)	5 (10%)
Gastrooesophageal reflux disease	3 (12%)	1 (4%)	4 (8%)

Source: Module 5.3.5.2, AB-106-G208 Cohort 5 Analysis Report

In comparison to 600 mg QD, lower incidences of Grade ≥3 TEAEs, SAEs, AEs leading to treatment interruption and dose modification were reported at 400 mg QD. In addition, there is a trend for lower frequency of diarrhea and vomiting at 400 mg QD.

2) **Positive E-R for safety:**

Per FDA's independent analysis, E-R relationship for safety showed positive trends for Grade ≥3 TEAEs, Grade ≥3 AST increase and ALT increase, and AEs leading to dose modification, while the efficacy (ORR) is expected to retain given the flat E-R trend for efficacy over the dose range of 400 mg and 600 mg QD. See **Section 19.4.4** for details.

3) Improving safety profile, especially alleviation of gastrointestinal toxicity, with food intake:

High rates of gastrointestinal AEs were reported for 600 mg QD in the pivotal studies, including diarrhea 64%, nausea 46%, and vomiting 44%. The results of food effect study AB-106-U113 showed that taletrectinib AUC and Cmax increased by 1.5-fold following administration with a high-fat meal (1000 calories, 50% fat), as compared to the overnight 10 hours fasting condition. In contrast to the higher exposure, the incidence of TEAEs was lower when taletrectinib was administered with food (32% versus 62% under fasted condition). In particular, the rates of gastrointestinal AEs decreased under the fed dosing condition, as compared to fasted condition (10% versus 28% for diarrhea and 0 versus 12% for nausea). These data suggest taking taletrectinib with a standard meal increases its exposure and improves its gastrointestinal tolerability.

Taken together, the available data suggested that the taletrectinib dosage should be further optimized with regard to food intake. A PMR will be issued to further characterize known serious risks with taletrectinib including severe hepatotoxicity, interstitial lung disease, other serious adverse reactions, and the risk of gastrointestinal toxicity, by evaluating the safety, activity, and pharmacokinetics of taletrectinib 400 mg daily taken with standard meals, in patients with advanced or metastatic *ROS1* positive non-small cell lung cancer who are naïve to prior ROS1 tyrosine kinase inhibitors (TKIs) and in patients who have received one prior ROS1 TKI.

6.2.2.2. Therapeutic Individualization

Data:

Drug Interactions

Effects of other drugs on taletrectinib

- Plasma taletrectinib C_{max} and AUC_{inf} were increased by 76% and 228% when co-administered with itraconazole, respectively; plasma taletrectinib C_{max} and AUC_{inf} were decreased 42% and 86% when co-administered with rifampin, respectively.
- Plasma taletrectinib C_{max} and AUC_{inf} were decreased by 65% and 40% when co-administered with omeprazole, respectively, suggesting that bioavailability of taletrectinib is decreased when gastric pH is increased.
- The physiologically based pharmacokinetic model predicted an approximately 2-fold increase in taletrectinib AUC and a 1.2- to 1.5-fold increase in C_{max} when co-administered with moderate CYP3A inhibitors. The increase in taletrectinib AUC and C_{max} when co-administered with weak CYP3A4 inhibitors was predicted to be less than 20% and is not expected to be clinically significant. Moderate and weak CYP3A inducers were predicted to decrease taletrectinib AUC by 66% and 36%, respectively.

Effects of taletrectinib on other drugs

- No clinically significant drug interactions were observed between taletrectinib and digoxin.

Specific Populations

Organ impairment

- PK in cancer participants with mild hepatic impairment (National Cancer Institute [NCI] classification) are similar to cancer participants with normal hepatic function; data in moderate and severe hepatic impairment have not been generated.
- PK in cancer participants with mild to moderate renal impairment are similar to cancer participants with normal renal function. The PK of taletrectinib have not been studied in participants with severe renal impairment, end stage renal disease, or participants on dialysis. Although the PK of taletrectinib in participants with severe renal impairment is unknown, a significant effect of severe renal impairment on taletrectinib exposure is not expected based on the minimal involvement of renal elimination.

Other intrinsic factors

- There is no clinically significant effect of age, weight, sex, and disease status on taletrectinib PK. Asian participants exhibit approximately 16.5% lower drug clearance compared to Caucasian participants, resulting in approximately 20% higher drug exposure. Black or African American participants fall between these 2 groups with <5% different from Caucasian. Overall, the magnitude of the race effect on PK is not considered clinically significant.

The Applicant's Position:

Taletrectinib may be administered without dose adjustment in patients with mild hepatic impairment (according to NCI classification), mild to moderate renal impairment, and regardless of age (≥18 years), sex, race, or body weight.

Coadministration of taletrectinib with strong or moderate CYP3A inhibitors, strong or moderate CYP3A inducers, proton pump inhibitors (PPIs), H2 receptor antagonists, locally acting antacids, and hormonal contraceptives should be avoided.

The FDA's Assessment:
FDA assessed therapeutic individualization in the following clinical pharmacology areas of interest:

1) DDI – Taletrectinib as a substrate

i. Strong CYP3A4 inhibitors and inducers

CYP3A is the primary CYP450 enzyme involved in taletrectinib metabolism. Clinical DDI study AB-106-C110 evaluated the effect of itraconazole (a strong CYP3A and P-gp inhibitor) and rifampin (a strong CYP3A and P-gp inducer) on the PK of taletrectinib in healthy subjects (n=56). Taletrectinib Cmax increased by 1.8-fold and AUC by 3.3-fold following concomitant administration of itraconazole 200 mg daily. Taletrectinib Cmax decreased by 42% and AUC by 86% following concomitant administration of rifampin (strong CYP3A and P-gp inducer) 600 mg daily.

Based on the mass balance study AB-106-U112, only 15% of radiolabeled dose of taletrectinib was recovered in feces as the parent drug, indicating a good extent of absorption of the drug. Hence, inhibiting intestinal P-gp is not anticipated to further increase the exposure of taletrectinib. In addition, the metabolism process of taletrectinib may not be a rapid process given the long half-life, and therefore, it is not expected that taletrectinib undergoes significant first-pass intestinal metabolism for which P-gp might play a role by coordinating with CYP3A. Lastly, itraconazole increased taletrectinib Cmax by1.8-fold, less than the AUC increase (3.3-fold), which suggests that P-gp does not play a significant role in drug metabolism.

ii. Moderate CYP3A4 inhibitors and inducers

The effects of moderate CYP3A4 inhibitors and inducers on the PK of taletrectinib were simulated using PBPK approach. Based on FDA's independent analysis, concomitant use with moderate CYP3A inhibitors (i.e., fluconazole, erythromycin, or verapamil) is predicted to increase taletrectinib AUC up to 2.6-fold and Cmax up to 1.5-fold, and concomitant use with a moderate CYP3A inducer (efavirenz) is predicted to reduce taletrectinib AUC by 66% and its Cmax by 40%. See **Section 19.4.6** for details.

In summary, the above results support labeling recommendations to avoid concomitant use of strong and moderate CYP3A4 inhibitors and inducers.

iii. Gastric acid reducing agents

Taletrectinib displays pH-dependent aqueous solubility. The results of clinical DDI study AB-106-C114 showed that taletrectinib Cmax decreased by 65% and AUC decreased by 40% following concomitant administration of omeprazole (a PPI) 40 mg daily. Therefore, taletrectinib

should not be concomitantly used with PPIs. To potentially expand the use of acid-reducing agents (e.g., H2 receptor antagonists) in the targeted patient population, a PMC will be issued to evaluate if staggered administration of an H2-receptor antagonist can mitigate the decrease in the exposure of taletrectinib and allow for taking taletrectinib with staggered dosing of H2-receptor antagonists.

2) DDI – Taletrectinib as a Precipitant

i. P-gp substrate

In vitro DDI study showed that taletrectinib is an inhibitor of P-gp. The clinical DDI study AB-106-C111 evaluated the effect of taletrectinib on the PK of digoxin (a sensitive P-gp substrate). No clinically significant differences in the pharmacokinetics of digoxin were observed when used concomitantly with taletrectinib (i.e., digoxin Cmax increased by no more than 1.2-fold and AUC increased by 1.1-fold).

ii. CYP1A2, CYP3A4, CYP2C8, CYP2D6, OATP1B1, BCRP, and MATEs

In vitro DDI studies showed that taletrectinib inhibits CYP2C8, CYP2D6, and CYP3A4, and induces CYP1A2 and CYP3A4. Taletrectinib also inhibits P-gp, BCRP, OATP1B1, MATE1, and MATE2-K in vitro. The effects of taletrectinib on the PK of the substrates of the above CYP450 enzymes and transporters were predicted using PBPK approach. Based on FDA's independent analysis, the available data cannot rule out the potential inhibitory effect of taletrectinib on CYP3A4, CYP2D6, BCRP, OATP1B1, and OATP1B3 and the potential induction effect of taletrectinib on CYP3A4 and CYP1A2 (see **Section 19.4.6** for details). A PMR and a PMC will be issued to assess the above-mentioned inhibitory effect and induction effect of taletrectinib, respectively.

Note that taletrectinib is both an inhibitor and inducer of CYP3A4. FDA's independent PBPK analysis suggests that the inhibitory effect of taletrectinib is more potent than the induction effect. Therefore, there is no strong evidence to indicate that the concentration and effectiveness of hormonal contraceptives will be decreased with concomitant use of taletrectinib.

3) Intrinsic factors:

FDA agrees that no clinically significant differences in the PK of taletrectinib were observed based on age (18 to 80 years), sex, race (22% White, 5% Black), mild and moderate renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (total bilirubin >1 to 1.5 times ULN or AST >ULN). FDA's independent analysis showed that Asian patients (66%) with a lower weight distribution compared to non-Asian patients, are associated with a 30% increase in exposure (AUC) compared to White patients, which likely attributed to a higher rate of ≥ Grade 3 ALT/AST increase in Asian population. However, specific instructions for this subgroup

are not considered necessary due to the similarity between Asian and White patients in AE profiles and proportion of dose reductions related to hepatotoxicity (the main clinically relevant adverse event), especially under frequent AST/ALT monitoring as proposed in the labeling. See **Section 19.4.3** for details.

Hepatic impairment:
Taletrectinib is eliminated primarily through hepatic metabolism with approximately 75% of administered dose found in the feces (15% as the parent drug). Patients with hepatic impairment may have serious risk of increased exposure to taletrectinib. Based on exposure-response analyses, increased exposure of taletrectinib is associated with higher incidences of Grade 3 or greater adverse events, Grade 2 liver enzyme elevation, and adverse events leading to dose modification. The PK and safety of taletrectinib in patients with moderate and severe hepatic impairment have not been evaluated, and therefore a clinical hepatic impairment study is warranted to assess the PK and safety of taletrectinib and to support dosage recommendations in patients with moderate and severe hepatic impairment.

Renal impairment:
The renal elimination plays a minimal role in taletrectinib clearance with approximately 11% of total dose (< 5% as the parent drug) found in urine. Therefore, a clinically meaningful effect of severe renal impairment on taletrectinib exposure is not expected.

6.2.2.3. Outstanding Issues

The Applicant's Position:

Based on a clinical mass balance study that identified the fecal/biliary route as the major route of taletrectinib elimination (approximately 75% of administered dose eliminated in the feces), a hepatic impairment study is planned.

The FDA's Assessment:

FDA acknowledges the Applicant's plan to conduct a hepatic impairment study and a PMR will be issued accordingly. In addition, the following PMRs and PMCs for further dosage optimization and DDI evaluations will also be issued.

1) **PMR for dosage optimization**
   Conduct a multicenter trial to further characterize known serious risks with taletrectinib including severe hepatotoxicity, interstitial lung disease, other serious adverse reactions and the risk of gastrointestinal toxicity, by evaluating the safety, activity, and pharmacokinetics of taletrectinib 400 mg daily taken with standard meals, in patients with advanced or metastatic *ROS1* positive non-small cell lung cancer who are naïve to prior ROS1 tyrosine kinase inhibitors (TKIs) and in patients who have received one prior ROS1 TKI. Include an

adequate number of patients from each subgroup (i.e., ROS1 TKI-naïve and previously treated with ROS1 TKI).

2) **PMR for hepatic impairment study**
Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dosage of taletrectinib in patients with moderate and severe hepatic impairment.

3) **PMR for CYP enzymes and transporters inhibition**
Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A, CYP2D6, BCRP, OATP1B1, and OATP1B3 (b) (4) and serious potential risk of increased drug toxicity, and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP and transporter substrates.

4) **PMC for CYP enzymes induction**
Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A and CYP1A2 in healthy subjects and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP substrates.

5) **PMC for ARA effect**
Conduct a clinical trial to evaluate if staggered administration of an H2-receptor antagonist decreases the exposure of taletrectinib and to inform instructions for taking taletrectinib with H2-receptor antagonists.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Mechanism of Action

Taletrectinib is a CNS-penetrant inhibitor of proto-oncogene tyrosine-protein kinase ROS1, including *ROS1* resistance mutations G2032R, L1951R, L2026M, and D2033N. Taletrectinib also showed inhibitory effects on tropomyosin receptor kinase (TRK) A/B/C, with approximately 11- to 20-fold selectivity over TRKB.

Fusion proteins that include ROS1 domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Taletrectinib exhibited growth inhibition of cancer cells expressing *ROS1* fusion genes and mutations including *CD74-ROS1, CD74-ROS1*^{G2032R}, *CD74-ROS1*^{L1951R}, *CD74-ROS1*^{L2026M}, *CD74-ROS1*^{D2033N}, *SLC34A2-ROS1, SLC34A2-ROS1*^{G2032R}, *SLC34A2-ROS1*^{L2026M}, and

SLC34A2-ROS1^{D2033N}. In mice subcutaneously implanted with tumors harboring *ROS1* fusions, including the G2032R mutation, administration of taletrectinib resulted in tumor regression. Taletrectinib also increased survival in an intracranial (IC) NSCLC xenograft model harboring a *SDC4-ROS1* fusion.

Clinical Pharmacokinetics

- Taletrectinib PK exposure increased approximately proportionally with doses from 50 to 1200 mg taken QD.
- Following repeat dosing, a steady state was achieved on Day 8 after approximately 7 days of dosing, and taletrectinib showed time-invariant PK; accumulation ratios after 600 mg QD dosing were approximately 3.3 to 4.5 based on area under the concentration-time curve overdosing interval tau (AUC_τ).
- Following oral administration of the capsule formulation, taletrectinib is absorbed with time of maximum concentration (t_{max}) in the range of 2 to 6 hours for the tested dose levels of 50 to 1200 mg QD, and a terminal phase half-life ($t_{1/2}$) of approximately 80 to 100 hours and an effective $t_{1/2}$ of approximately 66 hours. The PK of taletrectinib is well described by a 3-compartment model with linear elimination. The estimated apparent clearance (CL/F) and apparent steady state volume of distribution (V_{ss}/F) are approximately 94 L/hr and 9820 L based on the population PK (popPK) model.
- Taletrectinib is highly bound to plasma proteins and exhibits concentration-dependent binding. The estimated percentage of binding in human plasma ranges from 92.6% (10000 ng/mL) to 96.5% (100 ng/mL).
- In vitro partitioning of taletrectinib into human red blood cells was moderate, with blood/plasma ratios of 1.29 to 1.44 across concentrations tested (100 to 1000 ng/mL).
- Taletrectinib is eliminated primarily through hepatic metabolism with minimal renal elimination of unchanged taletrectinib (less than 5% of the total dose). Total mean radioactivity recovery of taletrectinib was 86.2% (75.1% excreted in feces and 11.1% excreted in urine). Hydroxylation via CYP P450 3A4 is the primary route of metabolism, with sulfation, dealkylation, and N-acetylation as notable additional metabolic pathways; sulfate conjugates are the major circulating metabolites.
- Taletrectinib PK is similar between healthy participants and participants with NSCLC.
- In healthy participants, taletrectinib has low to moderate intersubject and intrasubject PK variability and intrasubject and intersubject variability are comparable between participants with cancer and healthy participants: the inter-subject variabilities in participants with cancer at clinical dose of 600 mg QD were estimated to be 15% to 40% for steady-state AUC, maximum plasma concentration (C_{max}), and trough plasma concentration (C_{trough}) concentration in 2 pivotal studies.

QTc-C-QTc

- Taletrectinib has been shown to increase QTc intervals in a concentration-dependent manner. The concentration-QT interval corrected using Fridericia's formula (QTcF) relationship indicates that the predicted mean change in QTcF from baseline (ΔQTcF) is approximately 12.76 msec, with an upper bound of 90% confidence interval (CI) of 15.43 msec at the mean steady-state maximum concentration ($C_{max,ss}$) in participants following the administration of 600 mg of taletrectinib QD.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of ADME properties and PK data of taletrectinib. Based on FDA's QT-IRT analysis (Reference ID: 5545184) of the clinical data from studies DS6501-A-U101 and DS6051-A-J102, FDA confirmed the Applicants' analysis, i.e., the largest mean increase in the QTc interval was 12.8 ms (upper confidence interval of 15.4 ms) at the mean steady-state maximum concentration ($C_{max,ss}$) after administration of taletrectinib 600 mg QD in patients. The increase in the QTc internal was concentration-dependent. At plasma concentrations achieved with administration of 600 mg QD with high fat food, the predicted increase in the QTc interval is 20.5 (16.3, 24.7) msec.

6.3.2. Clinical Pharmacology Questions

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

The Applicant's Position:

The majority of studies in the clinical pharmacology program for taletrectinib were conducted in healthy volunteers. The primary evidence of effectiveness comes from the pooled results from Studies G208 and C203 and is discussed in **Section 8.1.1**.

The FDA's Assessment:
Yes. The primary evidence of effectiveness is ORR in patients with locally advanced or metastatic *ROS1*-positive NSCLC, obtained from the pivotal Phase 2 trials, Studies G208 and C203 (refer to **Section 8.1.1**). There was no apparent E-R relationship for the main efficacy endpoint (ORR) identified over the dose range of 400 mg and 600 mg QD. See **Section 19.4.4** for details of E-R efficacy analysis.

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

Data:

Taletrectinib at a dose of 600 mg QD presented with TEAEs that were clinically manageable and an overall safety profile typical of TKIs. The majority of patients (approximately 70%) in safety populations were able to continue treatment at the starting dose of 600 mg taletrectinib without a dose reduction due to an AE. Additional details regarding the safety of taletrectinib are provided in **Section 8.2**.

A popPK model was developed to characterize the PK of taletrectinib in healthy participants and in participants with cancer with *ROS1* positive tumors as well as other tumor types and to assess sources of variability (i.e., intrinsic and extrinsic factors) that may impact the exposure of taletrectinib. Overall, taletrectinib demonstrates low inter-individual variability in clearance and volume after accounting for covariates.

An E-R analysis was conducted to characterize the E-R relationships between taletrectinib exposures and selected efficacy and safety endpoints.

For the primary efficacy endpoint objective response, no relationship was identified between taletrectinib exposure measures ($C_{avg,ss}$) and probability of achieving objective response in logistic regression model. Prior TKI treatment history was identified as the only significant predictor of objective response rate (ORR). As a supportive analysis, linear regression models utilizing taletrectinib popPK predicted exposure measures ($C_{avg.ss}$) as a covariate did not indicate a clear clinically relevant association between best percent change in tumor size and exposure to taletrectinib. Similarly, prior TKI treatment history was identified as a significant predictor of tumor size change.

For safety endpoints, no apparent trend between taletrectinib exposure and SAEs, Grade ≥3 ALT/AST elevations, or Grade ≥2 GI AEs was observed. Although a statistically significant relationship was observed between taletrectinib exposure and AEs leading to dose modification, as well as Grade ≥3 TEAEs, the trend was relatively modest. For both AEs leading to dose modification and Grade ≥3 TEAEs, the hazard ratios (HR) were estimated to be 1.0017, which is a relatively shallow ER relationship.

Among all the covariates evaluated, Eastern Cooperative Oncology Group (ECOG) status was identified as a predictor of SAE rates, with higher ECOG scores associated with a greater risk of experiencing SAEs. Baseline albumin level was significantly related to the risk of SAEs, Grade ≥3 TEAEs, and Grade ≥2 GI AEs. Participants with lower albumin levels demonstrated a higher risk of experiencing these AEs. Additionally, baseline weight and sex were identified as predictors for Grade ≥3 TEAEs and Grade ≥2 GI AEs, respectively, with lighter participants having a higher risk of experiencing Grade ≥3 TEAEs and female participants having a higher risk of experiencing Grade ≥2 GI AEs. Lastly, race was identified as a significant predictor for Grade ≥3 TEAEs and AEs leading to dose modification. This racial effect is likely due to different follow-up times across 2 pivotal studies. As shown in the visual predictive check plots

of the model (Report ANTX-Proj1-24-0002, Figures A-6 and A-7), participants are balanced across most covariates. However, the follow-up time for Asian participants is significantly longer than for Caucasian participants, which can potentially lead to estimation bias for race effect.

The Applicant's Position:

The proposed dosing regimen of 600 mg QD is supported by clinical efficacy and safety data as well as the popPK and E-R analyses.

The FDA's Assessment:

FDA agrees that taletrectinib 600 mg QD is an effective dosage based on the ORR obtained from the pivotal trials in the targeted patient population (refer to **Section 6.2.2** for detailed FDA assessment on the dosage). However, FDA does not agree that the proposed dosage is optimized due to the following reasons:

1) Potential for similar efficacy and improved safety at a lower dosage
2) Positive E-R relationship for safety
3) Potential for improving the safety profile, especially alleviation of gastrointestinal toxicity, with food intake.

Given the lack of dosage optimization and potential for an improved benefit-risk profile with a lower dosage of taletrectinib taken with food, a PMR is to be issued to further characterize known serious risks with taletrectinib including severe hepatotoxicity, interstitial lung disease, other serious adverse reactions, and the risk of gastrointestinal toxicity, by evaluating the safety, activity, and pharmacokinetics of taletrectinib 400 mg daily taken with standard meals, in patients with advanced or metastatic *ROS1* positive non-small cell lung cancer who are naïve to prior ROS1 tyrosine kinase inhibitors (TKIs) and in patients who have received one prior ROS1 TKI. See **Section 6.2.2.3** for details.

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors (e.g. Race, Ethnicity, Age, Performance Status, Genetic Subpopulations, etc.)?

Data:

Data for intrinsic patient factors are presented in **Section 6.2.2.2**.

The Applicant's Position:

Taletrectinib is recommended to be taken without food (e.g., no food 2 hours before or after dose). Low to moderate variability in taletrectinib exposure parameters was observed among participants. PopPK analysis suggests that no dose adjustments are required based on intrinsic factors. Therefore, taletrectinib may be administered without dose adjustment in patients with

mild hepatic impairment (according to NCI classification), mild to moderate renal impairment, and regardless of age (≥18 years), [redacted] race, or body weight.

The PK of taletrectinib has not been studied in participants with moderate and severe hepatic impairment, but a study in participants with different degrees of hepatic impairment is planned.

The FDA's Assessment:

FDA generally agrees with the Applicant that no clinically significant differences in PK of taletrectinib were observed based on the intrinsic factors evaluated. It is noted that further dosage optimization to study taletrectinib at a lower dosage taken with food should be conducted as a PMR, given the high incidences of gastrointestinal AEs reported at the proposed dosage of 600 mg QD taken on an empty stomach and the potential for alleviation of gastrointestinal toxicity with food intake.

***ROS1* fusion partner and *ROS1* secondary TKI resistance mutations.** Enrollment in Studies C203 and G208 was based on documented *ROS1* positive status in tumor specimens as determined by local testing using next-generation sequencing (NGS, 47.8%), polymerase chain reaction (PCR, 41.5%), fluorescence in situ hybridization (FISH, 7.8%), immunohistochemistry (IHC, 2.2%), or unknown (0.7%). In ROS1 TKI-naïve patients, 135/157 (86.0%) patients had their locally determined *ROS1* positive status confirmed by central testing using NGS (26.7%), PCR (69.6%), or both NGS and PCR (3.7%), with 14.0% not confirmed centrally. In ROS1 TKI-pretreated patients, 67/113 (59.3%) patients had their locally determined *ROS1* positive status confirmed by central testing using NGS (56.7%), PCR (35.8%), or both NGS and PCR (7.5%), with 40.7% not confirmed centrally.

ROS1 fusions with various partner genes encode oncogenic proteins that may exhibit differential sensitivity to TKI inhibitors due to altered subcellular localization and signaling properties (Drilon et al., 2021; Gendarme et al., 2022). A subset of 37 ROS1 TKI-naïve patients (23.6% of the Response Evaluable Population, REP) and 33 ROS1 TKI-pretreated patients (29.2% of REP) had the type of *ROS1* fusion partner identified by central NGS testing. In response to an FDA IR dated January 23, 2025, the Applicant provided analyses of BOR stratified by the type of *ROS1* fusion partner (**Table 16**). The approximate frequencies and types of *ROS1* fusion partner genes were in line with estimates from the literature (Drilon et al., 2021). In ROS1 TKI-naïve patients, the ORR was 86.5% (32/37), with BOR of CR in 8.1% (3/37) and PR in 78.4% (29/37, **Table 16**). In ROS1 TKI-pretreated patients, the ORR was 51.5% (17/33), with BOR of PR in 51.5% (17/33). In both groups of ROS1 TKI-naïve patients and ROS1 TKI-pretreated patients, there were no apparent trends in BOR by the type of *ROS1* fusion partner (**Table 16**). These data suggest that taletrectinib has clinical activity in ROS1 TKI-naïve and ROS1 TKI-pretreated patients with tumors carrying *ROS1* fusions with various partners.

Resistance to therapy with TKIs is mediated in part by the development of secondary mutations in the kinase domain of *ROS1* (Drilon et al., 2021). A total of 32 TKI-pretreated patients (28.3% of

REP) from C203 (N = 28, 87.5%) and G208 (N = 4, 12.5%) had tumor samples obtained following progression on prior TKI therapy analyzed by local or central NGS tests for the presence of *ROS1* secondary resistance mutations. Samples from 15 patients (46.9%) tested positive for secondary resistance mutations, including 14 from C203 (43.8%) and 1 from G208 (3.1%). **Table 17** shows the distribution of resistance mutations by *ROS1* fusion partner in the group of patients with tumors identified as having secondary resistance mutations. Among the 13 patients with tumors harboring the most common secondary resistance mutation, G2032R solvent front mutation (86.7%), the ORR was 62.0%, with BOR of PR in 62.0% (8/13). Responses were only observed in patients whose tumors had the G2032R solvent front mutation. CD74 was the most common *ROS1* fusion partner in patients' tumors with resistance mutations (10/15, 66.7%) and for 4 patients the *ROS1* fusion partner was unknown (26.7%. **Table 17**). These limited data suggest that taletrectinib has clinical activity in TKI-pretreated patients with tumors carrying the G2032R TKI resistance mutation in *ROS1*.

Table 16. BOR and ORR in ROS1 TKI-Naïve and ROS1 TKI Pre-Treated Cohorts Stratified by *ROS1* Fusion Partners

	Fusion partner (N)	BOR N (%)					ORR N (%)
		CR	PR	SD	PD	NE	
ROS1 TKI-naïve (N = 157)	*CD74* (19)	1 (5.3)	15 (78.9)	3 (15.8)	-	-	16 (84.2)
	SDC4 (6)	-	4 (66.7)	-	2 (33.3)	-	4 (66.7)
	EZR (5)	-	5 (100)	-	-	-	5 (100)
	SLC34A2 (2)	1 (50.0)	1 (50.0)	-	-	-	2 (100)
	TPM3 (2)	-	2 (100)	-	-	-	2 (100)
	TPR (1)	-	1 (100)	-	-	-	1 (100)
	LRIG1 (1)	-	1 (100)	-	-	-	1 (100)
	MYH9 (1)	1 (100)	-	-	-	-	1 (100)
	Unknown (120)	5 (4.2)	102 (85.0)	7 (5.8)	3 (2.5)	3 (2.5)	107 (89.2)
ROS1 TKI-pretreated (N = 113)	*CD74* (17)	-	10 (58.8)	3 (17.6)	2 (11.8)	2 (11.8)	10 (58.8)
	CD74 + ARSB (1)	-	1 (100)	-	-	-	1 (100)
	CD74 + KCNQ5 (1)	-	-	1 (100)	-	-	-
	CD74 + LRPPRC (1)	-	-	1 (100)	-	-	-
	EZR (6)	-	4 (66.7)	2 (33.3)	-	-	4 (66.7)
	SDC4 (3)	-	1 (33.3)	2 (66.7)	-	-	1 (33.3)
	LNX1 + SDC4 (1)	-	-	1 (100)	-	-	-
	MPRIP (1)	-	1 (100)	-	-	-	1(100)
	PWWP2A (1)	-	-	1 (100)	-	-	-
	TPM3 (1)	-	-	1 (100)	-	-	-
	Unknown (80)	5 (6.2)	41 (51.3)	24 (30.0)	6 (7.5)	4 (5.0)	46 (57.5)

Source: Adapted from Applicant response to FDA IR dated January 23, 2025.

Table 17. BOR an ORR Stratified by Type of *ROS1* Fusion Partner in ROS1 TKI-Pretreated Patients With Secondary Resistance Mutations in Tumor Re-Biopsy Samples

Resistance mutation (N)	Fusion partner (N)	BOR N (%)				ORR N (%)
		CR	PR	SD	PD	
G2032R (13)	*CD74* (6)		5 (83.3)	1(16.7)		5 (83.3)
	CD74 and *ARSB* (1)		1 (100)			1 (100)
	CD74 and *KCNQ5* (1)			1 (100)		-
	SDC4 (1)			1 (100)		-
	Unknown (4)*		2 (50.0)	1 (25.0)	1 (25.0)	2 (50)
G2032R and G2101A (1)	*CD74* (1)			1 (100)		-
L2026M (1)	*CD74* (1)				1 (100)	-

Source: Adapted from Applicant response to FDA IR dated January 23, 2025.
Information on secondary resistance mutation and fusion partner of 3 patients are based on the local test results.
*Fusion partner was not detected.

6.3.2.4. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What Is the Appropriate Management Strategy?

Data:

Food effect studies demonstrated that, compared with the fasted condition, a high-fat meal (800 to 1000 calories with approximately 50% of calories from fat) can increase exposure, both in terms of area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}), by approximately 50%. A low-fat meal (340 calories with 80 calories from fat) can increase C_{max} to a similar magnitude as a high-fat meal; however, the effect on AUC is only about half that of the high-fat meal.

Data related to potential drug-drug interactions are presented in **Section 6.2.2.2**.

The Applicant's Position:

The effects of food on taletrectinib absorption can be clinically significant and depend on the content of the meal. These findings support the proposed labeling recommendation that taletrectinib should be administered on an empty stomach (2 hours before or after a meal).

Concomitant use of the following should be avoided:

- Strong and moderate CYP3A inhibitors. Concomitant use of taletrectinib with a strong or moderate CYP3A inhibitor may increase taletrectinib exposure, which may increase the incidence and severity of adverse reactions of taletrectinib. Discontinue CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor prior to initiation of taletrectinib.
- Strong and moderate CYP3A inducers. Concomitant use of taletrectinib with a strong or moderate CYP3A inducer may decrease taletrectinib plasma concentrations, which may decrease efficacy of taletrectinib. Discontinue CYP3A inducers for 3 to 5 elimination half-lives of the CYP3A inducer prior to initiation of taletrectinib.

- Gastric acid reducing agents. Coadministration of gastric acid reducing agents decreased taletrectinib concentrations, which may reduce the efficacy of taletrectinib. Avoid coadministration of taletrectinib with PPIs, H2 receptor antagonists, and locally acting antacids. If coadministration with an acid-reducing agent cannot be avoided, administer taletrectinib 2 hours before or 2 hours after administration of a locally acting antacid.
- Hormonal contraceptives. In vitro, taletrectinib is a CYP3A4 inducer, which may decrease progestin or estrogen exposure to an extent that could reduce the effectiveness of hormonal contraceptives. Avoid concomitant use of taletrectinib with hormonal contraceptives. Advise women of childbearing potential to use an effective nonhormonal contraceptive.

The FDA's Assessment:
FDA does not agree with the Applicant's position on proposed fasted dosing condition and restrictions of using H2 receptor antagonists and hormonal contraceptives.

The results of food effect study AB-106-U113 suggest taking taletrectinib with a standard meal increases its exposure and improves its gastrointestinal tolerability (see **Section 6.2.2.1** for details). In addition, given the potential comparable efficacy and improved safety profile of a lower dosage of 400 mg QD, further dosage optimization with regard to food intake should be conducted. A PMR will be issued to further characterize known serious risks with taletrectinib including severe hepatotoxicity, interstitial lung disease, other serious adverse reactions, and the risk of gastrointestinal toxicity, by evaluating the safety, activity, and pharmacokinetics of taletrectinib 400 mg daily taken with standard meals, in patients with advanced or metastatic *ROS1* positive non-small cell lung cancer who are naïve to prior ROS1 tyrosine kinase inhibitors (TKIs) and in patients who have received one prior ROS1 TKI.

As stated in **Section 6.2.2.2**, to potentially expand the use of acid-reducing agents (e.g., H2 receptor antagonists) in the targeted patient population, a PMC will be issued to evaluate if staggered administration of an H2-receptor antagonist can mitigate the decrease in exposure of taletrectinib and allow for taking taletrectinib with staggered dosing of H2-receptor antagonists. Given that there is lack of evidence that taletrectinib decreases the concentration of hormonal contraceptives i.e., taletrectinib CYP 3A inhibitory effect is predicted to be stronger than the induction effect, FDA recommends removal of the restriction for using taletrectinib with hormonal contraceptives.

X _____ X _____

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

The clinical studies comprising this application are summarized in **Table 18**.

Table 18. Applicant - Listing of Clinical Trials Relevant to This NDA

Trial Identity/ Status/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Participants Enrolled	Study Population	No. of Centers, Countries
	Studies to Support Efficacy and Safety						
AB-106-G208[a] / Ongoing/ NCT04919811	Phase 2, global, multicenter, open-label, single-arm study	**Cohorts 1 to 4:** Taletrectinib 600 mg PO QD in 21-day cycles **Cohort 5:** Randomized 1:1 to taletrectinib 400 mg PO QD versus taletrectinib 600 mg PO QD **Cohort 6:** Taletrectinib 400 or 600 mg PO QD in combination with carboplatin + pemetrexed	Efficacy, safety, and PK of taletrectinib as monotherapy or in combination with chemotherapy	Dosing continued until discontinuation criteria are met	Approximately 224 total participants. A total of 164 participants were enrolled as of the data cutoff. **Cohort 1:** Approximately 53 planned, 55 enrolled **Cohort 2:** 46 planned, 50 enrolled **Cohort 3:** Up to 35 planned, 35 enrolled **Cohort 4:** Up to 20 planned, 13 enrolled **Cohort 5:** Approximately 40 planned, 11 enrolled **Cohort 6:** Up to 30 planned[a]	Participants with locally advanced or metastatic NSCLC harboring *ROS1* fusion and other solid tumors which are *ROS1*-positive	74 centers, 9 countries

Trial Identity/ Status/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Participants Enrolled	Study Population	No. of Centers, Countries
AB-106-C203/ Ongoing/ NCT04395677	Phase 2, multicenter, single-arm, open-label study	**Stage 1** 400 or 600 mg PO QD in 21-day cycles **Stage 2** 600 mg PO QD	Efficacy, safety, and PK of taletrectinib as monotherapy	Dosing continued until discontinuation criteria are met	**Stage 1** 6 participants planned and enrolled **Stage 2** 167 participants planned and enrolled	Locally advanced or metastatic *ROS1* fusion gene positive NSCLC and had not undergone any *ROS1*-TKI treatment or had experienced treatment failure following crizotinib therapy	33 centers, 1 country
	Studies to Support Safety						
AB-106-C205/ Ongoing/ NCT04617054	Phase 2, multicenter, open-label, basket study of taletrectinib	600 mg PO QD	Efficacy, safety, and PK of taletrectinib as monotherapy	Dosing continued until discontinuation criteria are met	40 participants were planned. 14 participants were enrolled as of the data cutoff.	Chinese participants with locally advanced or systemic metastatic solid tumor with an *NTRK* rearrangement	10 centers, 1 country

Trial Identity/ Status/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Participants Enrolled	Study Population	No. of Centers, Countries
DS-6051-A-U101/ Completed/ NCT02279433	Phase 1/1b, multicenter, nonrandomized, open-label, multiple-dose, first-in-human study. The Phase 1 portion consisted of the Dose Escalation Phase and the Food Effect Phase. The Phase Ib portion was planned to consist of the Dose Expansion Phase with 3 cohorts	**Dose Escalation Cohorts 1 to 6:** 50, 100, 200, 400, 800, and 1200 mg QD PO in 21-day cycles **Exploratory Expansion Cohorts 8 to 9:** 400 mg BID and 800 mg QD PO in 21-day cycles **Food Effect Cohort 7:** Single 400 mg PO dose on Day -7 and Day -1 followed by 800 mg QD from Day 1 in 21-day cycles	Safety, tolerability, PK, and preliminary efficacy of taletrectinib	**Dose Escalation:** 21-day cycles **Exploratory Expansion** 21-day cycles **Food Effect:** Taletrectinib on Day -7 and Day -1 as food effect substudy then 21-day cycles	**Dose Escalation (Planned and Enrolled):** 50 mg (n=1), 100 mg (n=1), 200 mg (n=3), 400 mg (n=3), 800 mg (n=11), and 1200 mg (n=3) **Exploratory Expansion (Planned and Enrolled):** 13 total (400 mg [n=6], 800 mg [n=7]) **Food Effect (Planned and Enrolled):** 11	Advanced solid tumors for which no standard therapy is available or refractory to standard therapy, and documented *ROS1*, *NTRK1*, *NTRK2*, or *NTRK3* rearrangements	5 centers, 1 country
DS6051-A-J102[b]/ Completed/ NCT02675491	Phase 1, multicenter, non-randomized, open-label, multiple-dose study	400, 600, or 800 mg PO QD All administered in 21-day cycles	Safety and PK	Dosing continued until discontinuation criteria were met	15 total Japanese participants planned and enrolled. 400 mg (n=6) 600 mg (n=6) 800 mg (n=3)	Participants with advanced solid tumors with either a ROS1 or NTRK fusion gene	3 centers, 1 country

Trial Identity/ Status/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Participants Enrolled	Study Population	No. of Centers, Countries
	Clinical Pharmacology Studies						
AB-106-C110/ Completed/ NCT05357820	Open-label, nonrandomized, fixed sequence, 2-cohort study	Cohort 1 Period 1: taletrectinib 200 mg PO on Day 1 Period 2: itraconazole 200 mg QD PO from Day 1 to Day 15 and taletrectinib 200 mg PO once on Day 4 Cohort 2 Period 1: taletrectinib 200 mg PO on Day 1 Period 2: rifampin 600 mg QD PO from Day 1 to Day 19 and took taletrectinib 200 mg PO once on Day 8	Evaluation of the effect of itraconazole (strong CYP3A4 inhibitor) and rifampin (strong CYP3A4 inducer) on the PK of taletrectinib	Single dose	56 healthy Chinese male adults planned: Taletrectinib versus taletrectinib + itraconazole (n=28) OR Taletrectinib versus taletrectinib + rifampin (n=28) 59 participants were enrolled. Three subjects withdrew prior to receiving the first dose of study drug.	Healthy participants	1 center, 1 country
AB-106-C111/ Completed/ NCT05357911	Single center, open-label, fixed sequence study	Period 1: digoxin 0.25 mg PO once Period 2: taletrectinib 600 mg PO once followed by digoxin 0.25 mg PO once 1 hour post taletrectinib	Evaluation of the effect of taletrectinib on the PK of digoxin (P-gp substrate)	Single dose	16 healthy Chinese male adults planned 18 participants were enrolled. Two subjects withdrew prior to receiving the first dose of study drug.	Healthy participants	1 center, 1 country
AB-106-C114/ Completed/ NCT05609929	Single center, open-label, fixed sequence study	Period 1: taletrectinib 400 mg PO on Day 1 Period 2: omeprazole 40 mg QD PO from Day 1 to Day 5 and a single dose of taletrectinib 400 mg PO on Day 5	Evaluation of the effect of an acid reducing agent, omeprazole, on the PK of taletrectinib	Single dose	22 healthy Chinese male adults planned and enrolled	Healthy participants	1 center, 1 country

Trial Identity/ Status/ NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Participants Enrolled	Study Population	No. of Centers, Countries
AB-106-U112/ Completed/ None	Open-label, mass balance study	200 mg PO taletrectinib/5 µCi [^{14}C]-taletrectinib	Investigation of the absorption, metabolism, and elimination after an oral dose of [^{14}C]-taletrectinib	Single dose	10 healthy male adults planned and 8 enrolled	Healthy participants	1 center, 1 country
AB-106-U113/ Completed/ None	Open-label, randomized, single dose, crossover study	Single dose of 400 mg PO (2 × 200 mg capsules) under fasted and fed conditions	PK and safety of taletrectinib following oral administration with or without food	Single dose	32 healthy adults planned and enrolled	Healthy participants	1 center, 1 country

Abbreviations: BID, twice daily; CYP, cytochrome P450; NDA, New Drug Application; NSCLC, non-small cell lung cancer; NTRK, neurotropic tyrosine receptor kinase; P-gp, p-glycoprotein; PK, pharmacokinetic(s); PO, orally; QD, once daily; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.

[a] Cohort 6 (combination use of taletrectinib and carboplatin and pemetrexed) is not included in the initial NDA submission, as enrollment is expected to initiate in late 2024.

[b] Four participants from J102 were rolled over to J102-EXT, an extension study of J102 after J102 study closure. Considering the small sample size (n=4) and limited information collected, J102-EX was not included in the pooled analyses and in the initial NDA submission.

The Applicant's Position:

All studies pertinent to the evaluation of the efficacy and safety of taletrectinib are summarized in **Table 18**.

The FDA's Assessment:

FDA agrees with the Applicant's description of clinical trial data to be evaluated in the review of this application. The efficacy review assessed data from Studies G208 (Cohorts 1 and 2, n=101) and C203 (n=169 after excluding three patients with a starting dose of taletrectinib 400 mg QD) with the data cutoff date of October 28, 2024. FDA's safety review included data from Studies AB-106-C203, AB-106-C205, and AB-106-G208 (DCO June 7, 2024); Study DS6051-A-J102 (DCO December 28, 2021); and Study DS6051-A-U101 (DCO September 16, 2021).

8 Statistical and Clinical Evaluation

8.1. Review of Efficacy

8.1.1. Assessment of Efficacy Across Trials

8.1.1.1. Analysis Populations for Integrated Efficacy Assessment

The Applicant's Description:

The primary efficacy analysis population to support the integrated efficacy assessment is the Response Evaluable Population (REP), defined as all ROS1+ NSCLC participants in Studies G208 and C203 who had at least one measurable lesion at baseline per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by Independent Review Committee (IRC) and received at least one dose of taletrectinib with a starting dose of 600 mg QD.

In total, the REP included a total of 270 participants, including:

- **ROS TKI Treatment-naïve REP (N=157**): This cohort consists of 54 participants from Cohort 1 of Study G208 and 103 participants from the ROS1 TKI-naïve cohort of Study C203.
- **ROS TKI-Pretreated REP (N=113**): This cohort consists of 47 participants from Cohort 2 of Study G208 and 66 participants from the ROS1 TKI-pretreated cohort of Study C203.

Efficacy analysis was based on the data cutoff date of 07 Jun 2024 (original NDA cutoff date) except for time to event analyses (DOR, PFS, OS), which are based on a later cutoff date of 28 Oct 2024 (90-day safety update cutoff date).

As of 28 Oct 2024, the majority of responders (97.1%) in the treatment-naïve REP had at least 12 months of follow-up from the onset of response, and all responders (100%) in the pretreated REP had at least 6 months of follow-up from the onset of response. The IRC-assessed efficacy results from the treatment naïve- REP and pretreated REP are provided in **Section 8.1.1.4**. The efficacy results from the 2 REPs form the primary basis of efficacy evaluation for taletrectinib.

Efficacy results from 3 supplementary analysis populations are provided as supportive evidence or sensitivity analysis for the integrated analysis of efficacy, as follows:

- **Response Evaluable Population per Investigator Assessment (REP2):** This population includes all ROS1+ NSCLC participants in Cohorts 1 and 2 of Studies G208 and C203 who had at least one measurable lesion at baseline per RECIST v1.1 by investigator assessment, received at least one dose of taletrectinib with a starting dose of 600 mg QD.
- **Response Evaluable Population with ≥14 Months of Follow-up (REP3):** This population includes all participants in the REP who had at least one measurable lesion at baseline per RECIST v1.1 by IRC assessment, and who were followed up for at least 14 months since the first dose of study drug.

- **IC Analysis Population (IAP):** This population includes all participants in the REP who had at least one measurable brain metastatic lesion at baseline per modified RECIST (mRECIST) v1.1 by IRC assessment.

The number of participants included in each analysis population is provided in **Table 19**.

Table 19. Applicant - Analysis Populations for ISE

Category, n (%)[a]	ROS1 TKI-Naïve	ROS1 TKI-Pretreated	Overall
Response evaluable population set (REP) - IRC[b]	157	113	270
Response evaluable population 2 set (REP2) – Investigator[c]	158	116	274
Response evaluable population 3 set (REP3) - IRC[d]	134 (85.4)	93 (82.3)	227 (84.1)
Intracranial metastasis population set (IAP) – IRC, mRECIST v1.1[e]	17 (10.8)	32 (28.3)	49 (18.1)

Abbreviation: IRC, Independent Review Committee; ISE, integrated summary of efficacy; mRECIST, modified Response Evaluation Criteria in Solid Tumors; n, subset of total number of participants; NSCLC, non-small cell lung cancer; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Pooled studies include AB-106-C203 and G208.
[a] Percentage was calculated based on the REP.
[b] All participants satisfied the following 4 criteria: 1. participants diagnosed with NSCLC; 2. documented ROS1 fusion from central or local testing; 3. have at least one measurable lesion at baseline by the IRC according to RECIST v1.1; and 4. receive 1 or more doses of taletrectinib with a starting dose of 600 mg QD.
[c] All participants satisfied the following 4 criteria: 1. participants diagnosed with NSCLC; 2. documented ROS1 fusion from central or local testing; 3. have at least one measurable lesion at baseline by investigator according to RECIST v1.1; and 4. receive 1 or more doses of taletrectinib with a starting dose of 600 mg QD.
[d] All REP participants who have been followed up for at least 14 months.
[e] All REP participants have at least one measurable brain metastatic lesion at baseline per mRECIST v1.1 by the IRC.
Source: ISE Table 1.1.A2

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the analysis populations, noting that in addition to an integrated assessment of efficacy that pools patients from Studies G208 and C203 within their respective ROS TKI pre-treated or treatment-naïve cohorts, FDA's efficacy review also focused on individual trial level results separated by ROS TKI pre-treatment status.

8.1.1.2. Endpoints for Integrated Efficacy Analyses

The Applicant's Description:

The primary endpoint for the integrated efficacy analysis was ORR as assessed by IRC per RECIST v1.1 for the REP. The confirmed ORR (cORR) was determined as the proportion of participants with confirmed objective response (confirmed complete response [cCR] or confirmed partial response [cPR]) along with the two-sided 95% CI using the Clopper-Pearson method.

The secondary objectives were:

1. Duration of response (DOR) assessed by IRC per RECIST v1.1
2. PFS assessed by IRC per RECIST v1.1
3. Overall survival (OS)
4. Confirmed IC-ORR, IC-DOR, IC-PFS, and time to IC progression (TTiP) assessed by IRC per mRECIST v1.1

The FDA's Assessment:

FDA generally agrees with the Applicant's description of study endpoints.

FDA did not use inferential procedures to evaluate the results of these single arm trials. Instead, FDA relied on overall benefit-risk assessment to evaluate the outcome across primary and secondary endpoints. This evaluation included both the magnitude of BICR-assessed confirmed ORR as well as sufficiently mature DOR and whether the observed confirmed response rate and durability of the responses outweigh any concerns for toxicity and safety in the context of other available therapies. Analyses of time-to-event endpoints such as PFS, OS, TTiP are difficult to interpret in a single arm trial without the context of a comparator arm and are considered exploratory.

Per the protocols and Study Imaging Review Charters for Studies C203 and G208, patient imaging was reviewed by BICR with a dual-reader paradigm with a pre-specified process for adjudication. BICR independent reviewers were blinded to site response assessments and clinical information not related to the reading and to the other reader's assessment. FDA will refer to the independent review process as conducted by "BICR" for clarity and consistency throughout the review.

8.1.1.3. Statistical Analysis Plan and Amendments

The Applicant's Description:

The purpose of the integrated summary of efficacy (ISE) statistical analysis plan (SAP), finalized on 26 Jun 2024, was to document and specify the statistical analyses for the ISE of taletrectinib based on the results from two Phase 2 trials in support of the initial NDA submission in the US. The SAP described statistical analyses to be performed in addition to those performed for the

individual trial reports. In general, the strategy to derive and analyze variables, as already provided by methods and principles outlined in the SAPs for the individual trials, was followed. Per FDA request, the analysis was modified after NDA submission to exclude 3 participants in Study C203 with a starting dose lower than 600 mg QD from all efficacy analyses.

The FDA's Assessment:

While FDA acknowledges the Applicants ISE SAP plan, given the differences in baseline demographics and follow-up durations between Study C203 and Study G208, which enrolled its first patient approximately 14 months after the first patient enrolled on Study C203, it is not considered appropriate to present pooled efficacy results in the product label, particularly those dependent upon follow-up time such as median DOR. Instead, efficacy results are presented by individual study.

8.1.1.4. Pooled Efficacy Results Across Studies G208 and C203

8.1.1.5. Disposition, Demographics, and Baseline Characteristics

Data:

Table 20. Applicant - Summary of Participant Disposition Across Studies

Category	ROS1 TKI-Naïve N=157	ROS1 TKI-Pretreated N=113	Overall N=270
Treatment disposition, n (%)			
Ongoing	84 (53.5)	40 (35.4)	124 (45.9)
Discontinued	73 (46.5)	73 (64.6)	146 (54.1)
Adverse event	7 (4.5)	6 (5.3)	13 (4.8)
Death	6 (3.8)	3 (2.7)	9 (3.3)
Disease progression	48 (30.6)	53 (46.9)	101 (37.4)
Withdraw consent	3 (1.9)	0	3 (1.1)
Physician decision	1 (0.6)	1 (0.9)	2 (0.7)
Pregnancy	0	2 (1.8)	2 (0.7)
Poor compliance	1 (0.6)	1 (0.9)	2 (0.7)
Start new anti-cancer therapy	0	2 (1.8)	2 (0.7)
Other[a]	7 (4.5)	5 (4.4)	12 (4.4)

Category	ROS1 TKI-Naïve N=157	ROS1 TKI-Pretreated N=113	Overall N=270
Study disposition, n (%)			
Ongoing	118 (75.2)	65 (57.5)	183 (67.8)
Discontinued	39 (24.8)	48 (42.5)	87 (32.2)
Death	36 (22.9)	42 (37.2)	78 (28.9)
Lost to follow-up	2 (1.3)	2 (1.8)	4 (1.5)
Withdraw consent	1 (0.6)	3 (2.7)	4 (1.5)
Other[b]	0	1 (0.9)	1 (0.4)

Abbreviations: CSR, clinical study report; N, total number of participants; n, subset of total number of participants; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Pooled studies include AB-106-C203 and G208.
Note: Percentage was calculated based on the REP.
[a] Other reasons include abnormal liver function/disease progression, comprehensive assessment determined participant did not benefit, personal reasons (unwilling to tell), outside physician stopped the study drug when participant became unable to take oral meds, and withdrawal by participant.
[b] Other reason: participant refuses follow-up visit.
Source: ISE Table 1.1.A2, CSR AB-106-G208 Listing 16.2.1.3, CSR AB-106-C203 Listing 16.2.1.3

Table 21. Applicant - Demographics and Baseline Characteristics Across Studies

Category	ROS1 TKI-Naïve (N=157)	ROS1 TKI-Pretreated (N=113)	Overall (N=270)
Sex, n (%)			
Male	70 (44.6)	46 (40.7)	116 (43.0)
Female	87 (55.4)	67 (59.3)	154 (57.0)
Age (years)			
Median	57.0	53.0	56.0
Min, Max	26, 82	27, 79	26, 82
Age category, n (%)			
<65 years	119 (75.8)	89 (78.8)	208 (77.0)
≥65 years to <75 years	33 (21.0)	20 (17.7)	53 (19.6)
≥75 years	5 (3.2)	4 (3.5)	9 (3.3)
Weight (kg) at baseline			
n (missing)	157 (0)	111 (2)	268 (2)
Mean ±std	62.989 (13.0759)	66.839 ± 12.7070	64.584 (13.0396)
Median	61.000	66.000	63.250

Category	ROS1 TKI-Naïve (N=157)	ROS1 TKI-Pretreated (N=113)	Overall (N=270)
Q1, Q3	54.000, 69.000	56.900, 75.000	55.000, 72.000
Min, Max	38.30, 115.00	40.00, 109.40	38.30, 115.00
Race, n (%)			
Asian	138 (87.9)	88 (77.9)	226 (83.7)
White	12 (7.6)	16 (14.2)	28 (10.4)
Other[a]	7 (4.5)	9 (8.0)	16 (5.9)
Region category 1, n (%)			
Western	21 (13.4)	26 (23.0)	47 (17.4)
Asia	136 (86.6)	87 (77.0)	223 (82.6)
ECOG at baseline, n (%)			
0	41 (26.1)	40 (35.4)	81 (30.0)
1	116 (73.9)	73 (64.6)	189 (70.0)
Smoking status, n (%)			
Never	102 (65.0)	77 (68.1)	179 (66.3)
Former	47 (29.9)	34 (30.1)	81 (30.0)
Current	8 (5.1)	2 (1.8)	10 (3.7)
Disease stage at enrollment, n (%)			
III	14 (8.9)	3 (2.7)	17 (6.3)
IV	143 (91.1)	110 (97.3)	253 (93.7)
Prior chemotherapy, n (%)			
Yes	30 (19.1)	42 (37.2)	72 (26.7)
No	127 (80.9)	71 (62.8)	198 (73.3)
Lines of prior anti-cancer therapy, n (%)			
0	126 (80.3)	0	126 (46.7)
1	27 (17.2)	79 (69.9)	106 (39.3)
2	3 (1.9)	33 (29.2)	36 (13.3)
≥3	1 (0.6)	1 (0.9)	2 (0.7)
Prior TKI therapy, n (%)			
Entrectinib	0	10 (8.8)	10 (3.7)
Crizotinib	0	103 (91.2)	103 (38.1)

Category	ROS1 TKI-Naïve (N=157)	ROS1 TKI-Pretreated (N=113)	Overall (N=270)
Brain metastasis by IRC at baseline-mRECIST v1.1, n (%)			
No	120 (76.4)	58 (51.3)	178 (65.9)
Yes	37 (23.6)	55 (48.7)	92 (34.1)
Measurable	17 (10.8)	32 (28.3)	49 (18.1)
Non-measurable	20 (12.7)	23 (20.4)	43 (15.9)
Tumor type at enrollment			
Adenocarcinoma	152 (96.8)	107 (94.7)	259 (95.9)
Squamous cell carcinoma	1 (0.6)	4 (3.5)	5 (1.9)
Adeno-squamous carcinoma	3 (1.9)	2 (1.8)	5 (1.9)
Unknown	1 (0.6)	0	1 (0.4)
Study ID, n (%)			
AB-106-C203	103 (65.6)	66 (58.4)	169 (62.6)
AB-106-G208	54 (34.4)	47 (41.6)	101 (37.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; Max, maximum; Min, minimum; mRECIST, modified Response Evaluation Criteria in Solid Tumors; N, total number of participants; n, subset of total number of participants; Q1, first quartile; Q3, third quartile; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; std, standard deviation; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the Response Evaluable Population (REP).
[a] Other race includes 14 unknown (13 from France and 1 from Spain) and 2 Black or African American participants (both from North America).
Source: ISE Table 1.1.1.A2

The Applicant's Position:

The REP included 157 response evaluable participants in the treatment-naïve cohort and 113 participants in the pretreated cohort.

As of the NDA data cutoff (07 Jun 2024), in the ROS1 TKI-naïve cohort, the median follow-up time was 20.73 months; the majority of participants (118/157, 75.2%) remain in the study and over half (53.5%) have treatment ongoing. In the ROS1 TKI-pretreated cohort, the median follow-up time was 21.03 months; the majority of participants (65/113, 57.5%) remain in the study and 40 (35.4%) have treatment ongoing (Module 2.7.3 Table 8).

As of the 90-day safety update data cutoff (28 Oct 2024), in the ROS1 TKI-naïve cohort, the median follow-up time was 25.43 months; the majority of participants (111/157, 70.7%) remain in the study and over half (51.0%) have treatment ongoing. In the ROS1 TKI-pretreated cohort, the median follow-up time was 25.72 months; approximately half of participants (55/113, 48.7%) remain in the study and 27 (23.9%) have treatment ongoing (90-day ISE Table 3.6.1.1.A1, Table 1.1.A2).

In both the ROS1 TKI-naïve and ROS1 TKI-pretreated cohorts, a higher proportion of participants were female, under 65 years old, were never smokers, and had an ECOG performance status of 1 at baseline. A large majority of participants enrolled with adenocarcinoma and had Stage IV disease at enrollment. Among the 270 participants in the primary efficacy analysis population, 47 (17.4%) enrolled in North America and Europe and 223 (82.6%) enrolled in Asia.

In the ROS1 TKI-naïve cohort, 19.1% of participants had received prior chemotherapy. All participants were ROS1 TKI naïve. Approximately 24% of participants had brain metastasis at baseline.

In the ROS1 TKI-pretreated cohort, 37.2% of participants had received prior chemotherapy. All participants had received at least 1 line of prior ROS1 TKI therapy; 8.8% were previously treated with entrectinib and 91.2% were previously treated with crizotinib. Approximately 49% of participants had brain metastasis at baseline (Module 2.7.3 Table 10).

The FDA's Assessment:
FDA acknowledges the description of patient disposition noting that given the differences in follow-up between trials, these results are better interpreted within the context of each trial and each ROS-TKI naïve or pre-treated cohort. FDA acknowledges the presentation of demographics and baseline characteristics in the pooled populations separated by ROS1-TKI status. Refer to **Sections 8.1.3** and **8.1.5** for presentation of this data for each trial.

8.1.1.6. Integrated Efficacy Analysis Results

IRC-Assessed Efficacy Results

Data:

Table 22. Applicant - IRC-Assessed Efficacy in ROS1 TKI-Naïve and -Pretreated Participants Across Studies

	ROS1 TKI-Naïve			ROS1 TKI-Pretreated		
Category	**G208 N=54**	**C203 N=103**	**Pooled N=157**	**G208 N=47**	**C203 N=66**	**Pooled N=113**
Best overall response, n (%)						
CR	3 (5.6)	5 (4.9)	**8 (5.1)**	5 (10.6)	0	**5 (4.4)**
PR	43 (79.6)	88 (85.4)	**131 (83.4)**	24 (51.1)	34 (51.5)	**58 (51.3)**
SD	5 (9.3)	5 (4.9)	**10 (6.4)**	15 (31.9)	21 (31.8)	**36 (31.9)**
PD	2 (3.7)	3 (2.9)	**5 (3.2)**	3 (6.4)	5 (7.6)	**8 (7.1)**
NE	1 (1.9)	2 (1.9)	**3 (1.9)**	0	6 (9.1)	**6 (5.3)**
Objective response[a] rate (CR + PR), n (%)	46 (85.2)	93 (90.3)	**139 (88.5)**	29 (61.7)	34 (51.5)	**63 (55.8)**
Two-sided 95% CI[a]	[72.88, 93.38]	[82.87, 95.25]	**[82.49, 93.06]**	[46.38, 75.49]	[38.88, 64.01]	**[46.11, 65.09]**
Disease control rate (CR + PR + SD), n (%)	51 (94.4)	98 (95.1)	**149 (94.9)**	44 (93.6)	55 (83.3)	**99 (87.6)**
Two-sided 95% CI[a]	[84.61, 98.84]	[89.03, 98.41]	**[90.21, 97.77]**	[82.46, 98.66]	[72.13, 91.38]	**[80.09, 93.06]**
DOR[b] (months)						
Median [95% CI]	NR, [20.63, NR]	NR, [30.39, NR]	**43.3, [30.39, NR]**	19.4, [10.74, NR]	13.2, [7.66, 24.87]	**14.7, [10.61, 24.87]**

	ROS1 TKI-Naïve			ROS1 TKI-Pretreated		
Category	**G208 N=54**	**C203 N=103**	**Pooled N=157**	**G208 N=47**	**C203 N=66**	**Pooled N=113**
Min; Max	1.4+; 30.4+	1.1; 46.9+	**1.1; 46.9+**	1.7+; 30.4+	1.4; 38.7+	**1.4; 38.7+**
DOR rates [95% CI][c] up to						
6 months	91.1 [78.03, 96.57]	93.1 [85.28, 96.84]	**92.4 [86.36, 95.85]**	89.3 [70.36, 96.41]	83.9 [65.50, 92.95]	**86.4 [74.65, 92.97]**
12 months	74.2 [58.14, 84.83]	83.6 [73.87, 89.95]	**80.5 [72.50, 86.39]**	68.0 [45.39, 82.78]	55.9 [36.27, 71.63]	**61.5 [47.05, 73.09]**
18 months	68.0 [50.98, 80.19]	78.5 [68.01, 85.89]	**75.2 [66.56, 81.88]**	56.1 [32.45, 74.26]	41.0 [23.03, 58.18]	**47.3 [32.67, 60.57]**
24 months	60.4 [38.97, 76.42]	75.3 [64.22, 83.41]	**71.4 [61.99, 78.81]**	46.7 [21.91, 68.28]	31.9 [15.27, 50.01]	**38.3 [23.76, 52.59]**
36 months	0 [NR, NR]	61.2 [47.16, 72.56]	**58.3 [45.75, 68.93]**	0 [NR, NR]	16.0 [4.36, 34.16]	**22.6 [8.35, 41.02]**
Range of observed response[d] (months)						
≥6 months	39 (84.8)	80 (86.0)	**119 (85.6)**	24 (82.8)	25 (73.5)	**49 (77.8)**
≥12 months	29 (63.0)	67 (72.0)	**96 (69.1)**	13 (44.8)	15 (44.1)	**28 (44.4)**
≥18 months	14 (30.4)	57 (61.3)	**71 (51.1)**	7 (24.1)	11 (32.4)	**18 (28.6)**
≥24 months	4 (8.7)	33 (35.5)	**37 (26.6)**	5 (17.2)	6 (17.6)	**11 (17.5)**
≥36 months	NR	24 (25.8)	**24 (17.3)**	NR	1 (2.9)	**1 (1.6)**
PFS (months)[e]						
Median [95% CI]	NR, [15.87, NR]	44.6, [30.72, NR]	**44.6, [29.11, NR]**	11.8, [7.66, 20.57]	7.6, [5.52, 11.96]	**9.7, [7.43, 11.96]**

	ROS1 TKI-Naïve			ROS1 TKI-Pretreated		
Category	**G208 N=54**	**C203 N=103**	**Pooled N=157**	**G208 N=47**	**C203 N=66**	**Pooled N=113**
Min; Max	0.5; 31.6+	0.0; 48.3+	**0.0; 48.3+**	1.2; 31.6+	0.0; 42.8+	**0.0; 42.8+**
PFS rates [95% CI][c] up to						
6 months	81.0 [67.58, 89.31]	87.8 [79.47, 92.88]	**85.4 [78.72, 90.16]**	65.6 [50.11, 77.35]	58.5 [44.92, 69.81]	**61.5 [51.56, 70.06]**
12 months	73.0 [58.67, 83.06]	76.9 [67.03, 84.16]	**75.6 [67.74, 81.73]**	42.3 [27.00, 56.84]	37.1 [24.48, 49.74]	**39.4 [29.53, 49.04]**
18 months	60.8 [45.22, 73.21]	72.1 [61.77, 80.15]	**68.3 [59.90, 75.38]**	34.6 [19.58, 50.16]	26.2 [15.05, 38.75]	**29.4 [20.06, 39.30]**
24 months	53.2 [33.32, 69.61]	69.3 [58.49, 77.77]	**64.9 [55.97, 72.50]**	29.7 [14.86, 46.11]	24.0 [13.31, 36.45]	**26.3 [17.25, 36.21]**
36 months	0 [NR, NR]	56.3 [43.24, 67.43]	**53.0 [41.47, 63.22]**	0 [NR, NR]	9.0 [2.52, 20.70]	**13.1 [5.02, 25.22]**
OS[e] (months)						
Median [95% CI]	NR, [NR, NR]	NR, [41.56, NR]	**NR, [41.56, NR]**	NR, [15.70, NR]	25.6, [19.22, 31.90]	**26.7, [22.31, 40.80]**
Min; Max	0.5; 33.4+	0.9; 49.8+	**0.5; 49.8+**	1.4; 33.2+	0.8; 45.3	**0.8; 45.3**
OS rates [95% CI][c] up to						
12 months	90.6 [78.85, 95.97]	89.3 [81.55, 93.94]	**89.7 [83.78, 93.58]**	84.3 [69.82, 92.19]	75.3 [62.84, 84.06]	**78.8 [69.84, 85.40]**
24 months	74.4 [57.40, 85.38]	79.5 [70.37, 86.15]	**78.1 [70.43, 84.03]**	65.5 [47.48, 78.70]	55.9 [42.75, 67.09]	**58.4 [47.69, 67.66]**

	ROS1 TKI-Naïve			ROS1 TKI-Pretreated		
Category	**G208 N=54**	**C203 N=103**	**Pooled N=157**	**G208 N=47**	**C203 N=66**	**Pooled N=113**
36 months	0 [NR, NR]	68.4 [56.96, 77.34]	**67.4 [57.03, 75.82]**	0 [NR, NR]	36.2 [22.97, 49.62]	**41.0 [28.45, 53.07]**

Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; IRC, Independent Review Committee; Max, maximum; Min, minimum; N, total number of participants; n, subset of total number of participants; NE, not evaluable; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.

Note: Analysis was based on the Response Evaluable Population (REP).

Note: Data cutoff date was 07 Jun 2024 for best overall response, ORR, and DCR. Data cutoff date was 28 Oct 2024 for DOR, PFS, and OS.

[a] Objective response (CR or PR) was assessed by an IRC per RECIST v1.1. For the ORR and DCR, the method of Clopper and Pearson was used to calculate confidence interval.

[b] DOR was calculated among the participants with confirmed response and product-limit (Kaplan-Meier estimates), and CIs for the median were calculated according to Brookmeyer and Crowley.

[c] Percentage was based on Kaplan-Meier estimates.

[d] Percentage of observed DOR was calculated based on the following equation: Number of participants with DOR greater than or equal to the specified time point/total number of objective responders.

[e] Product-limit (Kaplan-Meier estimates) CIs for the median were calculated according to Brookmeyer and Crowley.

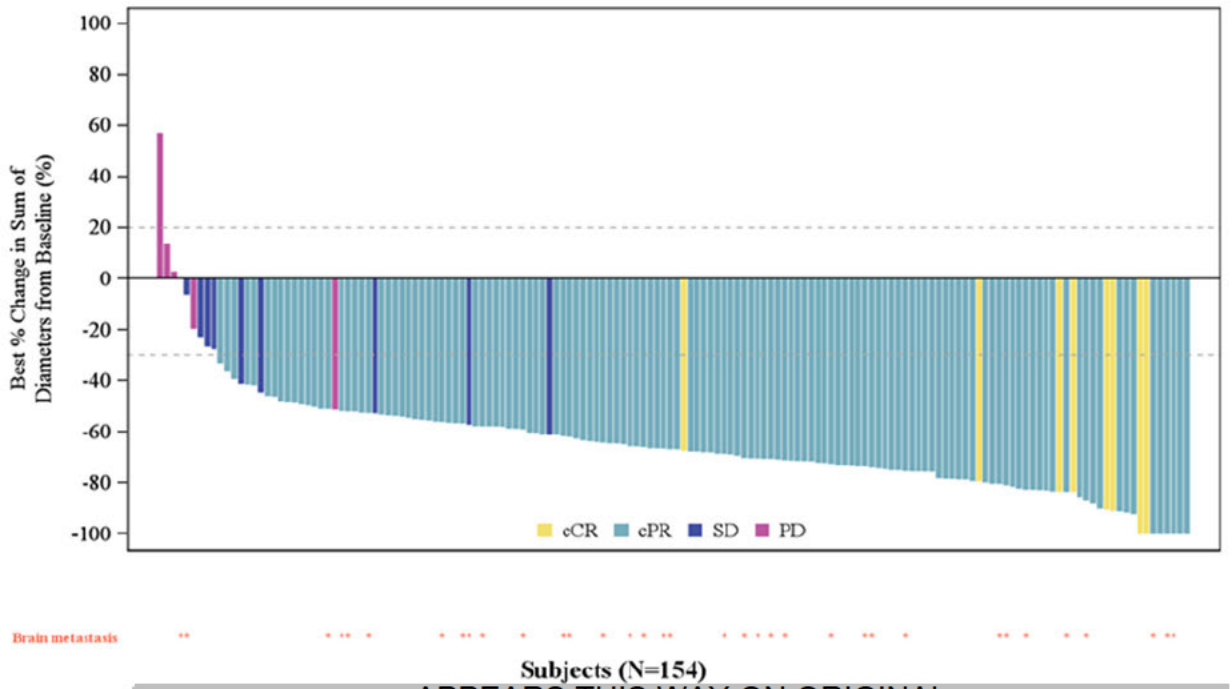
Source: CSR AB-106-G208 Table 18; 90-day G208 Table 14.2.2.1.1, 90-day G208 Table 14.2.2.2.1, 90-day G208 Table 14.2.3.1.1, 90-day G208 Table 14.2.3.2.1,90-day G208 Table 14.2.5.1.1, 90-day G208 Table 14.2.5.2.1; CSR AB-106-C203 Table 20, AB-106-C203 Table 14.2.1.1.1.A2; 90-day C203 Table 14.2.2.1.1.A1, 90-day C203, Table 14.2.2.2.1, 90-day C203 Table 14.2.3.1.1.A1, 90-day C203 Table. 14.2.3.2.1, 90-day C203 Table 14.2.5.1.1.A1, 90-day C203 Table 14.2.5.2.1; ISE Table 3.1.1.1.A2, ISE Table 3.1.2.1; 90-day ISE Table 3.2.1.1.A1, 90-day ISE Table 3.2.2, 90-day ISE Table 3.3.1.1.A1, 90-day ISE Table 3.3.2.1, 90-day ISE Table 3.4.1.1, 90-day ISE Table 3.4.2.1

Table 23. Applicant - IRC-Assessed Tumor Response in Treatment-Naïve and Pretreated Participants With and Without Prior Chemotherapy

Category	ROS1 TKI-Naïve			ROS1 TKI-Pretreated		
	With Prior Chemo N=30	Without Prior Chemo N=127	All ROS1 TKI-Naïve N=157	With Prior Chemo N=42	Without Prior Chemo N=71	All ROS1 TKI-Pretreated N=113
Responders by IRC (n)	26	113	139	25	38	63
Best overall response, n (%)						
CR	2 (6.7)	6 (4.7)	8 (5.1)	3 (7.1)	2 (2.8)	5 (4.4)
PR	24 (80.0)	107 (84.3)	131 (83.4)	22 (52.4)	36 (50.7)	58 (51.3)
SD	2 (6.7)	8 (6.3)	10 (6.4)	9 (21.4)	27 (38.0)	36 (31.9)
PD	2 (6.7)	3 (2.4)	5 (3.2)	4 (9.5)	4 (5.6)	8 (7.1)
Not evaluable	-	3 (2.4)	3 (1.9)	4 (9.5)	2 (2.8)	6 (5.3)
IRC ORR % [95% CI]	86.7 [69.28, 96.24]	89.0 [82.20, 93.84]	88.5 [82.49, 93.06]	59.5 [43.28, 74.37]	53.5 [41.29, 65.45]	55.8 [46.11, 65.09]
DCR, n (%) [95% CI]	28 (93.3) [77.93, 99.18]	121 (95.3) [90.00, 98.25]	149 (94.9) [90.21, 97.77]	34 (81.0) [65.88, 91.40]	65 (91.5) [82.51, 96.84]	99 (87.6) [80.09, 93.06]

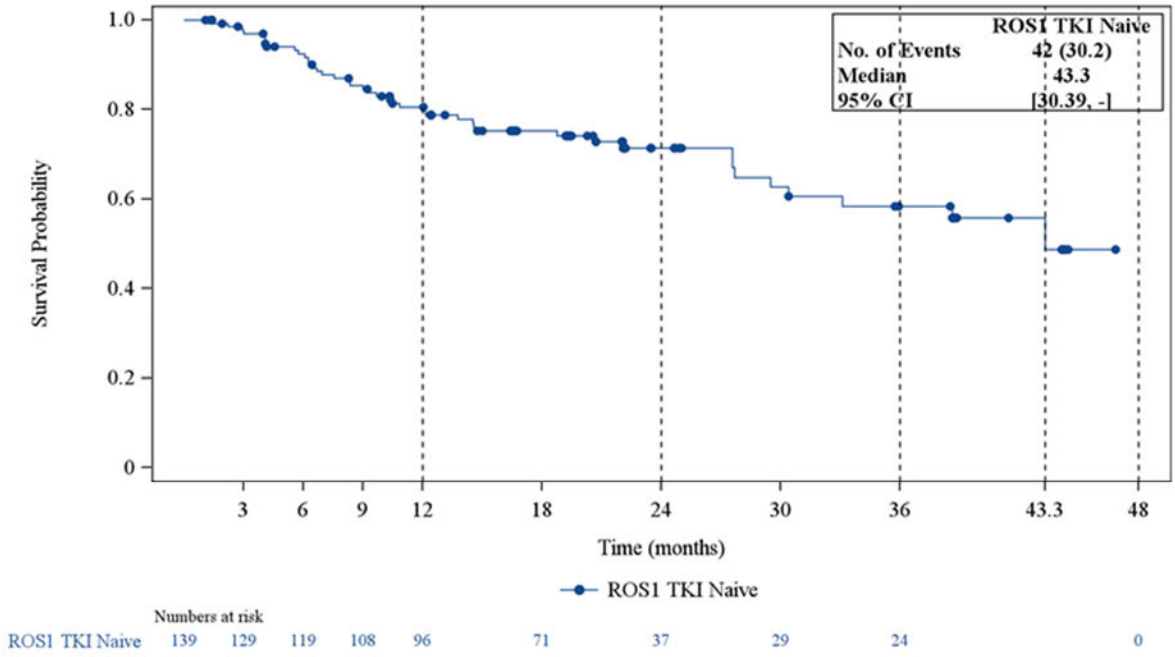
Abbreviations: Chemo, chemotherapy; CI, confidence interval; CR, complete response; DCR, disease control rate; IRC, Independent Review Committee; N, total number of participants; n, subset of total number of participants; ORR, objective response rate; PD, progressive disease; PR, partial response; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the Response Evaluable Population (REP).
Source: ISE Table 3.1.1.2.A2, ISE Table 3.1.1.1.A2, ISE Table 3.1.2.2, and ISE Table 3.1.2.1

Figure 7. Applicant - Best Percent Change From Baseline in Target Lesion Sum of Diameters: ROS1 TKI-Naïve Cohort



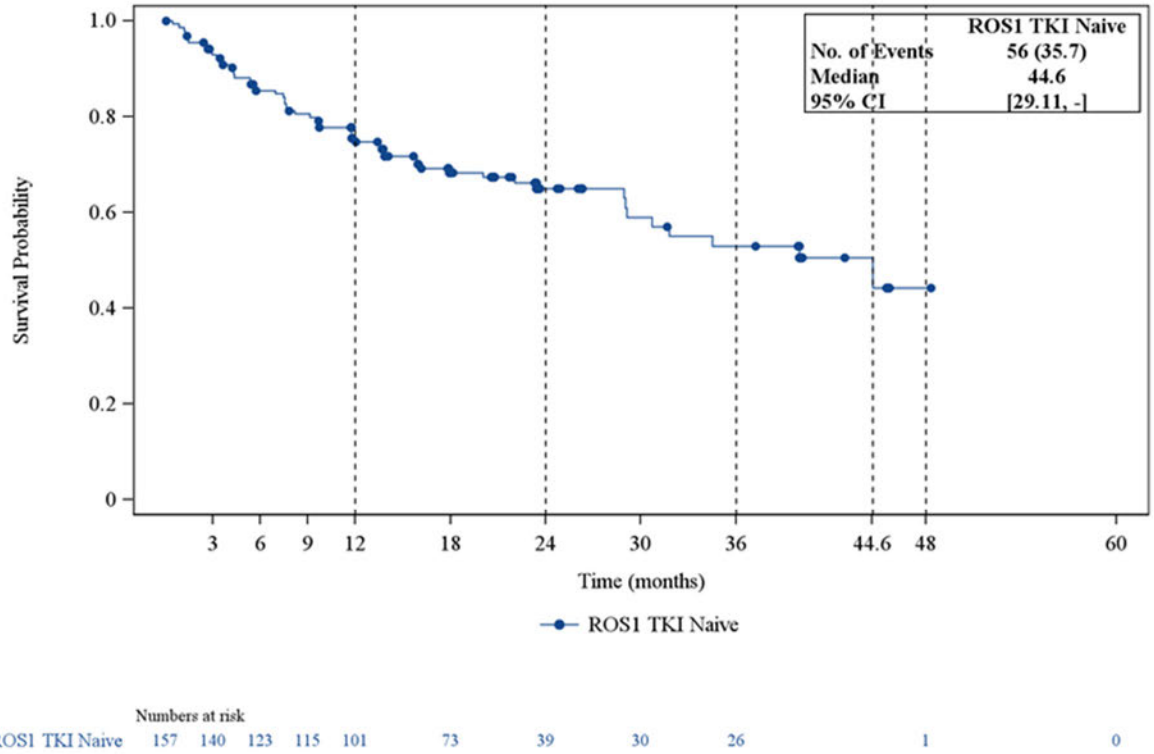
Abbreviations: cCR, confirmed complete response; cPR, confirmed partial response; IRC, Independent Review Committee; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor
Note: Analysis was based on the REP.
Note: Brain Metastasis: Indicating participants with brain lesion at baseline assessed by IRC according to mRECIST v1.1.
Note: Participants (n=3) with confirmed best overall response as not evaluable are not displayed in the figure.
Note: There is 1 participant with best % change as 0 and confirmed best overall response as SD, respectively.
Source: ISE Figure 3.1.1.1.A2

Figure 8. Applicant - Duration of Response in ROS1 TKI-Naïve Cohort



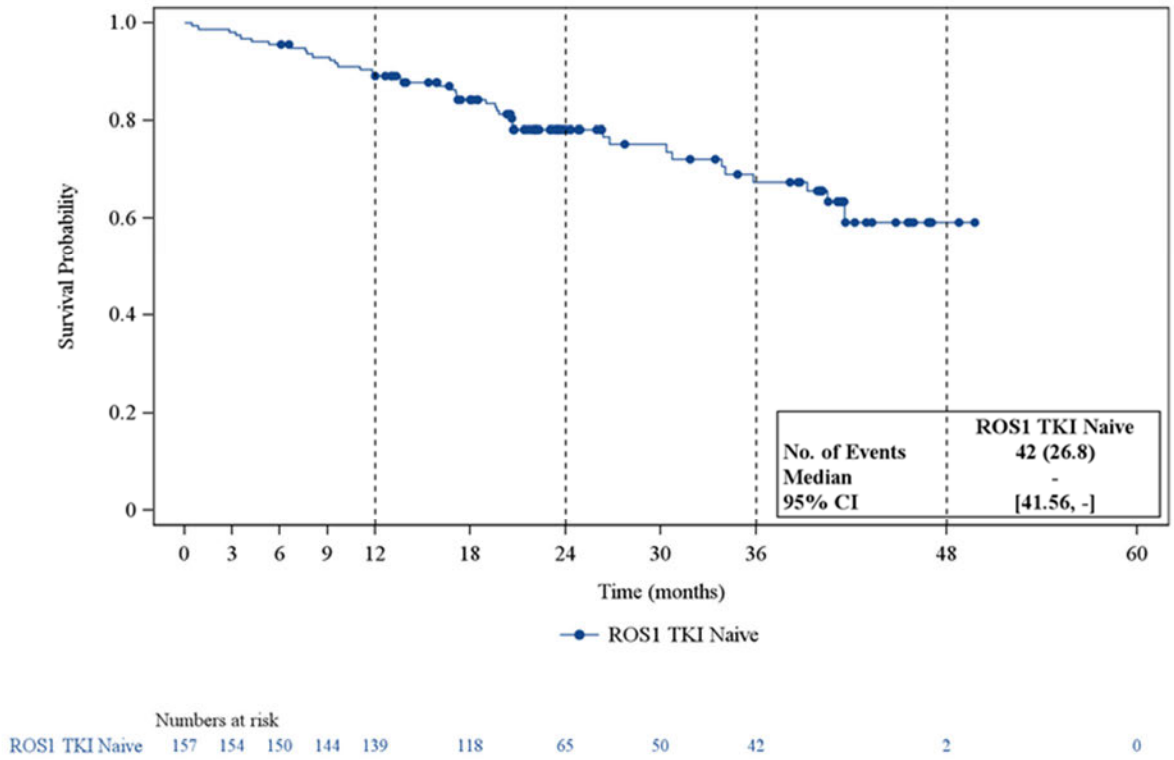
Abbreviations: CI, confidence interval; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Only participants who had confirmed response were included.
Note: Data cutoff of 28 Oct 2024.
Source: 90-day ISE Figure 3.2.1.1.A1

Figure 9. Applicant - Progression-Free Survival in ROS1 TKI-Naïve Cohort



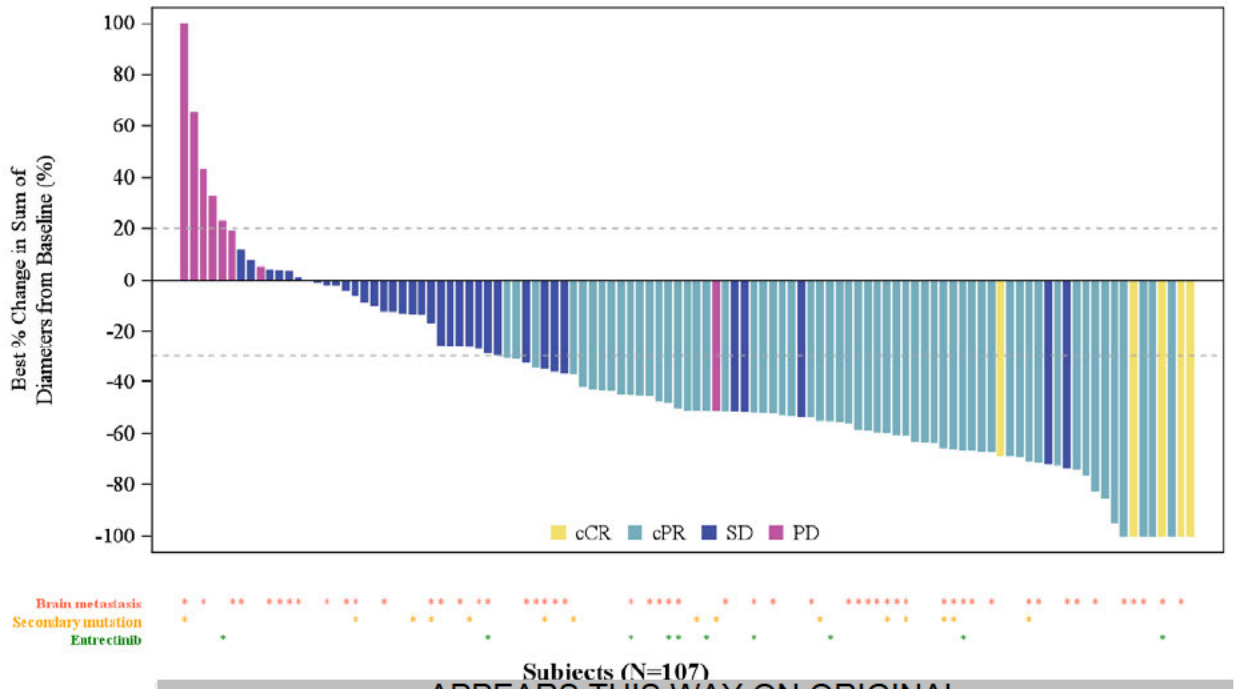
Abbreviations: CI, confidence interval; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Data cutoff of 28 Oct 2024.
Source: 90-day ISE Figure 3.3.1.1.A1

Figure 10. Applicant - Overall Survival in ROS1 TKI-Naïve Cohort



Abbreviations: CI, confidence interval; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Data cutoff of 28 Oct 2024.
Source: 90-day ISE Figure 3.4.1.1.A1

Figure 11. Applicant - Best Percent Change From Baseline in Target Lesion Sum of Diameters: ROS1 TKI-Pretreated Cohort



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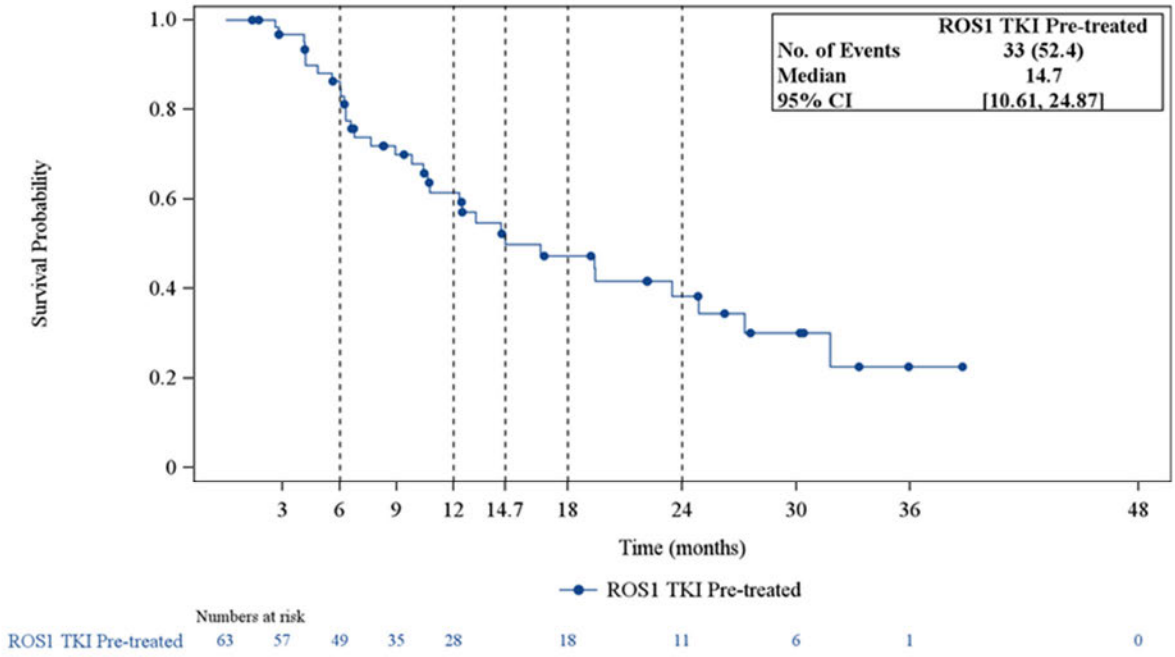
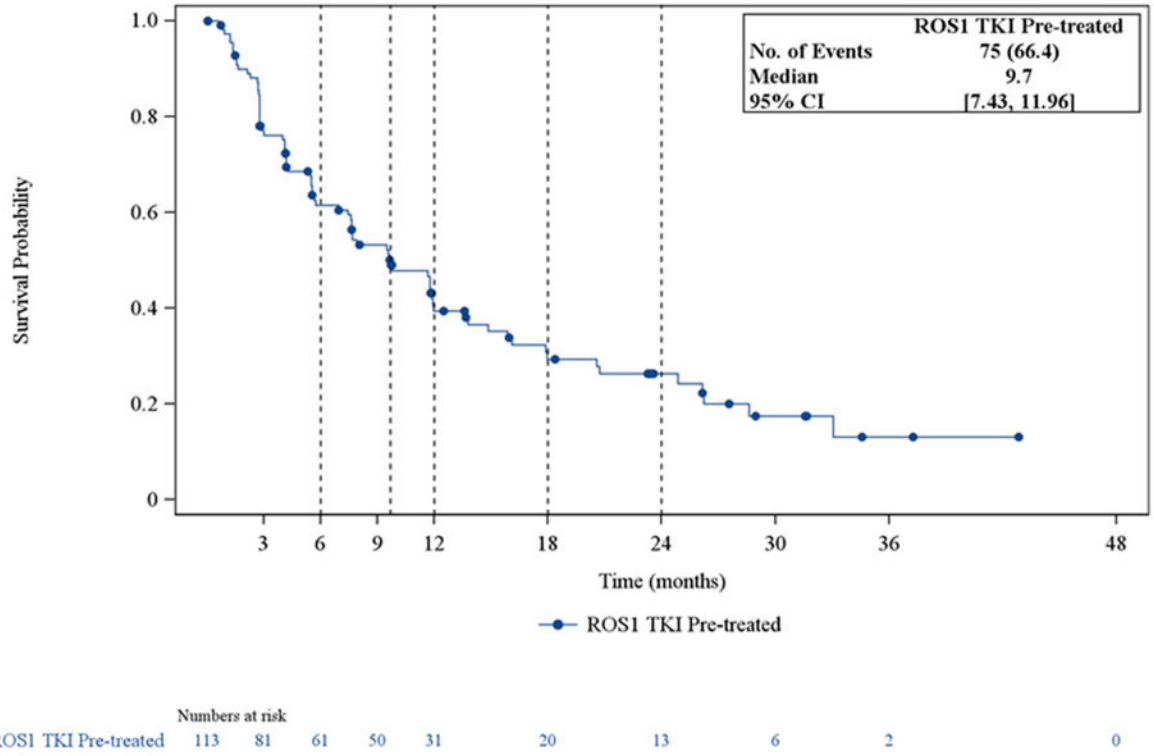
Abbreviations: cCR, confirmed complete response; cPR, confirmed partial response; IRC, Independent Review Committee; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PD, progressive disease; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Target lesion sum of longest diameters of one participant had increased 136.5%, which was cut at 100% in the figure due to page size limit.
Note: Brain Metastasis: Indicating participants with brain lesion at baseline assessed by IRC according to mRECIST v1.1.
Note: Participants (n=6) with confirmed best overall response as not evaluable are not displayed in the figure.
Note: There is 1 participant with best % change as 0 and confirmed best overall response as SD, respectively.
Source: ISE Figure 3.1.2.1

Figure 12. Applicant - Duration of Response in ROS1 TKI-Pretreated Cohort



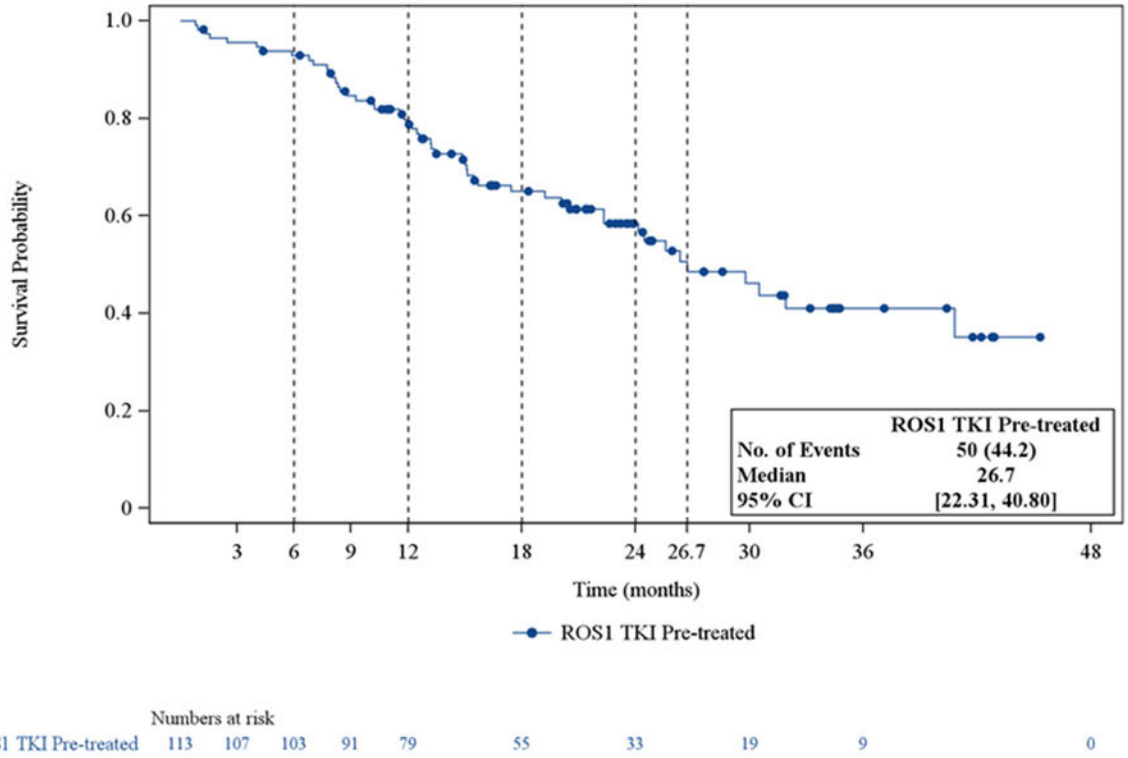
Abbreviations: CI, confidence interval; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Data cutoff of 28 Oct 2024.
Note: Only participants who had confirmed response were included.
Source: 90-day ISE Figure 3.2.2.1

Figure 13. Applicant - Progression-Free Survival in ROS1 TKI-Pretreated Cohort



Abbreviations: CI, confidence interval; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Data cutoff of 28 Oct 2024.
Source: 90-day ISE Figure 3.3.2.1

Figure 14. Applicant - Overall Survival in ROS1 TKI-Pretreated Cohort



Abbreviations: CI, confidence interval; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Data cutoff of 28 Oct 2024.
Source: 90-day ISE Figure 3.4.2.1

The Applicant's Position:

A full summary of efficacy endpoints from the individual studies and pooled data from both studies is provided in **Table 22**. The maximum reduction in target lesion size from baseline based on integrated efficacy results for the ROS1 TKI-naïve cohort and the ROS1 TKI-pretreated cohort are presented in **Figure 7** and **Figure 11**, respectively.

Based on available data, taletrectinib demonstrated clinically meaningful efficacy in participants with advanced ROS1+ NSCLC regardless of ROS1 TKI treatment history:

- The cORR by IRC assessment was 88.5% and 55.8% for ROS1 TKI-naïve and -pretreated participants, respectively.
- Responses occurred quickly and were durable (at the 28 Oct 2024 cutoff, ROS1 TKI-naïve participants: median DOR [mDOR], 43.3 months [**Figure 8**]; Kaplan-Meier estimate at 36 months, 58.3%; ROS1 TKI-pretreated participants: mDOR, 14.7 months [**Figure 12**]; Kaplan-Meier estimate at 24 months, 38.3%).

- The confirmed DCR was 94.9% and 87.6% for ROS1 TKI-naïve and -pretreated participants by IRC assessment, respectively.
- The control of disease also contributed to the prolonged PFS (median PFS [mPFS] was 44.6 months for ROS1 TKI-naïve [**Figure 9**] and 9.7 months for ROS1 TKI-pretreated participants [**Figure 13**] at the 28 Oct 2024 cutoff).
- The median OS (mOS) was not reached for the ROS1 TKI-naïve cohort (**Figure 10**) and at 36 months, the estimated OS rate was 67.4%; for the ROS1 TKI-pretreated cohort, the mOS was 26.7 months (**Figure 14**) and at 12 months, the estimated OS was 78.8% at the 28 Oct 2024 cutoff.
- Within the ROS1 TKI-naïve and ROS1 TKI-pretreated populations, the ORRs were comparable in subgroups of participants who received prior chemotherapy compared to those who did not receive prior chemotherapy (**Table 23**).

Investigator-assessed Efficacy Results – Sensitivity Analysis

The REP2 (defined in **Section 8.1.1.1**) included a total of 158 participants in the treatment-naïve cohort and 116 participants in the pretreated cohort. The investigator-assessed endpoints were similar to the IRC-assessed efficacy endpoints for both ROS1 TKI-naïve and ROS1 TKI-pretreated cohorts:

- ROS1 TKI-naïve participants: cORR 84.2%, DCR 94.9% (as of 07 Jun 2024); mDOR 39.1 months, mPFS 31.8 months (as of 28 Oct 2024)
- ROS1 TKI-pretreated participants: cORR 51.7%, DCR 87.1% (as of 07 Jun 2024); mDOR 12.4 months, mPFS 7.7 months (as of 28 Oct 2024)

Supplementary Analysis – IRC-assessed Efficacy in Participants with ≥14 Months of Follow-up

The REP3 (defined in **Section 8.1.1.1**) included a total of 134 participants in the treatment-naïve cohort and 93 participants in the pretreated cohort, and the results provided additional supportive efficacy evidence:

- ROS1 TKI-naïve participants: cORR 90.3%, DCR 94.0% (as of 07 Jun 2024); mDOR 43.3 months, mPFS 44.6 months (as of 28 Oct 2024)
- ROS1 TKI-pretreated participants: cORR 54.8%, DCR 86.0% (as of 07 Jun 2024); mDOR 14.7 months, mPFS 9.6 months (as of 28 Oct 2024)

Intracranial Efficacy Results

Data:

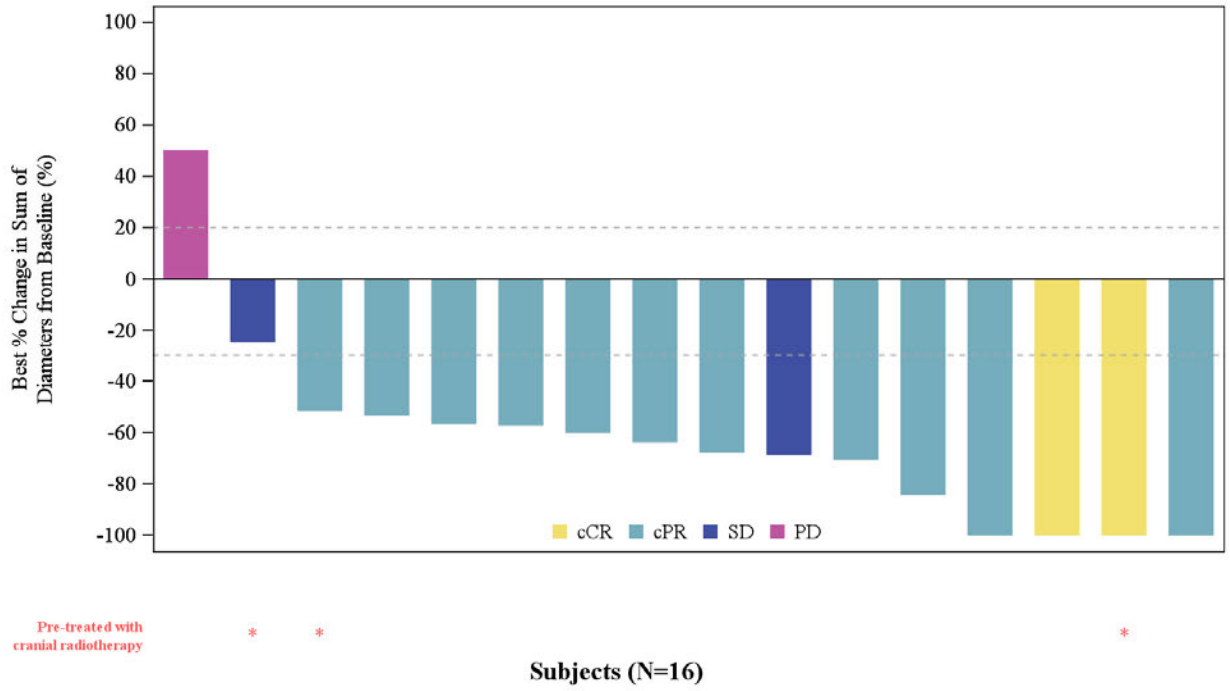
Table 24. Applicant - IRC-Assessed Intracranial Efficacy in ROS1 TKI-Naïve and -Pretreated Participants With Measurable Brain Lesions

Category	ROS1 TKI-Naïve N=17	ROS1 TKI-Pretreated N=32
Best overall response, n (%)		
CR	2 (11.8)	1 (3.1)
PR	11 (64.7)	20 (62.5)
SD	2 (11.8)	9 (28.1)
PD	1 (5.9)	1 (3.1)
NE	1 (5.9)	1 (3.1)
Objective response[a] rate (CR + PR), n (%)	13 (76.5)	21 (65.6)
Two-sided 95% CI	[50.10, 93.19]	[46.81, 81.43]
Disease control rate (CR + PR + SD), n (%)	15 (88.2)	30 (93.8)
Two-sided 95% CI	[63.56, 98.54]	[79.19, 99.23]
DOR		
Events/Censored (n)	9/4	13/8
Median DOR[b] (months) [95% CI]	14.7 [4.17, 30.23]	11.9 [6.93, 23.49]
Min; Max	2.9; 33.0+	2.7; 24.8+
DOR[b] rates [95% CI][c] up to		
6 months	76.9 [44.21, 91.91]	84.3 [58.71, 94.69]
12 months	51.3 [21.85, 74.58]	45.0 [21.96, 65.62]
24 months	32.1 [8.75, 58.77]	13.1 [0.92, 41.50]
30 months	32.1 [8.75, 58.77]	NR
TTiP		
Events/Censored (n)	9/8	20/12
Median TTiP (months)[d] [95% CI]	16.0 [5.19, NE]	11.7 [7.33, 15.51]
Min; Max	0.5; 34.5+	0.0; 26.2+

Category	ROS1 TKI-Naïve N=17	ROS1 TKI-Pretreated N=32
TTiP rates [95% CI][c] up to		
6 months	68.8 [40.46, 85.63]	74.4 [53.50, 86.98]
12 months	61.9 [33.93, 80.80]	39.2 [20.90, 57.06]
24 months	46.4 [20.41, 69.01]	20.3 [5.09, 42.62]
PFS (months)[d]		
Events/Censored (n)	12/5	23/9
Median PFS (months)[d] [95% CI]	13.8 [4.30, 31.70]	11.7 [5.59, 13.83]
Min; Max	0.5; 34.5+	0.0; 26.2+
PFS rates [95% CI][c] up to		
6 months	64.7 [37.71, 82.34]	69.3 [49.10, 82.75]
12 months	51.8 [26.16, 72.37]	36.5 [19.38, 53.79]
24 months	29.1 [8.80, 53.45]	17.0 [4.26, 37.01]

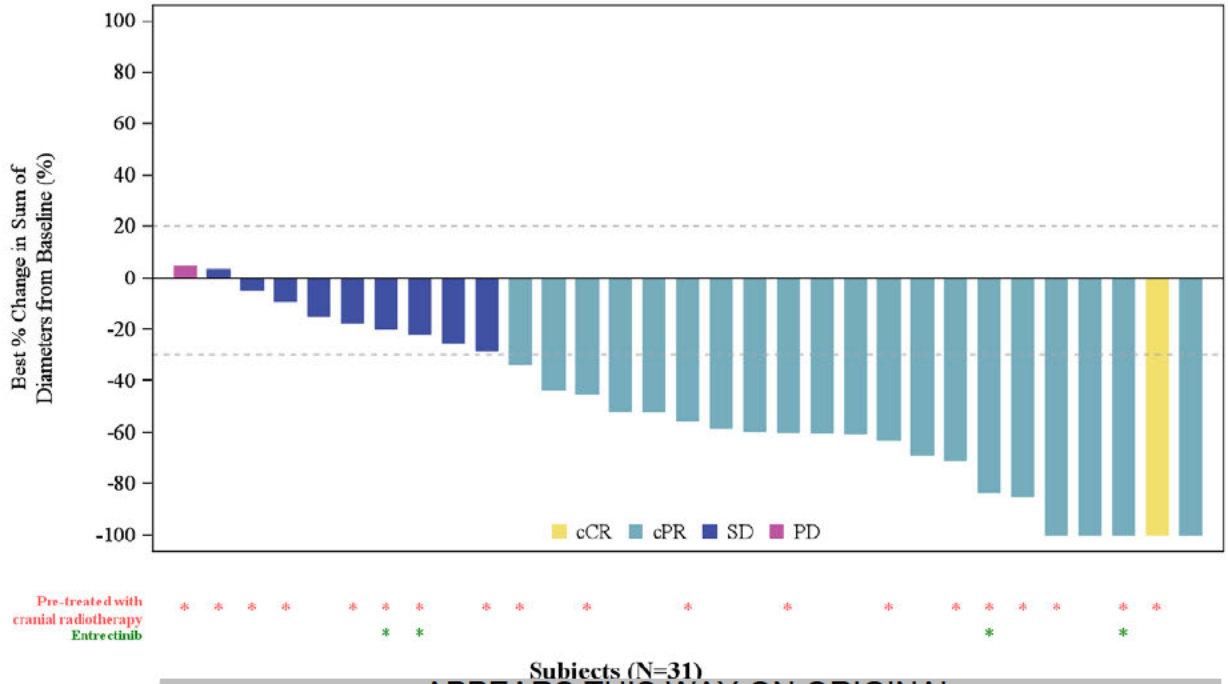
Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; IAP, Intracranial Analysis Population; IRC, Independent Review Committee; Max, maximum; Min, minimum; mRECIST, modified Response Evaluation Criteria in Solid Tumors; N, total number of participants; n, subset of total number of participants; NE, not evaluable; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor; TTiP, time to intracranial progression.
Note: Analysis was based on the IAP.
[a] Objective response (CR or PR) was assessed by an IRC per mRECIST v1.1 on measurable brain metastases.
[b] DOR was calculated among participants with confirmed response using Kaplan-Meier estimates.
[c] Percentage was based on Kaplan-Meier estimates.
[d] Product-limit (Kaplan-Meier estimates) CIs for the median are calculated according to Brookmeyer and Crowley.
Source: ISE Table 3.5.1.1, ISE Table 3.5.1.2, ISE Table 3.5.2.1, ISE Table 3.5.2.2, ISE Table 3.5.1.4, ISE Table 3.5.2.4, ISE Table 3.5.1.3, and ISE Table 3.5.2.3

Figure 15. Applicant - Maximum Change in Tumor Size in ROS1 TKI-Naïve Cohort



Abbreviations: cCR, confirmed complete response; cPR, confirmed partial response; IAP, Intracranial Analysis Population; PD, progressive disease; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the IAP.
Note: 1 participant with confirmed best overall response as not evaluable is not displayed in the figure.
Source: ISE Figure 3.5.1.1

Figure 16. Applicant - Maximum Change in Tumor Size in ROS1 TKI-Pretreated Cohort



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Abbreviations: cCR, confirmed complete response; cPR, confirmed partial response; IAP, Intracranial Analysis Population; PD, progressive disease; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the IAP.
Note: 1 participant with confirmed best overall response as not evaluable is not displayed in the figure. There is 1 participant with best percentage change as 0 and confirmed best overall response as SD, respectively.
Source: ISE Figure 3.5.2.1

The Applicant's Position:

The IAP (defined in **Section 8.1.1.1**) included a total of 17 participants in the treatment-naïve cohort and 32 participants in the pretreated cohort.

As of the data cutoff, intracranial taletrectinib activity was observed in participants with brain metastasis in the IAP (**Table 24**). In the ROS1 TKI-naïve cohort, an intracranial response occurred in 13 of 17 participants (76.5%; 95% CI: 50.10, 93.19), with 2 participants achieving a cCR and 11 participants achieving a cPR (**Figure 15**). In the ROS1 TKI-pretreated cohort, an IC response occurred in 21 of 32 participants (65.6%; 95% CI: 46.81, 81.43), with 1 participant achieving a cCR and 20 participants achieving a cPR (**Figure 16**).

Efficacy in Participants with G2032R Mutations

Data:

Table 25. Applicant - IRC-Assessed Efficacy in ROS1 TKI-Pretreated Cohort – Participants With G2032R Mutation at Baseline

Category	ROS1 TKI-Pretreated N=13
Best overall response, n (%)	
CR	0
PR	8 (61.5)
SD	4 (30.8)
PD	1 (7.7)
Not evaluable	0
Objective response rate (CR + PR), n (%)	8 (61.5)
Two-sided 95% CI[a]	[31.58, 86.14]
Disease control rate (CR + PR + SD), n (%)	12 (92.3)
Two-sided 95% CI[a]	[63.97, 99.81]

Abbreviations: CI, confidence interval; CR, complete response; IRC, Independent Review Committee; I mRECIST, modified Response Evaluation Criteria in Solid Tumors; N, total number of participants; n, subset of total number of participants; PD, progressive disease; PR, partial response; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Note: Brain metastatic status was based on mRECIST v1.1 by IRC in C203 and G208.
[a] The method of Clopper and Pearson is used to calculate CI.
Source: ISE Table 3.1.2.2

The Applicant's Position:

Of 32 participants in the ROS1 TKI-pretreated group who had a re-biopsied sample tested by next-generation sequencing after failure of crizotinib or entrectinib, there were 15 participants with resistance mutations at baseline; 13 of these 15 participants had a G2032R mutation at baseline. Responses were observed in 8 out of 13 participants with G2032R mutations (ORR of 61.5%), and all had cPR (**Table 25**).

The FDA's Assessment:

FDA generally agrees with Applicant's description of efficacy results, but notes that FDA did not consider it appropriate to present efficacy results using the pooled data in labeling due to differences in patient's baseline demographics and follow up duration across studies. As of data cut off October 28, 2024, the median follow-up time for patients in Study C203 was 40.9 months

(range: 22.0 to 50.1) and the median follow-up time for patients in Study G208 was 20.4 months (range: 8.6 to 34.5). Please refer to **Sections 8.1.3** and **8.1.5** for results presented by individual study.

Table 22 presents ORR according to the original DCO and DOR according to the October 2024 DCO. Although the ORR remained the same according to the October 2024 DCO, one patient in Study G208 who was ROS1 TKI-naïve with a PR demonstrated a confirmed CR. The FDA product labeling reflects the response according to the October 2024 DCO, with 7% of patients in the TKI-naïve cohort of Study G208 demonstrating a CR and 78% demonstrating a PR.

For IC-ORR in the IAP population (i.e., patients with at least one measurable brain metastatic lesion at baseline per mRECIST v1.1 by BICR assessment), FDA conducted a separate analysis excluding patients with brain metastases at baseline who received brain radiation within 60 days prior to the first dose of taletrectinib to account for the potential contribution of radiation to the observed treatment effect. The results of this analysis are presented **Table 26** and show consistent IC-ORR benefits in this subpopulation compared to the IAP population in **Table 24**.

Table 26. FDA Analysis - Intracranial Efficacy Results for Patients With *ROS1*-Positive NSCLC and Measurable CNS Metastases Excluding Those Who Received Brain Radiation Within 60 Days Prior to the First Dose Taletrectinib

Efficacy Parameters	ROS1 TKI-Naïve N=15	ROS1 TKI-Pretreated N=24
Confirmed IC-ORR, % (95% CI)	73% (45, 92)	63% (41, 81)
Complete Response	7%	4.1%
Partial Response	67%	58%
IC-ORR Responder	n= 11	n= 15
Range (months)	3.0, 38.5+	4.2, 24.8+

Abbreviations: CI = Confidence interval; IC = Intracranial; + indicating ongoing response
Source: ADSL, ADRS, ADTTE

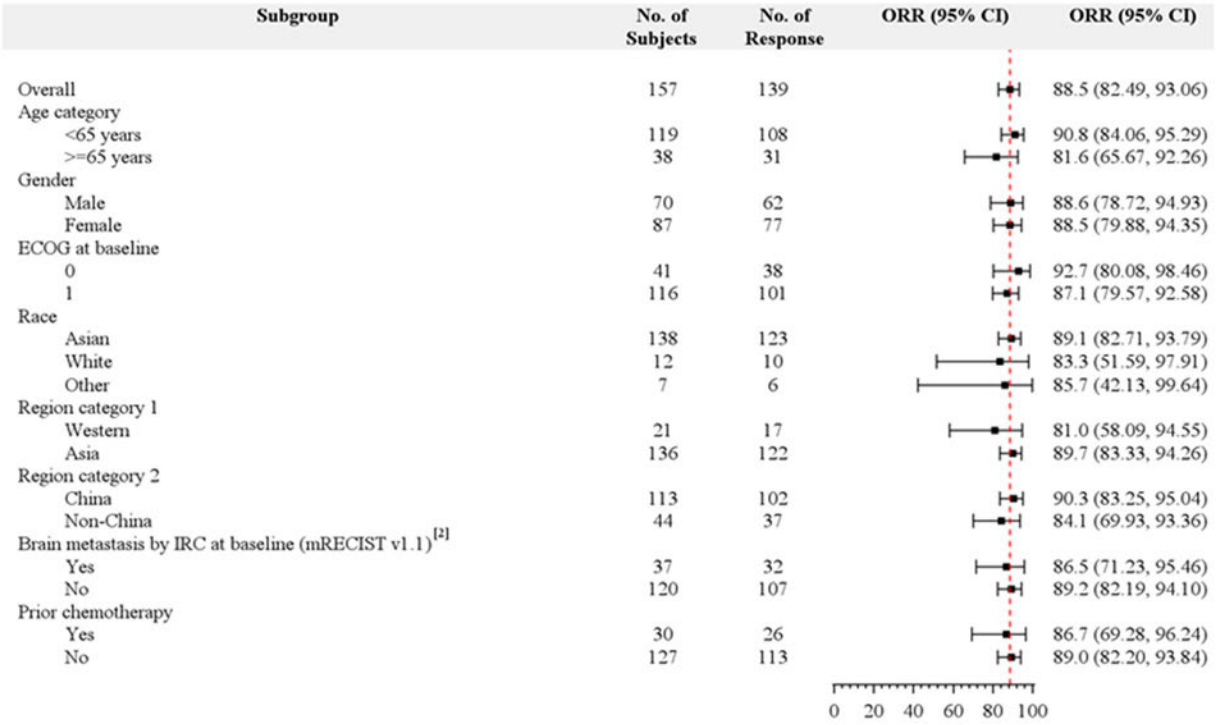
Of the 32 patients in the ROS1 TKI-pretreated group who had a re-biopsied sample after progression on crizotinib or entrectinib in Studies G208 and C203, 15 had resistance mutations including G2032R (n=13), G2032R & G2010A (n=1) and L2026M (n=1). Responses were observed in 8 of these 15 patients; all responding patients had tumors with solvent front mutation G2032R.

FDA acknowledges the Applicant's analyses of time-to-event endpoints such as PFS, OS and TTiP; however, these endpoints are difficult to interpret in a single arm trial and are considered exploratory.

8.1.1.7. Subpopulations

Data:

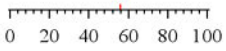
Figure 17. Applicant - Subgroup Analysis – IRC-Assessed Confirmed Objective Response Rate in ROS1 TKI-Naïve Participants



Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; REP, Response Evaluable Population; ROS1, c-os oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the Response Evaluable Population REP.
[2] Brain metastatic status was based on mRECIST v1.1 by IRC in C203 and G208.
Source: ISE Figure 3.1.1.4.A2

Figure 18. Applicant - Subgroup Analysis – IRC-Assessed Confirmed Objective Response Rate in ROS1 TKI-Pretreated Participants

Subgroup	No. of Subjects	No. of Response	ORR (95% CI)
Overall	113	63	55.8 (46.11, 65.09)
Age category			
<65 years	89	49	55.1 (44.14, 65.62)
>=65 years	24	14	58.3 (36.64, 77.89)
Gender			
Male	46	25	54.3 (39.01, 69.10)
Female	67	38	56.7 (44.04, 68.78)
ECOG at baseline			
0	40	20	50.0 (33.80, 66.20)
1	73	43	58.9 (46.77, 70.29)
Race			
Asian	88	46	52.3 (41.35, 63.04)
White	16	10	62.5 (35.43, 84.80)
Other	9	7	77.8 (39.99, 97.19)
Region category 1			
Western	26	17	65.4 (44.33, 82.79)
Asia	87	46	52.9 (41.87, 63.67)
Region category 2			
China	70	36	51.4 (39.17, 63.56)
Non-China	43	27	62.8 (46.73, 77.02)
Brain metastasis by IRC at baseline (mRECIST v1.1)[2]			
Yes	55	31	56.4 (42.32, 69.70)
No	58	32	55.2 (41.54, 68.26)
Prior chemotherapy			
Yes	42	25	59.5 (43.28, 74.37)
No	71	38	53.5 (41.29, 65.45)
Pre-treated with prior TKI therapy			
Entrectinib	10	8	80.0 (44.39, 97.48)
Crizotinib	103	55	53.4 (43.30, 63.29)
G2032R mutation at baseline			
Yes	13	8	61.5 (31.58, 86.14)
No	19	7	36.8 (16.29, 61.64)
Unavailable	81	48	59.3 (47.77, 70.05)



Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; REP, Response Evaluable Population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
[2] Brain metastatic status was based on mRECIST 1.1 by IRC in C203 and G208.

Source: ISE Figure 3.1.2.4

The Applicant's Position:

Best overall response by subgroup, including sex, age, region (Western, Asian), and race (Asian, White, Other) in the REP are presented in Module 2.7.3 Section 3.3 for ROS1 TKI-naïve participants and ROS1 TKI-pretreated participants. Across all subgroups, a consistent treatment effect on cORR was observed in the pooled analysis set in the subgroups analyzed, and the results were comparable and consistent. Subgroup analyses in G208 also showed similar consistency (presented in the Data Applicability justification).

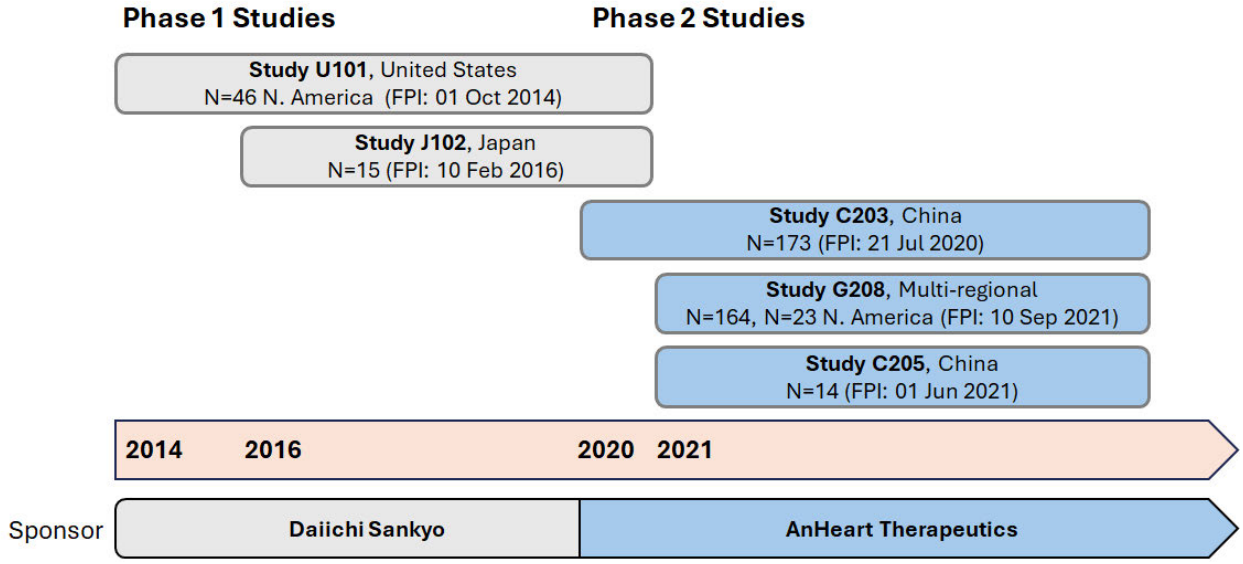
The FDA's Assessment:
FDA acknowledges a generally consistent treatment effect in the pooled subgroup analysis of ROS1 TKI-naïve and ROS1 TKI-pretreated cohorts. The subgroup analysis of ORR by study separated by ROS1 TKI pretreatment status is presented in **Sections 8.1.3** and **8.1.5**.

8.1.1.8. Data Applicability

The Applicant's Position:

A detailed justification of the applicability of the clinical results from Studies G208 and C203 to the US population is provided in Module 1. An illustration of the multi-regional clinical development program, which utilized a blended development approach for taletrectinib, is provided in **Figure 19**. The number of patients treated with taletrectinib in North America in relevant global and US studies is provided herein.

Figure 19. Applicant - Multi-Regional Characteristics of the Taletrectinib Development Program



Abbreviations: FPI, first participant in.
Source: CSR Addendum DS6051-A-U101 synopsis; CSR Addendum DS6051-A-J102 synopsis; CSR AB-106-C203 synopsis; CSR AB-106-G208 synopsis; CSR AB-106-G208, Table 12; Clinical Summary AB-106-C205

The pooled data from the Studies G208 and C203 are applicable to the advanced NSCLC ROS1+ patient population in the US due to the following:

- The biology of the disease is the same across races and regions.
- Patient characteristics of ROS1+ NSCLC are similar according to studies done in different world regions or races.
- Diagnosis and treatment paradigms are similar across regions of the world.
- There are no race or region differences in efficacy or safety profiles from approved ROS1-targeted therapies.
- Ethnic sensitivity analyses per International Council for Harmonisation (ICH) E5 showed taletrectinib is insensitive to racial or geographic factors, and no dose adjustment is needed based on race.
- Studies C203 and G208 are Good Clinical Practice (GCP)-compliant studies and were performed according to regulatory guidance.
- The efficacy and safety profiles of Studies C203 and G208 are comparable.
- Efficacy and safety profiles were comparable across subgroups including race and regions in Study G208 alone and when Studies G208 and C203 were pooled.

Taken together, the unmet medical need, the racial/geographic insensitivity, the robust efficacy, and the well-tolerated safety profile of taletrectinib justify data applicability to not only the US-representative patient population but also the global patient population.

The FDA's Assessment:

FDA acknowledges the Applicant's description of the multi-regional development program which includes a global patient population in Study G208 and a single country population in Study C203. FDA agrees with the applicability of data to the advanced NSCLC *ROS1*-positive patient population in the US.

Additional Efficacy Considerations

The FDA's Assessment:

To help further characterize the clinical benefit of taletrectinib for the treatment of adult patients with *ROS1*-positive metastatic NSCLC, a PMC will be included in the approval letter to provide additional follow-up for responders in the ROS1 TKI-naïve and ROS1 TKI-pretreated populations after all responders have been followed for at least 18 months from the date of initial response. Refer to **Section 13**.

8.1.2. Pivotal Trial To Support Efficacy of Taletrectinib – G208

Trial Design

The Applicant's Description:

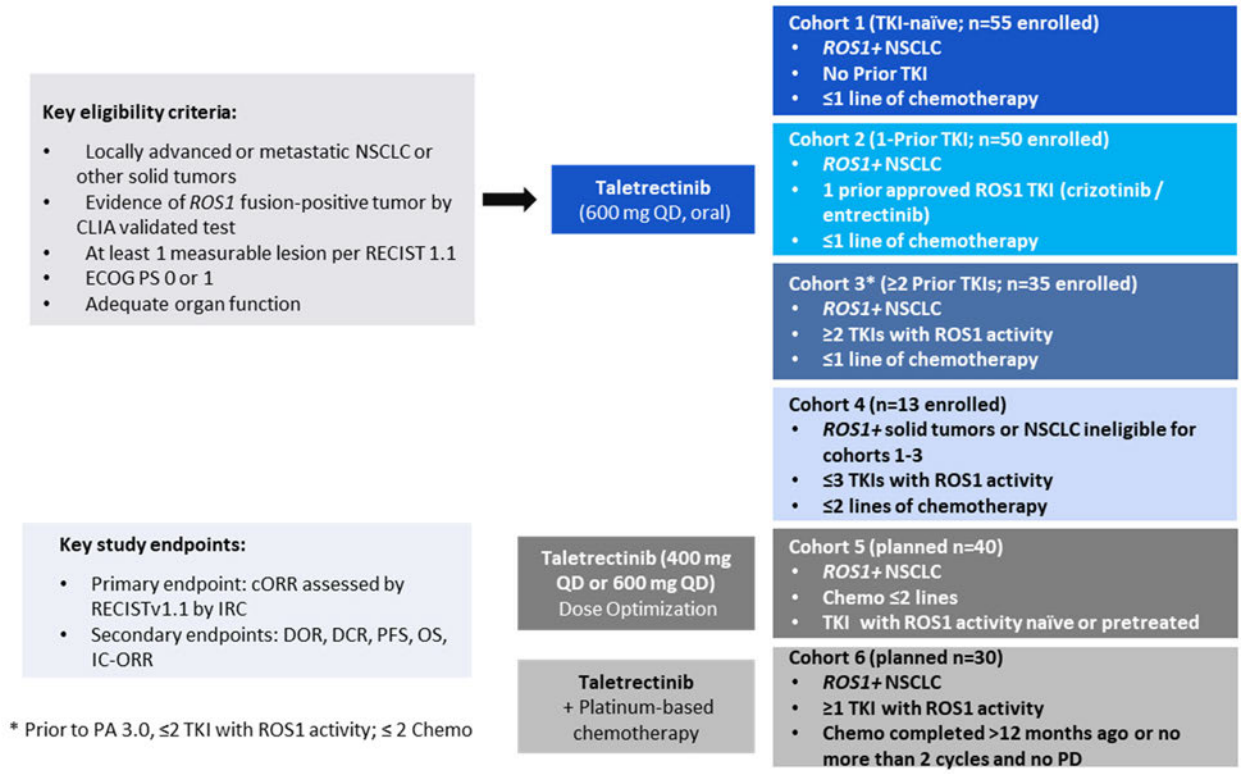
Study G208 was a Phase 2, global, multicenter, open-label, single-arm study to evaluate the efficacy and safety of taletrectinib in the treatment of locally advanced or metastatic NSCLC harboring ROS1 fusion and other solid tumors which were ROS1+ per local, Clinical Laboratory Improvement Amendments (CLIA)-validated or locally equivalent diagnostic assays. The study enrolled adult participants with a histologically or cytologically confirmed diagnosis of ROS1 fusion-positive, locally advanced or metastatic NSCLC, or other solid tumors who were either ROS1 TKI treatment-naïve or treated with prior ROS1 TKI(s).

The overall design of Study G208, including a description of all 6 cohorts, is presented in **Figure 20**.

Cohort 1 and Cohort 2 were designed in alignment with FDA, with registration intent to support taletrectinib for the treatment of locally advanced or metastatic ROS1+ NSCLC participants. Efficacy data from Cohort 1 and Cohort 2 based on the 07 June 2024 data cutoff are included in the initial NDA.

Cohort 5 (dose optimization cohort) is ongoing and results from this cohort will be provided during the initial NDA review.

Figure 20. Applicant - AB-106-G208 Study Design



Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; cORR, confirmed objective response rate; CSR, clinical study report; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; IC-ORR, intracranial objective response rate; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; OS, overall survival; PA, protocol amendment; PD, progressive disease; PFS, progression-free survival; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Source: CSR AB-106-G208 Table 14.1.1.1

Efficacy assessments: Diagnostic imaging and tumor evaluation were to be performed for all enrolled participants at screening (between Day -28 and Day -1), C3D1, and then performed every 2 cycles in first 8 cycles (C3D1, C5D1, C7D1, and C9D1), then every 3 cycles for 9th to 26th cycle (C12D1, C15D1, C18D1, C21D1, C24D1, and C27D1), and then every 4 cycles thereafter. A time window of ±7 days was acceptable. Tumor imaging assessment was also performed at the End of Treatment (EOT) visit if more than 6 weeks had passed since the last imaging assessment.

Safety assessments (laboratory tests, physical examinations, vital signs, ECGs) were to be collected at screening, C1D1, C1D8, C1D15, C2D1, Day 1 of each cycle from C3D1 to C9D1, then every 3 cycles for 9th to 26th cycle (C12D1, C15D1, C18D1, C21D1, C24D1, and C27D1),

and every 4 cycles thereafter until the EOT visit. AEs and concomitant medications were collected at every visit through the Safety Follow-up period.

The FDA's Assessment:
FDA agrees with the Applicant's description of the clinical trial design described above and as presented in **Figure 20**.

Efficacy results from the dose optimization cohort (Cohort 5) are discussed in **Section 6** (see **Table 13**).

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint in Cohort 1 and Cohort 2 of Study G208 was cORR assessed by IRC per RECIST v1.1.

The secondary efficacy endpoints in Cohort 1 and Cohort 2 of Study G208 include:

1. DOR assessed by IRC per RECIST v1.1
2. PFS assessed by IRC per RECIST v1.1
3. Time to treatment failure (TTF) assessed by IRC per RECIST v1.1
4. Time to response assessed by IRC per RECIST v1.1
5. ORR, DOR, and PFS assessed by Investigators per RECIST v1.1
6. Confirmed IC-ORR, IC-DOR, IC-PFS, and TTiP assessed by IRC per mRECIST v1.1
7. OS

The FDA's Assessment:

FDA generally agrees with the Applicant's description of study endpoints.

Refer to **Section 8.1.1.2** Endpoints for Integrated Efficacy Analysis for FDA comments on how endpoints were assessed in the review of this Application.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The final SAP (v3.0) was finalized on 26 Jun 2024.

Primary analysis

The primary endpoint, cORR according to RECIST v1.1 as assessed by IRC, was defined as the proportion of participants with cCR or cPR, along with the two-sided 95% CI using the Clopper-Pearson method.

If not specified, all ORRs were considered cORRs. A spider plot showed the participant profiles of the tumor load of target lesions (sum of longest diameters for non-nodal lesions, short axis for

nodal lesions) over time (presenting all participants on the same graph). A swimmer plot displayed the individual trajectories over time. A waterfall plot showed the best postbaseline change in sum of target lesion diameters from baseline for each participant. Different colors illustrated the best overall response (BOR).

Subgroup analysis on the primary endpoint was performed. All subgroup analyses were exploratory, and no multiplicity was considered. cORR and related 95% CI were displayed in forest plots.

Sensitivity or supplementary analyses, which were considered exploratory analyses, were performed on primary and secondary endpoints. The analytical approach for sensitivity analyses was similar to the one used for the primary analysis, but analyses were derived from investigator assessment using the REP2 set instead of IRC assessment. In addition, concordant and discordant assessments between IRC assessment versus investigator assessment were provided.

Secondary analyses

- The DCR was defined in a manner similar to cORR but, in addition to cCR and cPR, also included stable disease as assessed by IRC. The DCR was calculated along with the two-sided 95% CI using the Clopper-Pearson method. A similar statistical analysis approach was applied to DCR assessed by IRC and investigator according to RECIST v1.1. based on REP/REP2.
- DOR was defined that the time from the first objective response (CR or PR) to the first documented progressive disease (PD) or death, whichever occurred earlier, in participants with confirmed BOR (cBOR) of CR or PR determined by IRC based on RECIST v1.1. If a participant did not have an event of PD or death, DOR was censored at the date of last adequate tumor assessment. An adequate tumor assessment was defined as a tumor assessment performed prior to start of subsequent anticancer treatment with a result that was neither "not evaluable" nor "not applicable." Kaplan-Meier estimates (product-limit estimates) were presented with a summary of associated statistics, including the mDOR with two-sided 95% CIs. In particular, the DOR rate at 3, 6, 9 and 12 months and estimates for every 6 months thereafter were estimated with corresponding two-sided 95% CIs. The CIs for the median were calculated according to Brookmeyer and Crowley. The estimate of the standard error was computed using Greenwood's formula.
- PFS and time to response (TTR) assessed by IRC and investigator according to RECIST v1.1 based on REP and REP2, respectively, and TTF/OS based on REP. The statistical analysis approach was similar to that used for DOR..

IC-ORR, IC-DCR, IC-DOR, and TTiP by IRC according to mRECIST v1.1 based on IAP. Similar statistical analysis approach done for cORR or DOR was applied.

The FDA's Assessment:

FDA agrees with the Applicant's description of the final SAP.

Protocol Amendments

The Applicant's Description:

A brief summary of the global protocol amendments for Study G208 is provided in **Table 27**. Full details are available in the clinical study report (CSR).

The protocol amendments did not have an impact on the integrity of the trial or the interpretation of the results.

Table 27. Applicant - Protocol Amendment History

Protocol Version, Date	Key Updates
Original protocol, 06 Apr 2021	Initial protocol
Protocol v2.0, 09 Nov 2021	Amendment 1
	Further defined Cohorts 2 and 3 per FDA request, providing specific prior treatment regimen requirements
	Eligibility criteria were revised
	Possible dose modifications due to taletrectinib-related AEs were further defined per FDA request
	Restricted participants' use of P-gp inhibitors or inducers as well as any medications that had QTc prolongation or TdP as a risk
Protocol v3.0, 16 Dec 2022	Amendment 2
	Eligibility criteria were revised
	Added PRO collection and schedule
	Dose level updated to start all participants in Cohorts 1-4 at taletrectinib 600 mg QD
	Added intensive PK sampling for all participants in Cohorts 1-4 and added sampling times
Protocol v4.0, 17 Nov 2023 (not operationalized)	Amendment 3
	Aligned tumor assessment and clinic visit/PRO schedules to decrease participant burden
	Removed prohibition of P-gp inducers/inhibitors
Protocol v5.0, 05 Dec 2023	Amendment 4
	Added definition and details for Cohort 5 and 6 throughout the protocol, including but not limited to the schema, Schedule of Activities, objectives and endpoints, number of participants, participation criteria, and rationale for study design and dose
	Added text to indicate that intraparticipant dose escalation should occur only if ≤ Grade 2 dose-related toxicity was observed in the previous treatment cycle

Protocol Version, Date	Key Updates
	Clarified definition of dose-limiting toxicity definition for ≥Grade 3 nonhematologic toxicities as well as exceptions to the definition
	Changed the final dose optimization assessment in Cohort 5 to occur when the full cohort of 20 participants at each dose level were enrolled and had at least 1 postbaseline tumor assessment

Abbreviations: AE, adverse event; FDA, Food Drug and Administration; P-gp, P-glycoprotein; PK, pharmacokinetic; PRO, patient-reported outcome; QD, once daily; QTc, corrected QT; TdP, Torsade de Pointes.

The FDA's Assessment:

FDA agrees with the Applicant's summary of protocol amendments.

8.1.3. Study Results – G208

Compliance with Good Clinical Practices

Data and the Applicant's Position:

The conduct of G208 met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the ICH guideline E6: GCP.

The FDA's Assessment:

FDA agrees with the Applicant's position that the study was completed using Good Clinical Practice guidelines.

Financial Disclosure

The Applicant's Position:

Financial interests/arrangements with clinical investigators were tracked and disclosed. Details of financial disclosure are provided in **Section 0**. There were no concerns about the integrity of the study data.

The FDA's Assessment:

FDA agrees that financial disclosures are included without notable conflicts. A financial disclosure certification document was included in Module 1.3.4. Refer to **Section 0**.

Patient Disposition

Data:

Table 28. Applicant - Summary of Participant Disposition

	Cohort 1 N=54	Cohort 2 N=47	C1 and C2 Overall N=101
Treatment disposition, n (%)			
Ongoing	32 (59.3)	26 (55.3)	58 (57.4)
Discontinued	22 (40.7)	21 (44.7)	43 (42.6)
Withdrawal by participant	3 (5.6)	0	3 (3.0)
AE	2 (3.7)	2 (4.3)	4 (4.0)
Disease progression	15 (27.8)	17 (36.2)	32 (31.7)
Poor compliance	1 (1.9)	0	1 (1.0)
Death	0	2 (4.3)	2 (2.0)
Other	1 (1.9)	0	1 (1.0)
Study disposition, n (%)			
Ongoing	44 (81.5)	32 (68.1)	76 (75.2)
Discontinued	10 (18.5)	15 (31.9)	25 (24.8)
Death	9 (16.7)	12 (25.5)	21 (20.8)
Withdraw by participant	1 (1.9)	3 (6.4)	4 (4.0)

Abbreviations: AE, adverse event; N, total number of participants; n, subset of total number of participants; REP, response evaluable population.
Note: Percentages were based on REP.
[a] All participants with "Other" reasons for treatment discontinuation had clinical disease progression or had lost clinical benefit from study drug.
Source: CSR AB-106-G208 Table 14.1.1.1.A2

The Applicant's Position:

At the data cutoff, the REP included 101 participants who were enrolled and treated with taletrectinib globally, including 54 who were ROS1 TKI-naïve (Cohort 1) and 47 who were previously treated with one ROS1 TKI (Cohort 2).

In the ROS1 TKI-naïve cohort, the majority (44/54, 81.5%) remain on the study, and 59.3% have treatment ongoing. Disease progression has been the primary reason for treatment discontinuations in the study. As of 28 Oct 2024, 42 of the 46 responders (91.3%) had at least 12 months of follow-up from the onset of the response.

In the ROS1-pretreated cohort, the majority (32/47, 68.1%) remain on the study, and 55.3% have treatment ongoing. Disease progression has been the primary reason for treatment

discontinuations in the study. As of 28 Oct 2024, all of the 29 responders (100%) had at least 6 months of follow-up from the onset of the response.

The FDA's Assessment:

FDA agrees with the Applicant's summary of patient disposition in **Table 28**, noting Cohort 1 refers to the ROS1 TKI-naïve and Cohort 2 refers to the ROS1-pretreated cohort.

Protocol Violations/Deviations

Data and The Applicant's Position:

It is unlikely any protocol deviations had an effect on the integrity of the trial or the efficacy and safety conclusions. CSR AB-106-G208 Section 10.4 provides further detail for the reported protocol deviations and includes links to the full tabulations of critical, major, and minor protocol deviations in Section 14.

The FDA's Assessment:

FDA agrees the reported deviations are unlikely to have significantly impacted the results of this study. In Study G208, protocol deviations were classified by severity. A critical protocol deviation was defined as a deviation from protocol-related procedures that threatened data integrity, adversely affected patients and/or could have invalidated acceptability of a project or part of it and required immediate action. A major protocol deviation was defined as a deviation from protocol-related procedures that could have affected data integrity or adversely affected patients and required timely action. A minor deviation referred to a deviation from protocol-related procedures that did not adversely affect patients or data integrity but was to be dealt with appropriately.

Among the patients in the REP Cohorts 1 and 2 (n=101), critical protocol deviations were reported in 18 patients (18%) including protocol violations of concomitant medication (11%), safety (5%), laboratory assessment (2%), study procedures (2%), and informed consent and process (1%). Among the patients included in the safety analysis population (n=159), protocol deviations were reported in 25 patients (16%). The most common critical protocol deviations (≥ 1%) were concomitant medication (9%, such as drugs prohibited by the study protocol), safety (3.1%, including delayed SAE reports), study procedures (1.9%, such as missed eye exam at screening, extra blood sample drawn by mistake), laboratory assessment (1.3%, including blood draw without consent) and informed consent and process (1.3%, including missing witness signature). There was one critical protocol deviation in which the patient took Brucea javanica oil (BJO), which was identified as a plant-based anticancer herbal medicine in its Chinese label, while on study. Patient ID (b) (6) received BJO from Day 71 to Day 78 while hospitalized for pericardial and pleural effusion. Taletrectinib was discontinued on Day 127 due to disease progression. The patient died on Day 129 due to respiratory failure and was not included as a responder in the efficacy population.

FDA considers that the reported protocol violations are unlikely to have a significant impact on the results of the study.

Demographics, Baseline, and Disease Characteristics

Data:

Table 29. Applicant - Demographics and Baseline Characteristics

Category	Cohort 1 N=54	Cohort 2 N=47	C1 and C2 Overall N=101
Sex, n (%)			
Male	24 (44.4)	20 (42.6)	44 (43.6)
Female	30 (55.6)	27 (57.4)	57 (56.4)
Age (years)			
n (missing)	54 (0)	47 (0)	101 (0)
Mean ±std	57.2 ±11.89	54.6 ±12.20	56.0 ±12.04
Median	57.0	55.0	57.0
Q1, Q3	49.0, 67.0	47.0, 62.0	49.0, 64.0
Min, max	27, 82	27, 79	27, 82
Age category, n (%)			
<65 years	39 (72.2)	37 (78.7)	76 (75.2)
≥65 years to <75 years	12 (22.2)	7 (14.9)	19 (18.8)
≥75 years	3 (5.6)	3 (6.4)	6 (5.9)
Weight (kg) at baseline			
n (missing)	54 (0)	46 (1)	100 (1)
Mean ±std	65.58 ±14.285	70.17 ±13.725	67.69 ±14.147
Median	63.50	70.35	65.98
Q1, Q3	56.20, 74.90	59.00, 76.00	57.20, 75.00
Min, max	44.0, 101.0	46.3, 109.4	44.0, 109.4
Race, n (%)			
White	12 (22.2)	16 (34.0)	28 (27.7)
Black or African American	1 (1.9)	1 (2.1)	2 (2.0)
Asian	35 (64.8)	22 (46.8)	57 (56.4)
Unknown[a]	6 (11.1)	8 (17.0)	14 (13.9)

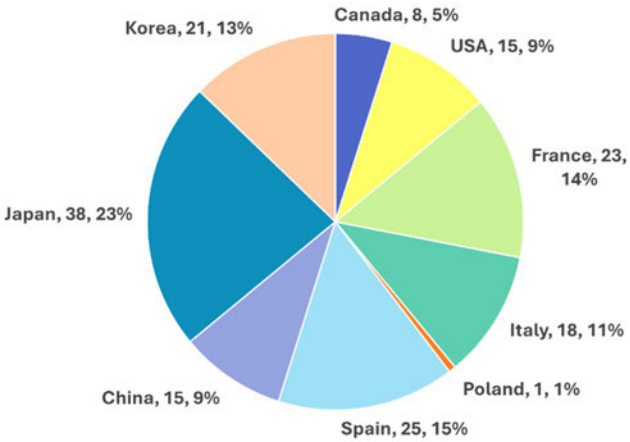
Category	Cohort 1 N=54	Cohort 2 N=47	C1 and C2 Overall N=101
Ethnicity, n (%)			
Hispanic or Latino	1 (1.9)	2 (4.3)	3 (3.0)
Not Hispanic or Latino	46 (85.2)	37 (78.7)	83 (82.2)
Unknown or not reported	7 (13.0)	8 (17.0)	15 (14.9)
Country, n (%)			
Canada	2 (3.7)	2 (4.3)	4 (4.0)
China	10 (18.5)	4 (8.5)	14 (13.9)
Spain	6 (11.1)	6 (12.8)	12 (11.9)
France	6 (11.1)	7 (14.9)	13 (12.9)
Italy	3 (5.6)	9 (19.1)	12 (11.9)
Japan	14 (25.9)	10 (21.3)	24 (23.8)
Korea	9 (16.7)	7 (14.9)	16 (15.8)
Poland	0	1 (2.1)	1 (1.0)
US	4 (7.4)	1 (2.1)	5 (5.0)
Region category 1, n (%)			
Western	21 (38.9)	26 (55.3)	47 (46.5)
Asian	33 (61.1)	21 (44.7)	54 (53.5)
Region category 2, n (%)			
China	10 (18.5)	4 (8.5)	14 (13.9)
Non-China	44 (81.5)	43 (91.5)	87 (86.1)
ECOG at baseline, n (%)			
0	21 (38.9)	21 (44.7)	42 (41.6)
1	33 (61.1)	26 (55.3)	59 (58.4)
Smoking status, n (%)			
Never smoker	27 (50.0)	29 (61.7)	56 (55.4)
Former smoker	25 (46.3)	17 (36.2)	42 (41.6)
Current smoker	2 (3.7)	1 (2.1)	3 (3.0)
Disease stage at enrollment, n (%)			
III	5 (9.3)	1 (2.1)	6 (5.9)
IV	49 (90.7)	46 (97.9)	95 (94.1)

Category	Cohort 1 N=54	Cohort 2 N=47	C1 and C2 Overall N=101
Tumor type at enrollment, n (%)			
Adenocarcinoma	53 (98.1)	46 (97.9)	99 (98.0)
Squamous cell carcinoma	1 (1.9)	1 (2.1)	2 (2.0)
Prior chemotherapy, n (%)			
Yes	10 (18.5)	19 (40.4)	29 (28.7)
No	44 (81.5)	28 (59.6)	72 (71.3)
Lines of prior anticancer therapy, n (%)			
0	44 (81.5)	0	44 (43.6)
1	7 (13.0)	26 (55.3)	33 (32.7)
2	2 (3.7)	21 (44.7)	23 (22.8)
≥3	1 (1.9)	0	1 (1.0)
Brain metastasis status by IRC-mRECIST v1.1 at baseline, n (%)			
No	35 (64.8)	20 (42.6)	55 (54.5)
Yes	19 (35.2)	27 (57.4)	46 (45.5)
Measurable	9 (16.7)	16 (34.0)	25 (24.8)
Nonmeasurable	10 (18.5)	11 (23.4)	21 (20.8)
Central *ROS1* status, n (%)			
Negative	6 (11.1)	5 (10.6)	11 (10.9)
Positive	28 (51.9)	15 (31.9)	43 (42.6)
Unavailable	20 (37.0)	27 (57.4)	47 (46.5)
Quality control failure	5 (9.3)	15 (31.9)	20 (19.8)
Not tested	15 (27.8)	12 (25.5)	27 (26.7)
Pretreated with entrectinib, n (%)			
Yes	0	10 (21.3)	10 (9.9)
No	54 (100.0)	37 (78.7)	91 (90.1)
Pretreated with crizotinib, n (%)			
Yes	0	37 (78.7)	37 (36.6)
No	54 (100.0)	10 (21.3)	64 (63.4)

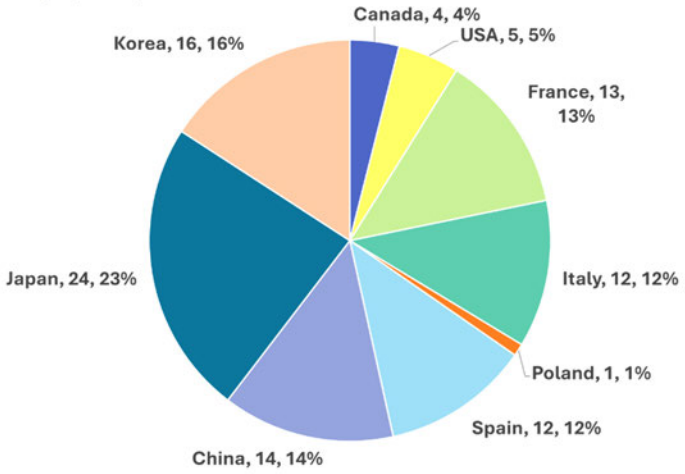
Abbreviations: ECOG, Eastern Cooperative Oncology Group; IAP, Intracranial Analysis Population; IRC, independent radiology review committee; max, maximum; min, minimum; mRECIST, modified Response Evaluation Criteria in Solid Tumors; N, total number of participants; n, subset of total number of participants; Q1,

first quartile; Q3, third quartile; REP, response evaluable population; ROS1, c-ros oncogene 1; std, standard deviation; TKI, tyrosine kinase inhibitor; US, United States.
Note: Analysis was based on REP.
[a] Of participants with unknown race, 13 were from France and 1 were from Spain.
Source: CSR AB-106-G208 Table 14.1.3.1.A2 and Table 14.1.5.1.A2

Figure 21. Applicant - Enrollment by Country in Study G208
A. All Cohorts (SS)



B. Cohorts 1 and 2 Only (REP)



Note: Data are shown as country, number of participants enrolled, %.
Source: CSR AB-106-G208, Table 12, G208 Table 14.1.3.1.A2

The Applicant's Position:

Demographics and baseline characteristics are presented in **Table 29**. Among the 101 participants dosed in the 600 mg QD REP in Cohort 1 and Cohort 2, the majority of participants were female (56.4%), under 65 years old (75.2%), and never smokers (55.4%). The majority of them were either Asian (56.4%) or White (27.7%), and 2% were Black or African

American. Approximately 13.9% of participants had unknown status of race, mostly due to reporting restrictions in France. A majority of the participants were enrolled from Asian countries (53.5%) and had an ECOG PS of 1 at baseline (58.4%).

At enrollment, a large majority of participants had Stage IV disease (94.1%), and most participants had adenocarcinoma (98.0%).

In TKI-naïve participants (Cohort 1), 35.2% had brain metastases at baseline. Prior chemotherapy use was 18.5%. In accordance with the protocol eligibility, no participant had crizotinib, entrectinib, or other ROS1-targeted TKIs.

In TKI-pretreated participants (Cohort 2), 57.4% had brain metastases at baseline. Prior chemotherapy use was 40.4%; 78.7% of participants had prior crizotinib treatment, and 21.3% had prior entrectinib treatment.

A detailed summary of enrollment in all cohorts by country in Study G208 is presented in **Figure 21**A. Overall, the Applicant believes that the sample size of participants from North America is reasonable as a subgroup in the multi-regional clinical trial Study G208, especially given the rarity of this cancer. Further, subgroup analyses within Study G208 by geography show similar efficacy outcomes, which are also similar to results from the regional study, C203.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of demographics and baseline characteristics, noting that the efficacy labeling claim is based only on Cohorts 1 and 2 of Study G208 (see **Figure 21**B). The patient population in Cohorts 1 and 2 had a multi-regional representation. The observed demographics are aligned with the demographics of *ROS1*-positive NSCLC as reported in the literature.

Based on the 90-day safety update, the percentage of Hispanic patients in Study G208 for TKI pre-treated patients was revised from 4.3% to 2.1% (correction of an error in the prior dataset).

Other Baseline Characteristics

Data and The Applicant's Position:

An overall summary of prior anticancer therapies and procedures for the Safety Analysis Set (SS) is presented in CSR AB-106-G208 Table 14. In the REP, a majority of participants had prior systemic anticancer therapies (58.4%), and targeted therapy was the most common (46.5%) (G208 Table 14.1.6.1.1.A2). Approximately 29.7% of participants had received prior radiotherapy, and approximately 19.8% of participants had prior anticancer surgeries or procedures.

A summary of prior systemic anticancer therapies used by ≥2% of participants in the SS is presented by Anatomic Therapeutic Chemical level and preferred term (PT) in CSR AB-106-G208 Table 15. In Cohort 1 (TKI-naïve) REP, 22.2% of participants had prior systemic anticancer therapy (G208 Table 14.1.6.1.1.A2). Platinum chemotherapy was the most frequently

administered (22.2%) (G208 Table 14.1.6.2.1.A2). In accordance with protocol eligibility criteria, no participants in Cohort 1 had prior TKIs.

In Cohort 2 (TKI-pretreated) REP, 100% of participants had prior systemic anticancer therapy, and in accordance with protocol eligibility, 100% had prior target therapy against ROS1 fusion (G208 Table 14.1.6.1.1.A2). Among target therapies, 78.7% had prior crizotinib and 21.3% had prior entrectinib (G208 Table 14.1.6.2.1.A2).

The FDA's Assessment:

FDA agrees with the Applicant's description of prior anticancer therapies in Cohorts 1 and 2. The percentages of patients who had prior platinum-based chemotherapy for advanced disease were 19% in Cohort 1 (TKI-naïve) REP and 40% in Cohort 2 (TKI-pretreated) REP.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance was assessed at each site visit by direct questioning, counting returned capsules, etc. during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen were to be recorded.

Participants were instructed that, if they vomited after taking the study drug, they were not to retake the study drug immediately and should have resumed the study drug at the next scheduled dose. If a participant missed a dose, he/she could have taken the missed dose within 8 hours of the regular dose time. Otherwise, the participant was to skip the dose and resume the study drug at the next scheduled dose.

A record of the quantity of taletrectinib dispensed to and administered by each participant was to be maintained and reconciled with study drug and compliance records. Study drug start and stop dates, including dates for study drug delays and/or dose reductions, were to be recorded.

Exposure results based on patient dosing reflect overall treatment compliance.

The overall most common Anatomic Therapeutic Chemical classes of concomitant medications were analgesics, antiemetics and antinauseants, and drugs for acid-related disorders. Concomitant medications that were taken in more than 10% of participants included paracetamol, metoclopramide, ursodeoxycholic acid, loperamide, dexamethasone, loperamide hydrochloride, magnesium oxide, metoclopramide hydrochloride, famotidine, and folic acid.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of treatment compliance. The median relative dose intensity in REP Cohorts 1 and 2 were 95% (range: 34-100) and 96% (range: 35-129), respectively. This is similar to the median relative dose intensity of 96% (range: 34-129) in the safety analysis population (n=159). There was one patient who overdosed (defined as taking

any dose of taletrectinib > 800 mg QD) with 1200 mg QD for one day with no clinical sequalae reported.

Efficacy Results

Data and the Applicant's Position:

The efficacy results of Study G208 are presented along with the integrated results in **Table 22**.

As of 28 Oct 2024, in the ROS1 TKI-naïve cohort, 91.3% of participants (N=42) who responded were followed for ≥12 months after initial response, and in the ROS1 TKI-pretreated cohort, 100% of participants (N=29) who responded were followed for ≥6 months after initial response. Tumor responses in exploratory Cohorts 3 (≥2 prior ROS1 TKIs, ≤1 prior line of chemotherapy) and 4 (≤3 prior ROS1 TKIs, ≤2 prior lines of chemotherapy) were less pronounced but still positive, which was in line with expectations given these participants' previous disease and treatment history.

ROS1 TKI Naïve (Cohort 1, N=54):

Taletrectinib treatment led to a high cORR.

- The IRC-assessed cORR was 85.2% (95% CI: 72.9, 93.4), the IRC-assessed DCR was 94.4% (95% CI: 84.6, 98.8).
- IRC-assessed cORR was comparable in ROS1 TKI-naïve participants who were previously treated with chemotherapy or naïve to prior chemotherapy.

Responses were durable.

- The responses were durable. As of 28 Oct 2024, the 12-month DOR rate was 74.2% (95% CI: 58.1, 84.8).

Taletrectinib treatment led to a prolonged PFS.

- As of 28 Oct 2024, the 12-month PFS rate was 73.0% (95% CI: 58.7, 83.1).

Response rates were similar between subgroups.

- cORR results were comparable across different subgroups, including participants in Western and Asian countries, participants with or without brain metastasis at baseline, participants with or without previous chemotherapy, and different racial groups.

Responses were observed in IC metastases.

- Additionally, a high IC-ORR based on mRECIST was observed in participants with measurable brain metastasis at baseline (N=9; 66.7% [95% CI: 29.9, 92.5]), and IC-DCR was 77.8% (95% CI: 40.0, 97.2).

Results were similar by IRC and Investigator.

- All investigator-assessed endpoints had similar results to the IRC-assessed endpoints.

ROS1 TKI-Pretreated (Cohort 2, N=47):

Taletrectinib treatment led to a high cORR.

- The IRC-assessed cORR was 61.7% (95% CI: 46.4, 75.5), and the IRC-assessed DCR was 93.6% (95% CI: 82.5, 98.7).
- IRC-assessed cORR was comparable in ROS1 TKI-pretreated participants who were previously treated with chemotherapy or naïve to prior chemotherapy.

Responses were durable.

- As of 28 Oct 2024, the mDOR was 19.4 months (95% CI: 10.7, not reached [NR]). The 12-month DOR rate was 68.0% (95% CI: 45.4, 82.8).

Taletrectinib treatment led to a prolonged PFS.

- As of 28 Oct 2024, the mPFS as per IRC assessment was 11.8 months (95% CI: 7.7, 20.6), and the 12-month PFS was 42.3% (95% CI: 27.0, 56.8).

Response rates were similar between subgroups.

- cORR results were comparable across different subgroups, including participants in Western and Asian countries, with or without brain metastasis at baseline, with or without prior chemotherapy at baseline, and different racial groups.

Responses were observed in IC metastases.

- Additionally, IC-ORR and IC-DCR based on mRECIST in 16 participants with measurable brain metastasis at baseline were 56.3% (95% CI: 29.9, 80.3) and 93.8% (95% CI: 69.8, 99.8), respectively.

Results were similar by IRC and Investigator.

- All investigator-assessed endpoints had similar results to the IRC-assessed endpoints.

The FDA's Assessment:

With the exception of the Applicant's statements that "taletrectinib treatment led to a prolonged PFS," FDA generally agrees with the efficacy results but notes that the median DOR was not reached in the ROS1 TKI-naïve cohort and has not stabilized in the ROS1 TKI pre-treated cohort. Therefore, the Kaplan-Meier estimate is not considered robust and may be overestimated, making it a less reliable method for estimating the duration of response. Instead, landmark analysis indicates that, in the ROS1 TKI-naïve cohort, the proportion of patients with observed DOR ≥12 months was 63%; DOR ranged from 1.4+ to 30.4+ months. In the ROS1 TKI-pretreated cohort, the proportions of patients with observed DOR ≥6 and ≥12 months were 83% and 45%, respectively; DOR ranged from 1.7+ to 30.4+ months (**Table 22**)

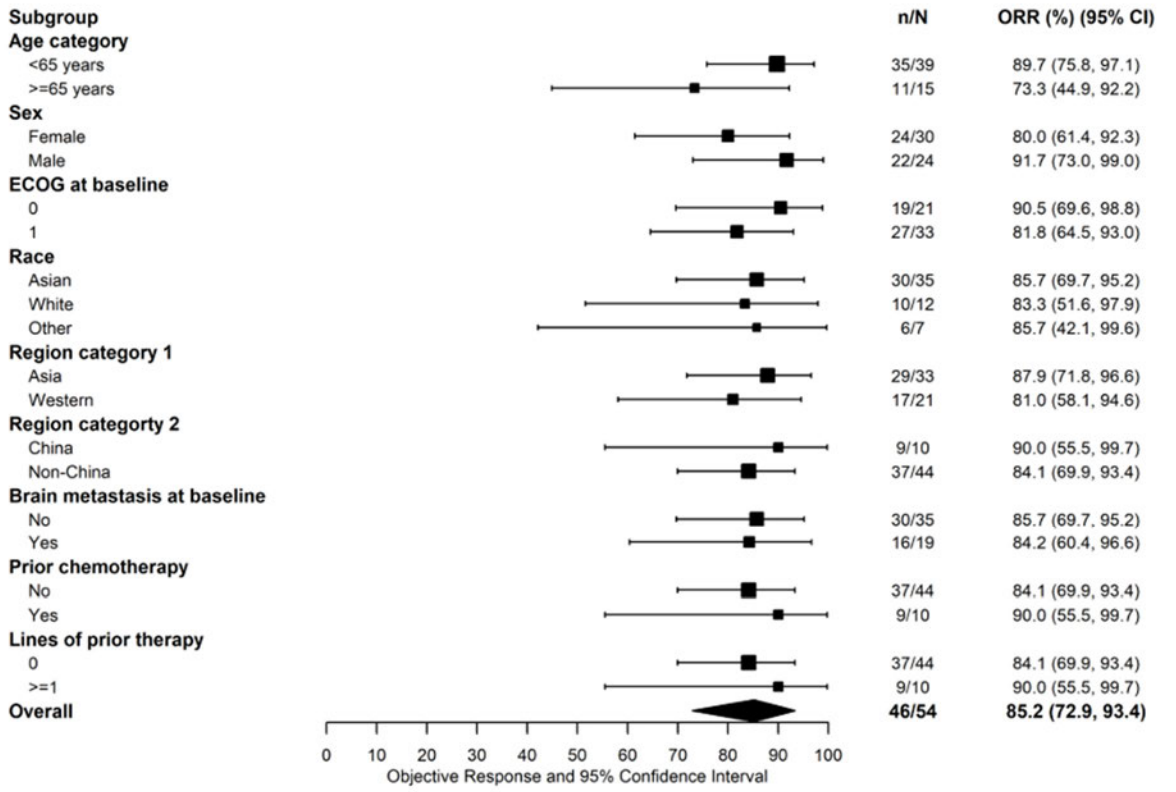
Additionally, in the ROS1 TKI-pretreated cohort, FDA review indicates that 6 out of 13 patients censored prior to median DOR were censored due to differences between investigator and BICR assessment, with 5 of those 6 patients experiencing disease progressions per investigator

assessment. This early potentially informative censoring is likely leading to an overestimation of median DOR.

Complete responses occurred in 7% of patients in Study G208, and 78% demonstrated a partial response; these numbers differ from those presented in **Table 22** to reflect one patient with a partial response later classified as having a complete response based on the 90-day safety update. The ORR subgroups analysis based on demographic and clinical characteristics were mostly consistent across subgroups in both cohorts.

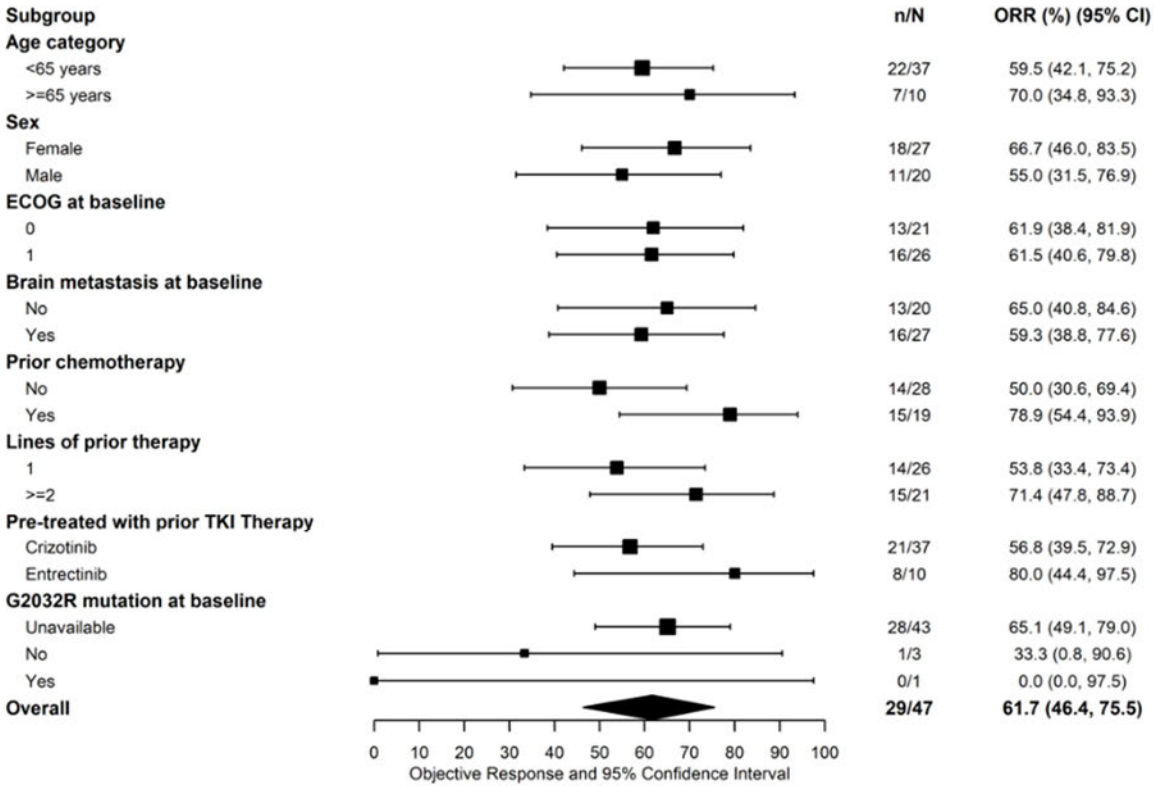
Refer to **Section 8.1.1.7** and **Table 26** for FDA's analysis of intracranial responses.

Figure 22. FDA Analysis – ORR Subgroup Analysis for Patients With ROS1 TKI Naïve in Study G208



Source: FDA reviewer generated analysis (Data: ADSL, ADRS)

Figure 23. FDA Analysis – ORR Subgroup Analysis for Patients With ROS1 TKI Pre-Treated in Study G208



Source: FDA reviewer generated analysis (Data: ADSL, ADRS)

Data Quality and Integrity

The Applicant's Position:

No meaningful concerns were identified in the quality and integrity of the submitted datasets, which were sufficiently complete to allow a thorough review of efficacy. Furthermore, no data integrity concerns were reported following completion of center inspections by the Applicant.

The FDA's Assessment:

FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a comprehensive review of the efficacy of taletrectinib in patients with *ROS1*-positive NSCLC. FDA issued information requests during the review cycle to obtain clarification and additional information regarding data included in the NDA, and all requests were addressed appropriately.

Dose/Dose Response

The Applicant's Position:

Data on dose response are presented in **Section 6.3.2**.

The FDA's Assessment:

Refer to FDA's assessment in **Section 6.3.2**.

Durability of Response

The Applicant's Position:

Data on durability of response are included in the efficacy results presented above.

The FDA's Assessment:

FDA generally agrees with the Applicant, and notes that the data in the 90-day safety update demonstrates that a majority of responders experienced a durable response: in the ROS1 TKI-naïve cohort, 63% remained in response at 12 months; in the ROS1 TKI-pretreated cohort, 83% and 45% remained in response at 6 and 12 months, respectively (**Table 22**).

Persistence of Effect

Data and the Applicant's Position:

In all clinical trials in participants with solid tumors, including Study G208, taletrectinib was dosed until PD that required an alternative therapy, intolerable toxicity, or another discontinuation criterion was met. Study drug was usually discontinued once the participants had disease progression. However, taletrectinib treatment could be continued after PD if, in the opinion of the investigator, the participant continued to experience clinical benefit including, but not limited to, systemic benefit if the site of progression was localized to the brain.

At the time of the 07 June 2024 data cutoff, the median follow-up time for ROS1 TKI-naïve participants was 15.82 months. In Study G208, 81.8% of ROS1 TKI-naïve participants remained on study and 60.0% were continuing to take study drug. For ROS1 pretreated participants, the median follow-up time was 15.74 months. In Study G208, 68.0% of ROS1 TKI-pretreated participants remained on study, and 54.0% were continuing on study drug.

As of the 90-day safety update data cutoff (28 Oct 2024), in the ROS1 TKI-naïve cohort of Study G208, the median follow-up time was 20.52 months; the majority of participants remain in the study (43/55, 78.2%) and over half (56.4%) have treatment ongoing. In the ROS1 TKI pretreated cohort, the median follow-up time was 20.44 months; over half of participants (33/50, 66.0%) remain in the study and 20 (40.0%) have treatment ongoing (90-day G208 Table 14.2.10.1, 90-day G208 Table 14.1.1.1).

The FDA's Assessment:

FDA agrees with the Applicant; the study design and drug administration schedule do not permit an assessment of persistence of effect beyond drug discontinuation.

Efficacy Results – Secondary or exploratory Clinical Outcome Assessment (patient-reported outcome [PRO]) endpoints

Data and the Applicant's Position:

Patient-reported outcome (PRO) questionnaires, which included the EORTC QLQ-30 and LC-31 and the EQ-5D-5L, were introduced in Amendment 2 (Protocol Version 3.0), resulting in PRO data being available for only the subset of participants enrolled after this amendment. Only participants with baseline results were included in the PRO analysis.

Forty participants completed at least 1 EORTC QLQ-C30 questionnaire. The mean change from baseline in Global Health Status/Quality of Life (GHS/QoL) score remained consistently at or above baseline over time. This trend was observed both in the overall population receiving 600 mg and in the subgroup Cohorts 1 and 2.

At C2D1, 21.4% (9/42) of participants showed improved GHS scores, while 61.9% (26/42) remained stable. At C7D1, 16.7% (5/30) of participants had improved scores, whereas 50.0% (15/30) remained stable. These results suggest a trend towards maintenance or improvement in overall health status throughout the treatment period.

Forty-three participants completed the EQ-5D-5L. The overall trend of visual analogue scale was stable over time and consistent with change from baseline GHS/QoL score.

The FDA's Assessment:

FDA acknowledges the Applicant's analysis of PRO endpoints. These conclusions should be interpreted with caution as the majority of patients in Study G208 did not complete the PRO questionnaires.

FDA did not independently verify the results for the PRO endpoints. In a single-arm setting, FDA generally considers PRO endpoints to be descriptive and exploratory due to the absence of a randomized comparator, which limits the ability to establish clinically meaningful evidence of benefit or tolerability. In addition, the concept of a global health score is generally subject to confounding by non-treatment and non-disease factors, which can complicate interpretation in the context of trial results.

Additional Analyses Conducted on the Individual Trial

Data:

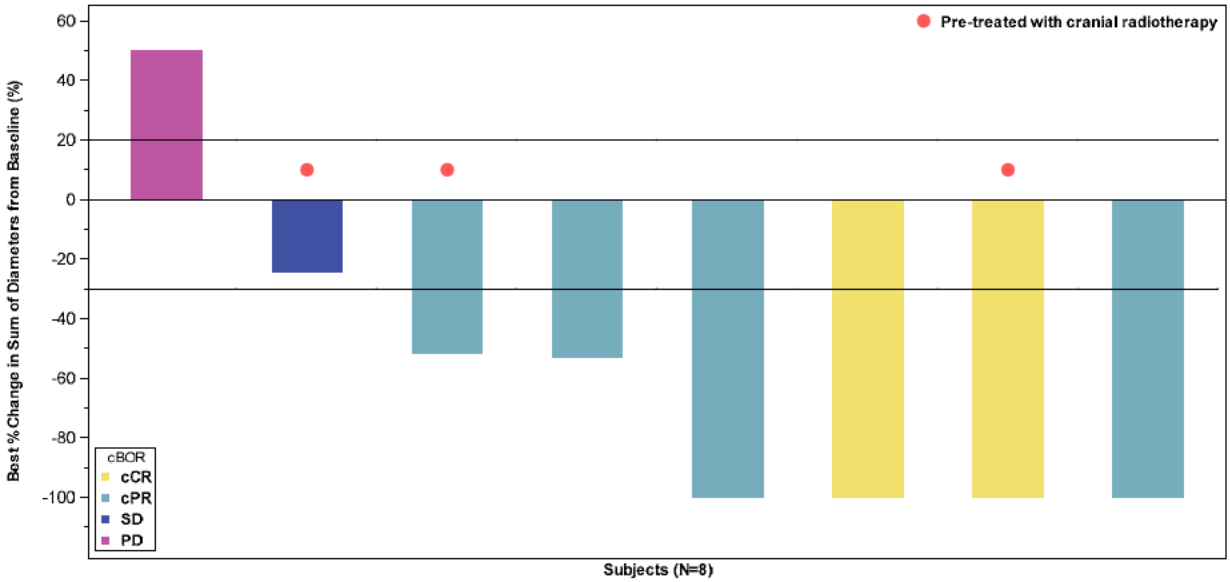
Table 30. Applicant - Summary of IRC-Based IC-ORR and IC-DCR Per mRECIST v1.1

Category	Cohort 1 N=9 (%)	Cohort 2 N=16 (%)
BOR		
CR	2 (22.2)	1 (6.3)
PR	4 (44.4)	8 (50.0)
SD	1 (11.1)	6 (37.5)
PD	1 (11.1)	1 (6.3)
Not evaluable	1 (11.1)	0
ORR (CR + PR)	6 (66.7)	9 (56.3)
Two-sided 95% CI[a]	[29.93, 92.51]	[29.88, 80.25]
DCR (CR + PR + SD)	7 (77.8)	15 (93.8)
Two-sided 95% CI[a]	[39.99, 97.19]	[69.77, 99.84]

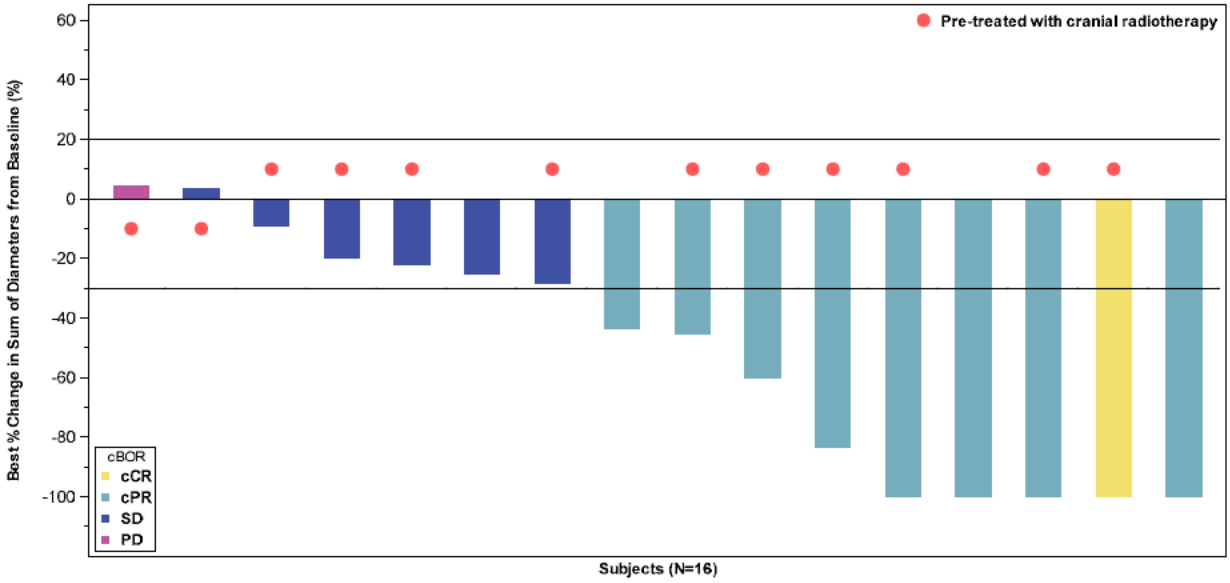
Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; IAP, Intracranial Analysis Population; IC, intracranial; IRC, Independent Review Committee; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Note: Analysis was based on the IAP.
[a] The method of Clopper and Pearson was used to calculate CI.
Source: CSR AB-106-G208 Table 24

Figure 24. Applicant - Waterfall Plots of IRC-Based IC Analyses

Cohort 1:



Cohort 2:



Abbreviation: cBOR, confirmed best overall response; cCR, confirmed complete response; cPR, confirmed partial response; IAP, Intracranial Analysis Population; IC, intracranial; IRC, independent radiology review committee; NE, not evaluable; PD, progressive disease; SD, stable disease.
Note: Analysis was based on the IAP. In Cohort 1, one participant with a cBOR of NE is not displayed.
Source: CSR AB-106-G208 Figure 14.2.6.1.1 and Figure 14.2.6.2.1

The Applicant's Position:

A high IC-ORR based on mRECIST was observed in participants with measurable brain metastasis at baseline, regardless of lines of prior therapy (N=9; 66.7% [95% CI: 29.9, 92.5] for TKI-naïve participants; N=16, 56.3% [95% CI: 29.9, 80.3] for TKI-pretreated participants).

The FDA's Assessment:

FDA performed a revised analysis of IC-ORR, accounting for brain radiation within 2 months before study entry to minimize bias in distinguishing radiation effects from drug effects on brain metastatic lesions. Refer to FDA's assessment in **Section 8.1.1.6**.

8.1.4. Supportive Trial to Support Efficacy of Taletrectinib – C203

Trial Design

The Applicant's Description:

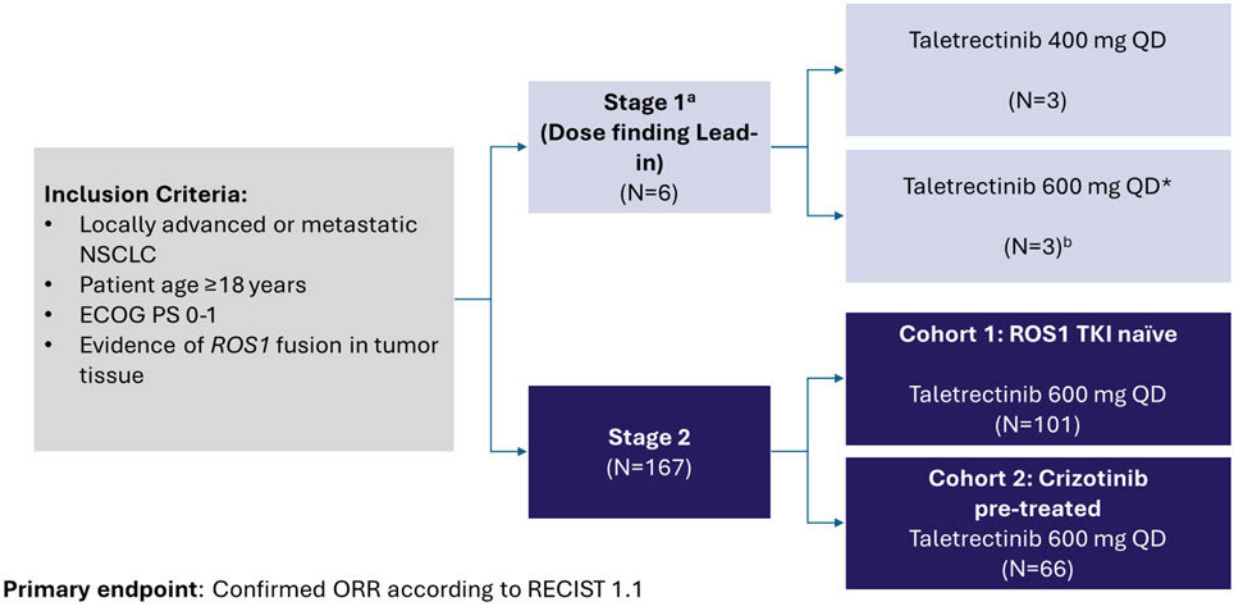
Study C203 was a Phase 2, multicenter, single-arm, open-label study of taletrectinib. The study was conducted in China and enrolled adult participants with a ROS1 fusion gene positive, locally advanced, or metastatic NSCLC who had either not received any ROS1-TKI treatment or previously treated with crizotinib.

The study included 2 stages. The first stage (Stage I) was to confirm the RP2D of taletrectinib. The safety, tolerability, and PK at 2 dose levels (400 mg QD and 600 mg QD) were evaluated (**Figure 25**). The dose moving to Stage II was confirmed as 600 mg QD. The second stage (Stage II) was to evaluate the efficacy and safety of taletrectinib at 600 mg QD (**Figure 25**).

The schedules for disease assessments, safety evaluation, and PK collection were the same for Stage I and Stage II. Disease assessments with computed tomography of the chest/abdomen/pelvis with contrast and other clinically relevant body parts at screening (between Day -28 and Day -1), C3D1, and then performed every 2 cycles in first 8 cycles (C3D1, C5D1, C7D1, and C9D1), then every 3 cycles for 9th to 26th cycle (C12D1, C15D1, C18D1, C21D1, C24D1, and C27D1), and then every 4 cycles thereafter. A time window of ±7 days was acceptable. Disease assessment was also performed at the EOT visit.

Safety assessments (laboratory tests, physical examinations, vital signs, ECGs, ophthalmologic examination) were to be collected at screening, C1D1 (except ophthalmologic examination), C1D8, C1D15, C2D1, Day 1 of each cycle thereafter, and the EOT visit. AEs and concomitant medications were collected at every visit through the Safety Follow-up period.

Figure 25. Applicant - AB-106-C203 Study Design



Abbreviations: CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; ORR, objective response rate; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
[a] Five participants in ROS1 TKI-naïve cohort; 1 participant in ROS1 TKI-pretreated cohort.
[b] Two participants were included in Cohort 1 for analysis; 1 participant was included in Cohort 2 for analysis.
Source: CSR AB-106-C203 Table 14.1.1.1

The FDA's Assessment:

FDA agrees with the Applicant's description of the clinical trial design. FDA considered data from Study C203 as part of the primary efficacy data supporting the application, rather than as supportive (as described by the Applicant), given the relatively small sample size of Study G208.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint in Cohort 1 and Cohort 2 of Study C203 was cORR assessed by IRC per RECIST v1.1.

The secondary efficacy endpoints for Cohort 1 and Cohort 2 include:

1. ORR assessed by the investigator per RECIST v1.1
2. DCR, DOR, time to response, and time to progression assessed by the IRC and investigator per RECIST v1.1 criteria
3. IC-ORR, IC-DOR, IC-PFS, and TTiP assessed by the IRC for participants with baseline IC metastases per mRECIST v1.1

4. PFS assessed separately by the IRC and investigator per RECIST v1.1
5. OS

The FDA's Assessment:

FDA generally agrees with the Applicant's description of study endpoints.

Refer to **Section 8.1.1.2** Endpoints for Integrated Efficacy Analysis for FDA comments on how endpoints were assessed in the review of this Application.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The final SAP (v2.0) was finalized on 26 Jun 2024.

Primary endpoint

The primary endpoint of this study was ORR based on IRC assessment in the REP. Per FDA request, the analysis was modified after NDA submission to exclude 3 participants in Study C203 with a starting dose lower than 600 mg QD from all efficacy analyses. ORR is defined as the proportion of participants with BOR as confirmed complete or partial response (CR or PR) among the analysis population. Two-sided 95% CI for the ORR was calculated by the Clopper-Pearson method. If not specified, mentions of ORR in the following text should be considered as cORR.

Subgroup analyses on primary endpoints were performed. All subgroup analyses were exploratory, and no multiplicity was considered. cORR and related 95% CI was displayed in the forest plots.

Sensitivity analysis was performed by using investigator assessment based on REP2 using similar analysis methods.

Secondary endpoints

- The approach to statistical analysis for DCR was similar to ORR: assessed by IRC and investigator according to RECIST v1.1 based on REP/REP2.
- DOR is defined that the time from the first objective response (CR or PR) to the first documented PD or death in participants with BOR of confirmed response (CR or PR) determined by IRC based on RECIST v1.1. Kaplan-Meier estimates were used. The CIs for the median were calculated according to Brookmeyer and Crowley (1982). Kaplan-Meier plots were also provided. The estimate of the standard error was computed using Greenwood's formula.
- PFS, TTR, TTP assessed by IRC and investigator according to RECIST v1.1 based on REP/REP2, and OS based on REP. A similar statistical analysis approach to DOR was applied to these endpoints.
- IC-ORR, IC-DOR, IC-PFS, and TTiP by IRC according to mRECIST v1.1 based on IAP. A similar statistical analysis approach to ORR and DOR was applied to these endpoints.

The FDA's Assessment:

FDA agrees with the final SAP; FDA requested the removal of the three patients who started on a dose lower than 600 mg QD from all efficacy analyses.

Protocol Amendments

The Applicant's Description:

A brief summary of the protocol amendments for Study C203 is provided in **Table 31**. Full details are available in the CSR.

The protocol amendments did not have an impact on the integrity of the trial or the interpretation of the results.

Table 31. Applicant - Protocol Amendment History

Protocol Version, Date, and Key Updates
Original Protocol v1.1, 27 Mar 2020, Initial protocol
Protocol v2.0, 30 Nov 2020, Amendment 1, Key Updates
• Revised secondary endpoints.
• Clarified responsibility for assessment of efficacy endpoints.
• Revised tumor assessment schedule.
• Revised eligibility criteria.
Protocol v3.0, 03 Nov 2021, Amendment 2, Key Updates
• Clarified frequency and requirements for study procedures, including time windows.
• Revised eligibility criteria.
• Specified the regulations on prohibited medications.
• Revised the rules for dose adjustment and criteria for discontinuation.
• Clarified the duration and requirements of the safety follow-up period.
• Revised the requirements regarding the time period and frequency for collecting information on AEs and SAEs; and specified the time limit for SAE reporting.
Protocol v4.0, 03 Mar 2022, Amendment 3, Key Updates
• Updated overall study design and revised the sample size.
• Revised AE, SAE, and AESI definitions, causality assessment, and recording procedures.

Protocol Version, Date, and Key Updates
• Revised handling of laboratory test abnormalities.
• Revised description of PD.
• Revised statistical analysis section.
Protocol v5.0, 06 Jun 2022, Amendment 4, Key Updates
• Updated overall study design and revised the sample size.
• Revised criterion #4 for treatment discontinuation.
• Revised the instructions for collection of AEs and SAEs.
• Revised statistical analysis section.

Abbreviations: AE, adverse event; AESI, adverse event of special interest; PD, progressive disease; SAE, serious adverse event.

The FDA's Assessment:

FDA agrees with the Applicant's summary of protocol amendments, noting that the revisions to study design and sample size in Amendments 3 and 4 were in relation to other cohorts in the study and did not impact the efficacy review in this submission.

8.1.5. Study Results – C203

Compliance with Good Clinical Practices

Data and the Applicant's Position:

The conduct of C203 met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the ICH guideline E6: GCP.

The FDA's Assessment:

FDA agrees with the Applicant's position that the study was completed using Good Clinical Practice guidelines.

Financial Disclosure

The Applicant's Position:

Financial interests/arrangements with clinical investigators were tracked and disclosed. Details of financial disclosure are provided in **Section 0**. There were no concerns about the integrity of the study data.

The FDA's Assessment:

FDA agrees that financial disclosures are included without notable conflicts. A financial disclosure certification document was included in Module 1.3.4. Refer to **Section 0**.

Patient Disposition

Data:

Table 32. Applicant - Summary of Participant Disposition

Category	ROS1 TKI-Naïve N=103	ROS1 TKI-Pretreated N=66	Overall N=169
Treatment disposition, n (%)			
Ongoing	52 (50.5)	14 (21.2)	66 (39.1)
Discontinued	51 (49.5)	52 (78.8)	103 (60.9)
Disease progression	33 (32.0)	36 (54.5)	69 (40.8)
Death	6 (5.8)	1 (1.5)	7 (4.1)
Adverse event	5 (4.9)	4 (6.1)	9 (5.3)
Poor compliance	0	1 (1.5)	1 (0.6)
Started new anticancer therapy	0	2 (3.0)	2 (1.2)
Pregnancy	0	2 (3.0)	2 (1.2)
Physician decision	1 (1.0)	1 (1.5)	2 (1.2)
Other[a]	6 (5.8)	5 (7.6)	11 (6.5)
Study disposition, n (%)			
Ongoing	74 (71.8)	33 (50.0)	107 (63.3)
Discontinued	29 (28.2)	33 (50.0)	62 (36.7)
Death	27 (26.2)	30 (45.5)	57 (33.7)
Lost to follow-up	2 (1.9)	2 (3.0)	4 (2.4)
Other[b]	0	1 (1.5)	1 (0.6)

Abbreviations: N, total number of participants; n, subset of total number of participants; REP, response evaluable population; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.
Note: Percentages were based on REP.
[a] In the ROS1 TKI-naïve cohort, of the 6 participants in the 'Other' category, all voluntarily withdrew from the study. In the ROS1 TKI-pretreated cohort, of the 5 participants in the 'Other' category, 3 voluntarily withdrew (for personal reasons), 1 was withdrawn due to abnormal liver function and disease progression, and 1 was withdrawn due to lack of clinical benefit.
[b] The participant who discontinued the study in the 'Other' category due to personally refusing the follow-up visit.
Source: CSR AB-106-C203 Table 14.1.1.2.A2

The Applicant's Position:

At the clinical data cutoff, the REP included 169 participants who enrolled and were treated with taletrectinib in China, 103 were ROS1 TKI naïve and 66 were previously treated with ROS1 TKI.

In the ROS1 TKI-naïve cohort, the majority (74/103, 71.8%) remain on the study, and 50.5% have treatment ongoing. As of 28 Oct 2024, all responders (100.0%) had at least 12 months of follow-up from onset of response.

In the ROS1 pretreated cohort, 33/66 participants (50.0%) remain on the study, and 21.2% have treatment ongoing. As of 28 Oct 2024, all responders (100.0%) had at least 6 months of follow-up from onset of response. CSR Section 10.4 provides further detail for the reported protocol deviations.

The FDA's Assessment:

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

Protocol Violations/Deviations

Data and the Applicant's Position:

About 10% of participants had at least one major protocol deviation during the study. The most common major protocol deviations were related to participant eligibility and safety reporting. However, these deviations had no overall impact on the primary and secondary endpoints.

The FDA's Assessment:

FDA agrees with the Applicant's description of protocol violations/deviations. In Study C203, a major protocol deviation was defined as a deviation from protocol-related procedures that threatened the integrity of data, adversely affected patients, and/or could have invalidated the acceptability of a project (or part of it), which required immediate action. A minor protocol deviation was defined as a deviation from protocol-related procedures that did not adversely affect patients or data integrity but should be dealt with appropriately.

Among the patients included in the safety analysis population (n=173), major protocol deviations were reported in 10% of patients. The most common (≥ 1%) major protocol deviations were related to safety (2.9%, including delayed SAE reporting), study eligibility (2.9%, including pre-existing condition not meeting stabilization period criterion, ECG QTc prolongation at Screening), concomitant medications (1.7%, including drugs prohibited by the study protocol), study drug (1.2%, including missed study drugs) and source documents (1.2%, including lost source documents and lost diary card). There were two major protocol deviations in which patients took other anti-cancer drugs while on study. Patient ID (b) (6) was informed to take taletrectinib 600 mg at a fixed time every day. However, the patient took lorlatinib on Day 5 and withdrew from the study on Day 8 due to compliance issues. Patient ID (b) (6) was reported to have received bevacizumab injection into the chest cavity for the treatment of pleural effusion

on Day 13. The patient discontinued study drug on Day 64 and died on Day 246 due to disease progression. Neither of the patients who received concomitant anticancer drugs were classified as responders in the efficacy population.

FDA considers that the reported protocol violations are unlikely to have a significant impact on the results of the study.

Demographics, Baseline, and Disease Characteristics

Data:

Table 33. Applicant - Demographics, Baseline, and Disease Characteristics

Category	ROS1 TKI-Naïve N=103	ROS1 TKI Pretreated N=66	Overall N=169
Sex, n (%)			
Male	46 (44.7)	26 (39.4)	72 (42.6)
Female	57 (55.3)	40 (60.6)	97 (57.4)
Age (years)			
n (missing)	103 (0)	66 (0)	169 (0)
Mean ±std	55.1 ±11.55	53.6 ±11.78	54.5 ±11.63
Median	56.0	51.0	55.0
Q1, Q3	48.0, 64.0	46.0, 62.0	47.0, 63.0
Min, max	26, 78	31, 77	26, 78
Age category, n (%)			
<65 years	80 (77.7)	52 (78.8)	132 (78.1)
≥65 years to <75 years	21 (20.4)	13 (19.7)	34 (20.1)
≥75 years	2 (1.9)	1 (1.5)	3 (1.8)
Weight (kg) at baseline			
n (missing)	103 (0)	65 (1)	168 (1)
Mean ±std	61.63 ±12.249	64.48 ±11.467	62.73 ±11.999
Median	60.00	63.40	61.75
Q1, Q3	53.00, 69.00	55.00, 71.50	54.00, 70.00
Min, max	38.3, 115.0	40.0, 92.0	38.3, 115.0

Category	ROS1 TKI-Naïve N=103	ROS1 TKI Pretreated N=66	Overall N=169
ECOG at baseline, n (%)			
0	20 (19.4)	19 (28.8)	39 (23.1)
1	83 (80.6)	47 (71.2)	130 (76.9)
Smoking status, n (%)			
Never smoker	75 (72.8)	48 (72.7)	123 (72.8)
Current smoker	6 (5.8)	1 (1.5)	7 (4.1)
Former smoker	22 (21.4)	17 (25.8)	39 (23.1)
Tumor type at enrollment, n (%)			
Adenocarcinoma	99 (96.1)	61 (92.4)	160 (94.7)
Squamous cell carcinoma	0	3 (4.5)	3 (1.8)
Adeno-squamous carcinoma	3 (2.9)	2 (3.0)	5 (3.0)
Unknown	1 (1.0)	0	1 (0.6)
Disease stage at enrollment, n (%)			
III	9 (8.7)	2 (3.0)	11 (6.5)
IV	94 (91.3)	64 (97.0)	158 (93.5)
Prior chemotherapy, n (%)			
Yes	20 (19.4)	23 (34.8)	43 (25.4)
No	83 (80.6)	43 (65.2)	126 (74.6)
Lines of prior anticancer therapy, n (%)			
0	82 (79.6)	0	82 (48.5)
1	20 (19.4)	53 (80.3)	73 (43.2)
2	1 (1.0)	12 (18.2)	13 (7.7)
≥3	0	1 (1.5)	1 (0.6)
Brain metastasis by IRC at baseline - mRECIST v1.1, n (%)[a]			
No	85 (82.5)	38 (57.6)	123 (72.8)
Yes	18 (17.5)	28 (42.4)	46 (27.2)
Measurable	8 (7.8)	16 (24.2)	24 (14.2)
Nonmeasurable	10 (9.7)	12 (18.2)	22 (13.0)
Central *ROS1* status, n (%)[b]			
Negative	0	9 (13.6)	9 (5.3)

Category	ROS1 TKI-Naïve N=103	ROS1 TKI Pretreated N=66	Overall N=169
Positive	103 (100.0)	50 (75.8)	153 (90.5)
Unavailable	0	7 (10.6)	7 (4.1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IRC, Independent Central Review; Max, maximum; Min, minimum; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; N, total number of participants; n, subset of total number of participants; Q1, first quartile; Q3, third quartile; REP, response evaluable population; ROS1, c-ros oncogene 1; std, standard deviation; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the REP.
Source: CSR AB-106-C203 Table 14.1.3.1a.A2 and Table 14.1.5.1a.A2

The Applicant's Position:

In both the ROS1 TKI-naïve and ROS1 TKI-pretreated cohorts, a higher proportion of participants were female, under 65 years old, were never smokers, and had an ECOG performance status of 1 at baseline. A large majority of participants enrolled with adenocarcinoma and had Stage IV disease at enrollment.

In the ROS1 TKI-naïve cohort, the majority of participants had no prior anticancer therapy. Under 20% of participants had brain metastasis at baseline.

In the ROS1 TKI-pretreated cohort, all participants had at least one prior line of therapy, and all patients had prior treatment with crizotinib. Under half of the participants had brain metastasis at baseline, and half of the participants with measurable brain lesion were pretreated with cranial radiotherapy.

The FDA's Assessment:

FDA agrees with the Applicant's description of the baseline demographics and disease characteristics. Note that all patients enrolled in Study C203 were from China, whereas Study G208 enrolled patients from the US, Canada, China, Japan, Korea, Poland, France, Spain and Italy. In the efficacy cohort of Study C203, the distribution of sex, age, disease stage, tumor type at enrollment, and prior chemotherapy are similar to what were observed in Study G208 (**Table 29**). Study C203 had a higher percentage of never-smokers (74% vs. 55%) and a lower percentage of patients with baseline brain metastases (27% vs. 46%) compared to Study G208. Overall, the distributions of sex, age, tumor type and smoking status are aligned with what have been reported in the literature for patients with *ROS1*-positive NSCLC.

According to the 90-day safety update, the percentage of non-smoker patients in Study C203 among ROS1 TKI pre-treated patients was revised from 73% to 74%.

Other Baseline Characteristics

Data and the Applicant's Position:

A low proportion of ROS1 TKI-naïve cohort participants had prior anticancer therapies. Of the participants in this cohort that did receive prior anticancer therapies, most were either chemotherapy only or chemotherapy + targeted therapy and were palliative in intent.

All participants in ROS1 TKI-pretreated cohort had prior anticancer therapies. Almost all prior systemic therapies in this cohort were palliative in intent. All participants in the ROS1 TKI-pretreated cohort received ROS1 targeted TKIs, and a smaller proportion of these received chemotherapies or other targeted therapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of prior systemic therapies. In the efficacy analysis population (n=169), 92 patients (54%) had prior systemic anticancer therapies, with targeted therapy being the most common (n=67, 40%). Approximately 13% of patients had received prior radiotherapy, and 14% of patients had prior anticancer surgeries or procedures.

In the ROS1 TKI-naïve REP (n=103), 25% of patients had prior systemic anticancer therapy. Nineteen percent of patients had prior platinum-based chemotherapy for advanced disease. In accordance with protocol eligibility criteria, no patients in Cohort 1 had prior ROS1 TKIs.

In the ROS1 TKI-pretreated REP (n=66), 100% of patients had prior systemic anticancer therapy. Thirty five percent of patients had prior platinum-based chemotherapy for advanced disease. In accordance with protocol eligibility, 100% had prior target therapy against *ROS1* fusion (crizotinib).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Participants were to return all taletrectinib capsules and their packaging at each visit. The number of capsules remaining was recorded upon the return of the vials to assess the participant's compliance.

Exposure results based on participant dosing reflect overall treatment compliance.

In the ROS1 TKI-naïve cohort, the classes of concomitant medications that were taken by ≥10% of participants included drugs for acid related disorders, cough and cold preparations, corticosteroids for systemic use, antibacterials for systemic use, antiemetics and antinauseants, anesthetics, drugs for obstructive airway diseases, immunostimulants, antithrombotic agents, and antineoplastic agents. In the ROS1 TKI-pretreated cohort, the classes of drugs that were taken by ≥10% of participants included bile and liver therapy, drugs for acid related disorders, cough and cold preparations, corticosteroids for systemic use, analgesics, drugs for obstructive airway diseases, and antihemorrhagics.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of treatment compliance. The median relative dose intensity in the REP (n=169) and safety analysis population (n=173) was 99%

(range: 34-100). In the REP (n=169), study drug compliance was reported as a major protocol deviation in three patients (1.8%) and minor protocol deviation in 128 patients (76%). Seventy-two patients (43%) were reported to have had missing study drug (defined as any missing dose on any day of a treatment cycle), with 65 of the 72 patients (90%) reported missing no more than two days of study drug in any given 21-day cycle. In the 15 patients with 18 overdose events (defined as any dose higher than the highest daily dose), 14 patients had overdose events for one day only. No clinical sequelae were reported in any of the overdose events.

Efficacy Results

Data and the Applicant's Position:

The efficacy results of Study C203 are presented along with the integrated results in **Table 22**.

In Study C203, taletrectinib demonstrated robust efficacy in both ROS1 TKI-naïve and ROS1 TKI-pretreated cohorts. In both cohorts, 100% of participants who responded were followed for ≥12 months after initial response.

ROS1 TKI Naïve (N=103):

Taletrectinib treatment led to a high ORR.

- The IRC-assessed cORR was 90.3% (95% CI: 82.9%, 95.3%), the IRC-assessed DCR was 95.1% (95% CI: 89.0%, 98.4%), and 5 participants (4.9%) achieved CR.

Responses were durable.

- As of 28 Oct 2024, the IRC-assessed mDOR was not reached (95% CI: 30.4, NR). The 24-month DOR rate was 75.3% (95% CI: 64.2%, 83.4%).

Taletrectinib treatment led to a prolonged PFS.

- The mPFS was 44.6 months (95% CI: 30.7, NR), and the 24-month PFS rate was 69.3% (95% CI: 58.5%, 77.8%).

Response rates were similar between subgroups.

- ORR results were comparable across different subgroups, including participants with brain metastasis at baseline and participants previously treated with chemotherapy.

Responses were observed in IC metastases.

- Additionally, a high IC-ORR based on mRECIST was observed in participants with measurable brain metastasis at baseline (n=8) (87.5% [95% CI: 47.4%, 99.7%]), and IC-DCR was 100% (95% CI: 63.1%, 100%).

OS rate was high.

- The mOS was not reached (95% CI: 41.56, NR), and the OS rate was 79.5% (95% CI: 70.4%, 86.2%) at 24 months.

Results were similar by IRC and investigator.

- All investigator-assessed endpoints had similar results to the IRC-assessed endpoints.

ROS1 TKI-Pretreated (N=66):

Taletrectinib treatment led to a high ORR.

- The IRC-assessed cORR was 51.5% (95% CI: 38.9%, 64.0%), and the IRC-assessed DCR was 83.3% (95% CI: 72.1%, 91.4%).

Responses were durable.

- As of 28 Oct 2024, the mDOR as per the IRC assessment was 13.2 months (95% CI: 7.7, 24.9). The 12-month DOR rate was 55.9% (95% CI: 36.3%, 71.6%).

Taletrectinib treatment led to a prolonged PFS.

- The mPFS was 7.6 months (95% CI: 5.5 to 12.0), and the 12-month PFS rate was 37.1% (95% CI: 24.5%, 49.7%).

Response rates were similar between subgroups.

- ORR results were comparable across different subgroups, including participants with brain metastasis at baseline and participants previously treated with chemotherapy.

Responses were observed in IC metastases.

- Additionally, IC-ORR and IC-DCR based on mRECIST in 16 participants with measurable brain metastasis at baseline were 75.0% (95% CI: 47.6%, 92.7%) and 93.8% (95% CI: 69.8%, 99.8%), respectively.

mOS was >24 months.

- mOS was 25.6 months (95% CI: 19.2, 31.9), and the 36-month OS rate was 36.2% (95% CI: 23.0%, 49.6%).

Results were similar by IRC and investigator.

- All investigator-assessed endpoints had similar results to the IRC-assessed endpoints.

Robust activity was observed against acquired resistance mutations, including G2032R.

- In crizotinib pretreated participants, *ROS1*-resistance mutations were detected by either tissue or liquid Next-Generation Sequencing in 50.0% (14/28). The IRC-assessed cORR in participants with G2032 mutations was 66.7% (8/12 participants; 95% CI: 34.9%, 90.1%).

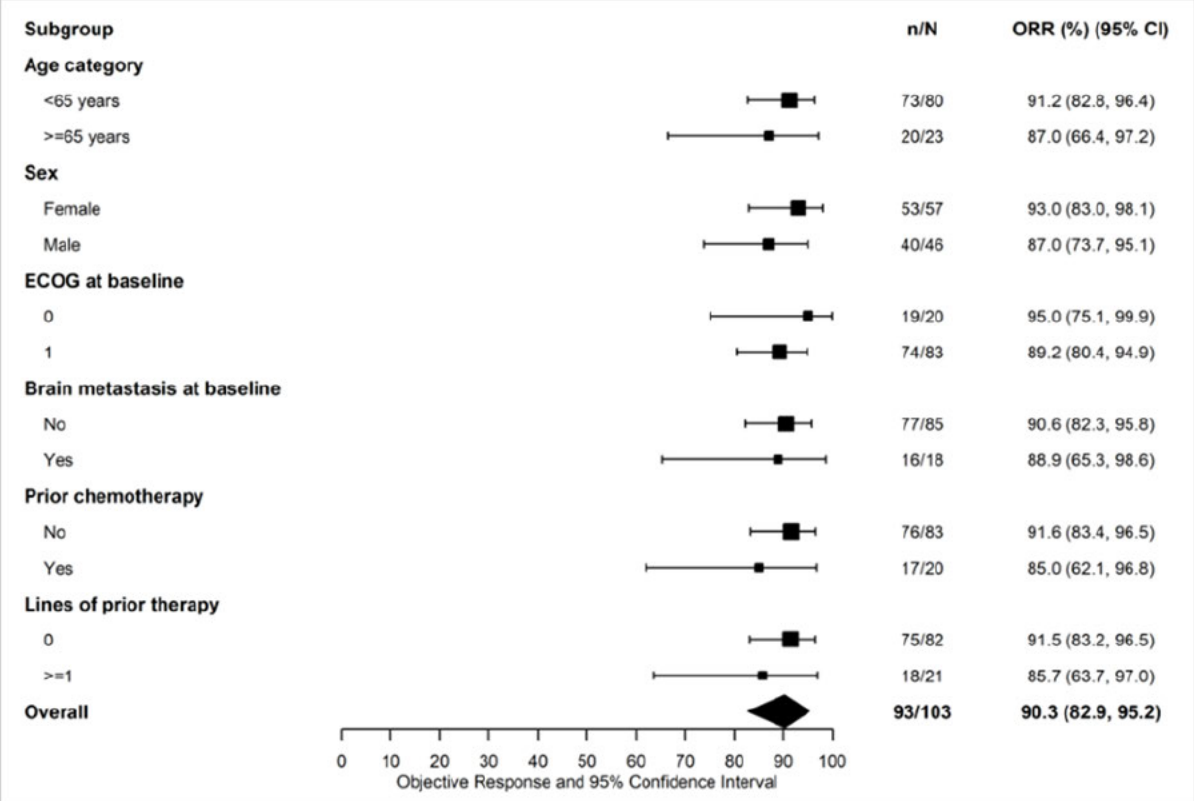
The FDA's Assessment:

FDA generally agrees with the efficacy results; however, given the single arm study design, it cannot be concluded that taletrectinib treatment led to prolonged PFS.

Complete responses were observed in 5% of patients in the TKI-naïve cohort, with 85% of patients demonstrating partial responses. The median DOR was not reached in the TKI-naïve cohort and the proportion of patients with observed DOR ≥12 months was 72% (**Table 22**); DOR ranged from 1.1 to 46.9+ months. In the TKI-pretreated group, all responders demonstrated partial responses (52% of patients); DOR ranged from 1.4 to 38.7 + months, with 74% and 44% of patients demonstrating responses of at least 6 and 12 months, respectively. The ORR subgroup analyses based on demographic and clinical characteristics were mostly consistent across subgroups in the ROS1 TKI-naïve cohort and the ROS1 TKI pre-treated cohorts as presented below.

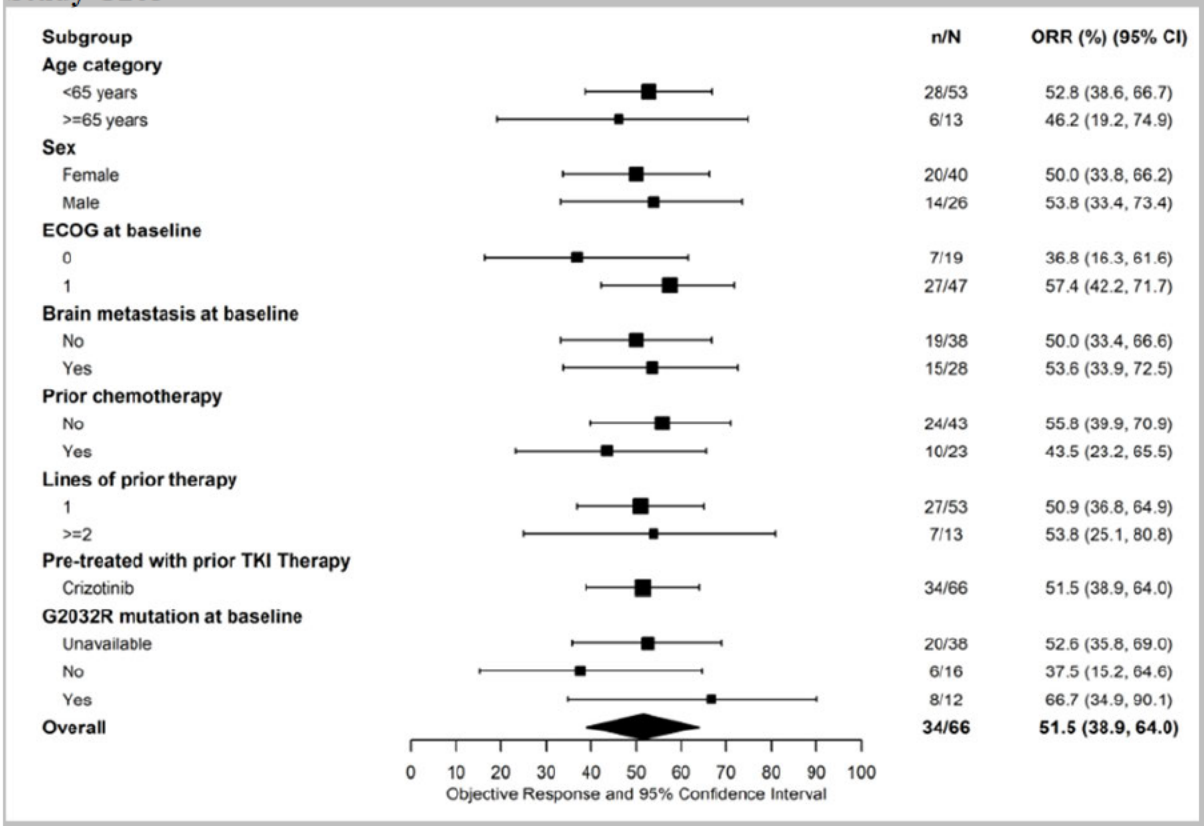
Please refer to **Section 8.1.1.7** and **Table 26** for FDA's analysis of intracranial responses.

Figure 26. FDA Analysis – ORR Subgroup Analysis for ROS1 TKI Naïve Patients in Study C203



Source: FDA reviewer generated analysis (Data: ADSL, ADSR)

Figure 27. FDA Analysis – ORR subgroup Analysis for ROS1 TKI Pre-Treated Patients in Study C203



Source: FDA reviewer generated analysis (Data: ADSL, ADSR)

Data Quality and Integrity

The Applicant's Position:

No meaningful concerns were identified in the quality and integrity of the submitted datasets, which were sufficiently complete to allow a thorough review of efficacy. Furthermore, no data integrity concerns were reported following completion of center inspections by the Applicant.

The FDA's Assessment:

FDA agrees with the Applicant's position. The data submitted were organized and adequate to perform a comprehensive review of the efficacy of taletrectinib in patients with *ROS1*-positive NSCLC. FDA issued information requests during the review cycle to obtain clarification and additional information regarding data included in the NDA, and all requests were addressed appropriately.

Dose/Dose Response

The Applicant's Position:

Data on dose response are presented in **Section 6.3.2**.

The FDA's Assessment:

Refer to FDA's assessment in **Section 6.3.2**.

Durability of Response

The Applicant's Position:

Data on durability of response are included in the efficacy results presented above.

The FDA's Assessment:

FDA generally agrees with the Applicant; the 90-day safety update demonstrated that a majority of responders experienced a durable response. In the ROS1 TKI-naïve cohort, at least 72% remained in response at 12 months; in the ROS1 TKI-pretreated cohort, 74% and 44% remained in response at 6 and 12 months, respectively (**Table 22**).

Persistence of Effect

Data and the Applicant's Position:

In all clinical trials in participants with solid tumors, including Study C203, taletrectinib was dosed until PD that required an alternative therapy, intolerable toxicity, or another discontinuation criterion was met. Study drug was usually discontinued once the participants had disease progression. However, taletrectinib treatment could be continued after PD if, in the opinion of the investigator, the participant continued to experience clinical benefit including, but not limited to, systemic benefit if the site of progression was localized to the brain.

At the time of the 07 June 2024 data cutoff, the median follow-up time for ROS1 TKI-naïve participants was 36.40 months. In Study C203, 71.8% of ROS1 TKI-naïve participants remained on study and 50.5% were continuing on study drug. For ROS1 pretreated participants, the median follow-up time was 30.37 months. In Study C203, 50.0% of ROS1 TKI-pretreated participants remained on study and 21.2% were continuing on study drug (90-day C203 Table 14.1.1.1.2.A2).

As of the 90-day safety update data cutoff (28 Oct 2024), in the ROS1 TKI-naïve cohort of Study C203, the median follow-up time was 40.94 months. In the ROS1 TKI pretreated cohort, the median follow-up time was 35.07 months (90-day C203 Table 14.2.10.1.A1, 90-day C203 Table 14.1.1.1).

The FDA's Assessment:

FDA agrees with the Applicant; the study design and drug administration schedule do not permit an assessment of persistence of effect beyond drug discontinuation.

Efficacy Results – Secondary or exploratory Clinical Outcome Assessment (PRO) endpoints

The Applicant's Position:

Not applicable, no PRO endpoints were included in C203.

The FDA's Assessment:

No PRO endpoints were included in Study C203.

Additional Analyses Conducted on the Individual Trial

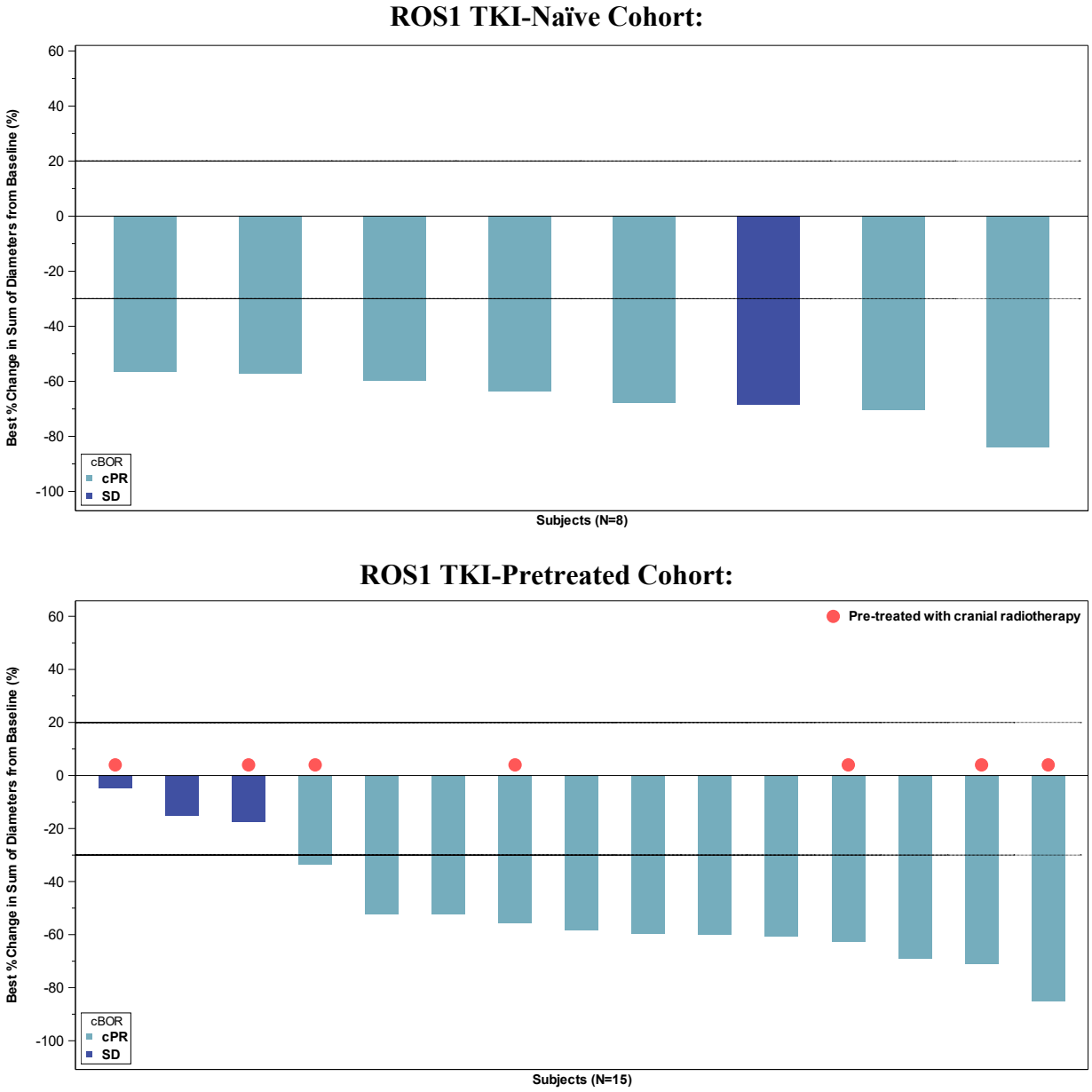
Data:

Table 34. Applicant - Summary of IRC-Assessed Intracranial Confirmed Objective Response Rate and Disease Control Rate Per mRECIST v1.1

Category	ROS1 TKI-Naïve N=8	ROS1 TKI-Pretreated N=16
Best overall response, n (%)		
CR	0	0
PR	7 (87.5)	12 (75.0)
SD	1 (12.5)	3 (18.8)
PD	0	0
Not evaluable	0	1 (6.3)
Objective response rate (CR + PR), n (%)	7 (87.5)	12 (75.0)
2-sided 95% CI[a]	[47.35, 99.68]	[47.62, 92.73]
Disease control rate (CR + PR + SD), n (%)	8 (100.0)	15 (93.8)
2-sided 95% CI[a]	[63.06, 100.00]	[69.77, 99.84]

Abbreviations: CI, confidence interval; CR, complete response; IAP, Intracranial Analysis Population; IRC, independent review committee; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; N, total number of participants; n, subset of total number of participants; NE, not evaluable; PD, progressive disease; PR, partial response; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the IAP.
[a] The Clopper and Pearson method was used to calculate CI.
Source: CSR AB-106-C203 Table 14.2.6.1.1 and Table 14.2.6.2.1

Figure 28. Applicant - Waterfall Plot of IRC-Assessed Best Overall Response, Per Intracranial mRECIST v1.1



Abbreviations: cBOR, confirmed best overall response; cPR, confirmed partial response; IRC, independent review committee; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; N, total number of participants; NE, not evaluable; ROS1, c-ros oncogene 1; SD, stable disease; TKI, tyrosine kinase inhibitor.
Note: Analysis was based on the Intracranial Analysis Population (IAP).
Note: Participants with cBOR as NE are not displayed in the figure.
Note: Dark blue bars indicate SD and teal bars indicate cPR. Red circles indicate participants previously treated with cranial radiotherapy.
Source: CSR AB-106-C203 Figure 14.2.6.1.1 and Figure 14.2.6.2.1

The Applicant's Position:

A high IC-ORR based on mRECIST was observed in participants with measurable brain metastasis at baseline (n=8, 87.5% [95% CI: 47.4%, 99.7%] for TKI-naïve participants; n=16, 75.0% [95% CI: 47.6%, 92.7%] for pretreated participants).

The FDA's Assessment:

FDA performed a revised analysis of IC-ORR, accounting for brain radiation within 2 months before study entry to minimize bias in distinguishing radiation effects from drug effects on brain metastatic lesions. Refer to FDA's assessment in **Section 8.1.1.6**.

8.1.6. Integrated Review of Effectiveness

Refer to **Section 8.1.1** for integrated efficacy assessment.

The FDA's Assessment:

FDA agrees with the Applicant.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

The efficacy evaluation of taletrectinib was primarily based on the integrated efficacy analysis of two Phase 2 pivotal studies (G208 and C203). As of the 28 Oct 2024 data cutoff, the median follow-up time was 25.0 months for ROS1 TKI-naïve participants and 23.0 months for ROS1 TKI-pretreated participants. The majority of responders (97.1%) in the treatment-naïve group had at least 12 months of follow-up from the onset of response, and all responders (100%) in the pretreated group had at least 6 months of follow-up from the onset of response. Demographics and baseline characteristics in G208, C203, and in the pooled analysis set were generally similar to the expected general NSCLC patient population with ROS1 fusion, i.e., participants tended to be female, younger, and most were never smokers and had adenocarcinoma (Chevallier et al., 2021). Nineteen percent to 40% of participants had been previously treated with systemic chemotherapy and 20% to 50% of participants had brain metastasis at baseline; both trends were higher in ROS1 TKI-pretreated participants.

Taletrectinib demonstrated clinically meaningful efficacy in participants with ROS1+ NSCLC regardless of ROS1 TKI treatment history.

- The cORR by IRC assessment was 88.5% (95% CI: 82.49, 93.06) and 55.8% (95% CI: 46.11, 65.09) for ROS1 TKI-naïve and -pretreated participants, respectively (as of 07 June 2024).
- Responses occurred quickly and were durable.

  ROS1 TKI-naïve participants (as of 28 Oct 2024).:

- mDOR, 43.3 months
- Kaplan-Meier estimate at 36 months, 58.3%

ROS1 TKI-pretreated participants (as of 28 Oct 2024):

- mDOR, 14.7 months
- Kaplan-Meier estimate at 24 months, 38.3%.

- The DCR was 94.9% and 87.6% for ROS1 TKI-naïve and -pretreated participants by IRC assessment, respectively (as of 07 June 2024).
- The activity (confirmed response) of taletrectinib in participants with G2032R mutation was observed in 61.5% (8 out of 13) of participants (as of 07 June 2024).
- The control of disease also contributed to the prolonged PFS (mPFS, 44.6 months for ROS1 TKI-naïve and 9.7 months for ROS1 TKI-pretreated participants) (as of 28 Oct 2024).
- Efficacy results by investigator assessment were consistent with those assessed by IRC.
- The mOS in the pooled analysis set was not reached for ROS1 TKI-naïve participants and the estimated OS was 67.4% at 36 months; the mOS was 26.7 months for ROS1 TKI-pretreated participants and the estimated OS was 41.0% at 36 months (as of 28 Oct 2024).
- Across different subgroups, a consistent treatment effect on cORR was observed in G208 and the pooled analysis set in the following subgroups: sex, age, ECOG, prior chemotherapy, brain metastasis at baseline, race and by geographic region (Western versus Asia-Pacific) (as of 07 June 2024).

Taken together, taletrectinib demonstrated clinically meaningful efficacy in participants with advanced ROS1 + NSCLC regardless of prior ROS TKI treatment status, brain metastasis, or resistance mutation status at baseline. Clinical meaningful efficacy was consistently observed across sex, age, race, and geographic regions. The efficacy demonstrated by taletrectinib as measured by ORR, DOR, PFS, and OS compared favorably to all available treatments including ROS1 TKIs.

An efficacy comparison of taletrectinib to the approved ROS1 TKIs is presented in **Table 35**.

Table 35. Applicant - Taletrectinib Cross Trial Efficacy Comparison to ROS1 Inhibitors Approved for ROS1+ NSCLC

Category	Crizotinib[a]	Entrectinib[b]	Repotrectinib[c]		Taletrectinib[d]	
Patient population	ROS1 TKI-naïve (N=50) 80% chemo pretreated	ROS1 TKI-naïve (N=92) 65% chemo pretreated	ROS1 TKI-naïve (N=71) 28% chemo pretreated	ROS1 TKI-pretreated (N=56) all chemo naïve	ROS1 TKI-naïve (N=157) 19% chemo pretreated	ROS1 TKI-pretreated (N=113) 37% chemo pretreated
ORR, % [95% CI]	72 [58, 83]	74 [64, 83]	79 [68, 88]	38 [25, 52]	89 [82, 93]	56 [46, 65]
Median DOR, months [95% CI]	24.7 [15.2, 45.3]	Range of observed DOR: 2.4, 55.2+	34.1 [25.6, NR]	14.8 [7.6, NR]	43.3 [30.4, NR]	14.7 [10.6, 24.9]

Abbreviations: CI, confidence interval; DOR, duration of response; NA, not applicable; NSCLC, non-small cell lung cancer; NR, not reached; ORR, objective response rate; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor.

[a] (XALKORI® (crizotinib), 2022)

[b] (ROZLYTREK™ (entrectinib), 2024)

[c] (AUGTYRO™ (repotrectinib), 2024)

[d] Source: ISE Table 3.1.1.1.A2, ISE Table 3.1.1.2, ISE Table 3.1.2.1, 90-day ISE Table 3.2.1.1.A1, and 90-day ISE Table 3.2.2.1

The FDA's Assessment:
FDA's efficacy evaluation is based on the magnitude of the observed confirmed ORR and durability of responses and considered in the context of an overall benefit-risk assessment. FDA notes that analyses for time-to-event endpoints such as PFS and OS are not interpretable for efficacy evaluation in non-comparative trials and are considered exploratory only. Furthermore, cross-trial comparison of single-arm trial results should be interpreted with caution due to variations in study design, patient populations, and endpoint assessments including handling of intercurrent events.

FDA agrees with the Applicant that the efficacy results demonstrate clinically meaningful antitumor activity of taletrectinib in both ROS1 TKI-naïve and ROS1 TKI-pretreated (one prior ROS1 TKI) patients with advanced or metastatic *ROS1*-positive NSCLC. The effectiveness of taletrectinib was consistent across prespecified subgroups (including in patients with CNS metastasis and resistance mutations) and supported by sustained durability of responses, providing substantial evidence of antitumor activity over time.

Among the 157 patients with NSCLC who were ROS1 TKI-naïve, the ORR was 90% (95% CI: 83, 95) in Study C203 and 85% (95% CI: 73, 93) in Study G208 per RECIST v1.1 by BICR. The median duration of response was not reached (NR) (95% CI: 30.4 months, NR) in Study C203. The median duration of response in study G208 was not reached (b) (4). In the ROS1 TKI-naïve population, 72% of responders in Study C203 and 63% of responders in Study G208 had an observed DOR ≥12 months as of the October 28, 2024 DCO. In addition, 15 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions were observed in 11 patients.

Among the 113 patients with NSCLC who were ROS1 TKI-pretreated, the ORR was 52% (95% CI: 39, 64) in Study C203 and 62% (95% CI: 46, 75) in Study G208 per RECIST v1.1 by BICR. The median duration of response in Study C203 was 13.2 months (95% CI: 7.7, 24.9). The median duration of response in study G208 was 19.4 months (95% CI: 10,7, NR) based on the 90-day safety update data. At the time of this update, 6 out of 13 patients were censored prior to median DOR based on differences in investigator and BICR assessment of response, with 5 of those 6 patients experiencing disease progressions per investigator assessment. This early potentially informative censoring is likely leading to an overestimation of median DOR. (b) (4) In the ROS1 TKI-pretreated population, as of the October 28, 2024 DCO, 74% of responders in Study C203 and 83% of responders in Study G208 had an observed DOR ≥6 months; 44% of responders in Study C203 and 45% of responders in Study G208 had an observed DOR ≥12 months.

8.2. Review of Safety

The Applicant's Position:

The safety data for this application focuses on the safety findings reported in 2 completed (Phase 1 studies DS6051-A-U101 and DS6051-A-J102) and 3 ongoing (Phase 2 studies AB-106-G208, AB-106-C203, and AB-106-C205) clinical trials in participants with solid tumors, and an overview of these studies is available in **Table 18**.

The safety data for this application includes the following 3 analysis populations:

- **ROS1+ NSCLC 600 mg QD Group:** Consists of all participants with ROS1+ NSCLC who received at least 1 dose of taletrectinib at 600 mg QD (N=337).
- **600 mg QD Group:** Consists of all participants with solid tumors who received at least 1 dose of taletrectinib at 600 mg QD (N=352).
- **Overall Group:** Consists of all participants with solid tumors who received at least 1 dose of taletrectinib (N=412).

A detailed analysis of safety for all 3 analysis populations is presented in Module 2.7.4. It is important to note there is a significant overlap across these 3 safety populations. For example, within the 412 participants in the overall safety population, 352 participants are in the 600 mg QD analysis population and 337 participants are included in the ROS1+ NSCLC 600 mg QD analysis population. As the AE profiles were comparable across the 3 pooled safety populations, this summary focuses on the 600 mg QD group (N=352), which includes both participants with ROS1+ NSCLC and those with other solid tumors, and provides a comprehensive presentation of safety data for the intended dose of taletrectinib as of the data cutoff. The data cutoffs to support the integrated assessment of safety for this NDA are as follows:

- 07 Jun 2024 for Studies AB-106-C203, AB-106-C205, and AB-106-G208
- 28 Dec 2021 for Study DS6051-A-J102
- 16 Sep 2021 for Study DS6051-A-U101

The FDA's Assessment:
FDA agrees with the Applicant's description of the pooled safety population. FDA's approach focused on the *ROS1*-positive NSCLC 600 mg QD group, which includes patients with *ROS1*-positive NSCLC who received at least one dose of taletrectinib at a dose of 600 mg QD (n=337), and the 600 mg QD group (n=352) comprising the *ROS1*-positive NSCLC 600 mg QD group plus 15 patients with solid tumors who received at least one dose of taletrectinib at 600 mg QD.

8.2.1. Safety Review Approach

The Applicant's Position:

The summary of safety includes information on study drug exposure; analyses of safety results including TEAEs and treatment-related TEAEs; any TEAE Grade 3 or higher; deaths; SAEs; AEs leading to dose interruption, dose reduction, or dose discontinuation; concomitant medications; AEs of special interest (AESIs); other safety events of interest (OSEIs); clinical laboratory evaluations; and vital signs and ECGs. In addition, this safety summary includes subgroup analyses.

The FDA's Assessment:

FDA completed a comprehensive analysis and review of safety datasets and patient narratives submitted for the pooled dataset. Refer to **Table 47** and **Table 55** for FDA's Definitions of grouped terms (GT) and safety events of interest. Given the clinical significance and serious outcomes of liver-related TEAEs, FDA has used the term "hepatotoxicity" to describe the reported terms of "hepatic function abnormal," "liver injury," "hepatic failure" and "drug-induced liver injury" in FDA's assessment of fatal adverse reactions, drug interruptions, dose reductions or drug discontinuations.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 36. Applicant - Summary of Participant Disposition

Treatment Disposition, n (%)	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Ongoing	146 (43.3)	151 (42.9)	156 (37.9)
Discontinued treatment	191 (56.7)	201 (57.1)	256 (62.1)
Adverse event	14 (4.2)	14 (4.0)	20 (4.9)
Death	10 (3.0)	11 (3.1)	13 (3.2)
Disease progression	132 (39.2)	138 (39.2)	174 (42.2)
Withdraw consent	6 (1.8)	6 (1.7)	12 (2.9)
Physician decision	3 (0.9)	4 (1.1)	4 (1.0)
Pregnancy	2 (0.6)	2 (0.6)	2 (0.5)
Poor compliance	2 (0.6)	2 (0.6)	2 (0.5)
Start new anticancer therapy	2 (0.6)	2 (0.6)	2 (0.5)
Completed	2 (0.6)	2 (0.6)	4 (1.0)

Treatment Disposition, n (%)	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Other[a]	18 (5.3)	20 (5.7)	23 (5.6)

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
[a] Participants discontinued for a variety of reasons described individually by the investigator and listed in the clinical study report for each study in Module 5.
Source: ISS Table 1.1.1

Table 37. Applicant - Taletrectinib Exposure

Category	ROS1+ NSCLC 600 mg QD N=337	600 mg QD N=352	Overall N=412
Duration of exposure (months)[a]			
n (missing)	337 (0)	352 (0)	412 (0)
Mean (standard deviation)	14.11 (12.183)	14.06 (12.166)	13.45 (13.260)
Median	11.14	11.14	9.68
Q1, Q3	4.60, 19.25	4.48, 19.33	3.15, 18.18
Minimum, Maximum	0.1, 64.1	0.1, 64.1	0.1, 77.5
Treatment duration			
Exposure time ≥3 months	277 (82.2)	287 (81.5)	311 (75.5)
Exposure time ≥6 months	229 (68.0)	238 (67.6)	258 (62.6)
Exposure time ≥9 months	195 (57.9)	203 (57.7)	219 (53.2)
Exposure time ≥12 months	157 (46.6)	164 (46.6)	178 (43.2)
Exposure time ≥18 months	95 (28.2)	101 (28.7)	110 (26.7)
Exposure time ≥24 months	56 (16.6)	59 (16.8)	65 (15.8)
Total actual dose received (mg)			
n (missing)	337 (0)	352 (0)	412 (0)
Mean (standard deviation)	232504.5 (211055.81)	230615.3 (210384.47)	218078.9 (221915.48)
Median	167200.0	166200.0	147000.0
Q1, Q3	78000.0, 327600.0	75900.0, 326700.0	50100.0, 305600.0
Minimum, Maximum	600, 1144200	600, 1144200	600, 1481600
Actual dose intensity (mg/day)[b]			

Category	ROS1+ NSCLC 600 mg QD N=337	600 mg QD N=352	Overall N=412
n (missing)	337 (0)	352 (0)	412 (0)
Mean (standard deviation)	538.72 (99.511)	537.43 (100.944)	539.73 (132.535)
Median	592.00	592.09	592.37
Q1, Q3	508.15, 600.00	505.29, 600.00	458.80, 600.00
Minimum, Maximum	200.4, 775.1	196.8, 775.1	36.4, 1200.0
Relative dose intensity (%)[c]			
N (missing)	337 (0)	352 (0)	412 (0)
Mean (standard deviation)	89.85 (16.439)	89.63 (16.687)	88.96 (17.939)
Median	98.70	98.73	98.68
Q1, Q3	84.69, 100.00	84.21, 100.00	83.03, 100.00
Minimum, Maximum	34.2, 129.2	32.8, 129.2	9.1, 129.2

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; Q, quartile; QD, once daily, ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
[a] Duration of exposure (months) was calculated as: (date of last dose - date of first dose+1)/30.4375.
[b] Actual dose intensity was calculated as: total actual dose received/duration of exposure.
[c] Relative dose intensity (%) was calculated as: (actual cumulative dose (mg)/planned cumulative dose (mg))×100.
Source: ISS Table 2.1.1

The Applicant's Position:

As of the data cutoff, 42.9% of participants remained on treatment in the 600 mg QD group (**Table 36**).

The most frequently reported reason for discontinuation of treatment was disease progression (39.2%). Treatment discontinuation due to AEs was 4.0%.

In the 600 mg QD group, the median (min, max) duration of exposure was 11.14 months (range: 0.1, 64.1) (**Table 37**). A majority of participants had treatment duration ≥6 months (67.5%), and 46.6% had treatment duration ≥12 months.

The median (min, max) actual dose intensity was 592.09 mg/day (range: 196.8, 775.1), close to the target dose.

The median (min, max) relative dose intensity was 98.73% (range: 32.8, 129.2).

The FDA's Assessment:

FDA agrees with the Applicant's summary of overall exposure to taletrectinib. The exposure characteristics are similar between the *ROS1*-positive NSCLC 600mg QD and the 600mg QD group.

In the 600mg QD group (n=352) group, the median duration of exposure to taletrectinib was 11.1 (range 0.1-64.1) months. The median relative dose intensity was 99% (range: 33-129). Sixty-eight percent of patients had treatment duration ≥ 6 months and 47% received treatment ≥ 12 months.

Relevant characteristics of the safety population:

Data:

Table 38. Applicant - Participant Demographics

Category	ROS1+ NSCLC 600 mg QD N=337	600 mg QD N=352	Overall N=412
Sex (n [%])			
Male	147 (43.6)	155 (44.0)	182 (44.2)
Female	190 (56.4)	197 (56.0)	230 (55.8)
Age (years)			
n (missing)	337 (0)	352 (0)	412 (0)
Mean (standard deviation)	55.3 (12.11)	55.4 (12.20)	55.9 (12.33)
Median	56.0	56.0	56.5
Q1, Q3	47.0, 64.0	47.0, 64.5	48.0, 65.0
Minimum, Maximum	26, 83	26, 83	24, 83
Age category (n [%])			
<65 years	256 (76.0)	264 (75.0)	303 (73.5)
≥65 years to <75 years	67 (19.9)	74 (21.0)	91 (22.1)
≥75 years	14 (4.2)	14 (4.0)	18 (4.4)
Weight (kg) at baseline			
n (missing)	334 (3)	349 (3)	409 (3)
Mean (standard deviation)	65.4 (13.98)	65.3 (14.02)	66.7 (15.12)
Median	64.0	63.5	65.0
Q1, Q3	55.0, 73.5	55.0, 73	56.0, 75.0
Minimum, Maximum	38.3, 115.0	38.3, 115.0	38.30, 125.2

Category	ROS1+ NSCLC 600 mg QD N=337	600 mg QD N=352	Overall N=412
Race (n [%])			
Asian	257 (76.3)	272 (77.3)	282 (68.4)
White	52 (15.4)	52 (14.8)	98 (23.8)
Other	28 (8.3)	28 (8.0)	32 (7.8)
Region category 1 (n [%])			
Western	85 (25.2)	85 (24.1)	136 (33.0)
Asia	252 (74.8)	267 (75.9)	276 (67.0)
Region category 2 (n [%])			
China	188 (55.8)	202 (57.4)	202 (49.0)
non-China	149 (44.2)	150 (42.6)	210 (51.0)
Region category 3 (n [%])			
United States	14 (4.2)	14 (4.0)	61 (14.8)
Asia	252 (74.8)	267 (75.9)	276 (67.0)
Other	71 (21.1)	71 (20.2)	75 (18.2)
ECOG at baseline (n [%])			
0	109 (32.3)	111 (31.5)	134 (32.5)
1	228 (67.7)	240 (68.2)	277 (67.2)
≥2	0	1 (0.3)	1 (0.2)
Tumor type (n [%])			
NSCLC	337 (100)	343 (97.4)	364 (88.3)
Other	0	9 (2.6)	48 (11.7)
Tumor stage at baseline (n [%])			
I	0	0	1 (0.2)
II	0	0	1 (0.2)
III	19 (5.6)	20 (5.7)	23 (5.6)
IV	318 (94.4)	331 (94.0)	383 (93.0)
Other	0	1 (0.3)	2 (0.5)
Missing	0	0	2 (0.5)
Study (n [%])			
AB-106-C203	173 (51.3)	173 (49.1)	173 (42.0)

Category	ROS1+ NSCLC 600 mg QD N=337	600 mg QD N=352	Overall N=412
AB-106-C205	0	14 (4.0)	14 (3.4)
AB-106-G208	158 (46.9)	159 (45.2)	164 (39.8)
DS6051-A-J102	6 (1.8)	6 (1.7)	15 (3.6)
DS6051-A-U101	0	0	46 (11.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; Q, quartile; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16
Source: ISS Table 1.1.2

The Applicant's Position:

In the 600 mg QD group, a higher proportion of participants were female, under 65 years old, and had an ECOG performance status of 1 at baseline (**Table 38**). Nearly all (97.4%) participants had NSCLC as the reported tumor type and most (94.0%) had Stage IV tumors.

Among the 352 participants in the 600 mg QD group, 85 (24.1%) enrolled in North America and Europe and 267 (75.9%) enrolled in Asia.

Overall, the participant population reflected demographic and clinical characteristics expected of patients diagnosed with ROS1+ advanced NSCLC in the US and globally.

The FDA's Assessment:
The demographic characteristics are generally similar between the *ROS1*-positive NSCLC 600 mg QD and 600 mg QD group. In both groups, a higher proportion of patients were female (56% and 56%, respectively), under 65 years old (76% and 75%), and Asian (76% and 77%). In the *ROS1*-positive NSCLC 600 mg QD, 0.6% were Black or African American and 1.8% were of Hispanic or Latino ethnicity. These demographic distributions for age and sex are aligned with the demographics of patients with *ROS1*-positive NSCLC reported in the literature. Literature suggests that the incidence of ROS1 fusions in Black and Hispanic patients with NSCLC is low; therefore, although few Black patients and patients of Hispanic ethnicity are included, this may reflect the low incidence of ROS1 fusions in these populations (Costa, 2021).

Adequacy of the safety database:

The Applicant's Position:

The population studied in G208 and C203 adequately represents the target population for the proposed indication, as supported by the demographic, disease, and other baseline characteristics described above. The safety database, including more than 400 participants with cancer

regardless of tumor type, with 352 of those patients receiving 600 mg QD, is considered adequate for the detection of safety signals for taletrectinib, to provide guidance regarding management of toxicities, and for assessment of the benefit-risk profile of taletrectinib.

The FDA's Assessment:

FDA agrees with the Applicant's position that the data from the pooled safety population adequately represents the target population, including demographics, disease, and other baseline characteristics. Please refer to FDA's comment under "Relevant characteristics of the safety population" above. The safety narratives provided in the NDA submission were adequate to allow evaluation of relevant safety signals.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues were identified regarding the integrity and quality of the safety data included in this submission. Studies were conducted in accordance with the ethical principles of GCP.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Categorization of Adverse Event

The Applicant's Position:

The severity of AEs was graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 or 5.0 toxicity grades. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 27.0.

For the pooled safety populations and subgroup populations, the number and percentage of participants in the treatment group who had AEs are displayed by MedDRA system organ class (SOC) and PT.

If an AE was reported for a given participant more than once during treatment, the worst toxicity grade and the worst relationship to study drug were tabulated.

A TEAE is defined as an AE with an onset date, or increase in severity level, after the first dose of study drug and within 30 days after the last dose of study drug (permanent discontinuation of study drug), or before initiation of new anticancer therapy, whichever occurs first. If an AE occurred after initiation of new anticancer therapy and is assessed as related by the investigator, it will be also considered a TEAE.

A treatment-related AE is an AE that is noted by the investigator as related, possibly, or probably related to study drug or with a missing causal relationship.

The AE relationship to study drug was recorded differently in each study. If the study did not collect information simply as related and unrelated, the input will be mapped according to the following rules: missing, unknown, related, possibly related, probably related, and definitely related as related; possibly unrelated and definitely unrelated as unrelated for the integrated summary of safety (ISS). The specific relationships collected during a trial can be found in the individual CSR.

An SAE is any untoward medical occurrence at any dose that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is considered a significant medical AE by the investigator based on medical judgment.

For the pooled analysis, AESI are events that meet the definition of Hy's Law criteria.

OSEIs include standardized MedDRA queries (SMQs) or customized PTs of interest, which are assessed to determine clinical relevance in the target patient population (refer to **Section 8.2.5** for further detail).

The FDA's Assessment:
FDA agrees with the Applicant's description of AE grading and the definitions of TEAE and SAE. FDA agrees with the Applicant's position on the medical concepts regarding AESI and OSEI. Refer to **Table 55** for FDA's Definition of safety events of interest and FDA's safety assessment in **Section 8.2**.

Routine Clinical Tests

The Applicant's Position:

Laboratory assessments, including clinical chemistry, hematology, and coagulation, were performed at baseline prior to taletrectinib dosing, at regularly scheduled intervals, and when medically necessary during drug administration. Additionally, vital sign measurements, physical examinations, performance status, ECGs, and pregnancy testing were performed to allow for adequate safety monitoring.

The FDA's Assessment:
FDA agrees with the Applicant's position. The schedule of safety assessments was adequate to inform a safety analysis.

8.2.4. Safety Results

Deaths

Data:

Table 39. Applicant - Deaths by Primary Reason

Category	ROS1+ NSCLC 600 mg QD (N=337) n (%)	600 mg QD (N=352) n (%)	Overall (N=412) n (%)
Number of participants who died	102 (30.3)	107 (30.4)	117 (28.4)
Primary reason for death			
Disease progression	61 (18.1)	63 (17.9)	71 (17.2)
Disease-related complication without disease progression	2 (0.6)	2 (0.6)	2 (0.5)
Adverse event	22 (6.5)	25 (7.1)	26 (6.3)
Unknown[a]	10 (3.0)	10 (2.8)	11 (2.7)
Other[b,c]	7 (2.1)	7 (2.0)	7 (1.7)
Number of participants who died more than 30 days after last dose of treatment	72 (21.4)	75 (21.3)	79 (19.2)
Disease progression	55 (16.3)	57 (16.2)	59 (14.3)
Disease-related complication without disease progression	2 (0.6)	2 (0.6)	2 (0.5)
Adverse event	2 (0.6)	3 (0.9)	4 (1.0)
Unknown[a]	8 (2.4)	8 (2.3)	9 (2.2)
Other[b]	5 (1.5)	5 (1.4)	5 (1.2)
Number of participants who died within 30 days after last dose of treatment	30 (8.9)	32 (9.1)	38 (9.2)
Disease progression	6 (1.8)	6 (1.7)	12 (2.9)
Adverse event	20 (5.9)	22 (6.3)	22 (5.3)
Unknown[a]	2 (0.6)	2 (0.6)	2 (0.5)
Other[c]	2 (0.6)	2 (0.6)	2 (0.5)

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily, ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.

[a] Primary reason for death not specified.
[b] Other reasons include COVID-19, pulmonary infection, lung tumor with infection, fall resulting in death and respiratory failure.
[c] Other reasons include medical assisted in dying and abnormal liver function/disease progression/other causes.
Source: ISS Table 3.1.11.1

Table 40. Applicant - Treatment-Emergent Adverse Events Leading to Death (Grade 5)

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
At least 1 TEAE leading to death	25 (7.4)	28 (8.0)	29 (7.0)
Infections and infestations			
Pneumonia	5 (1.5)	5 (1.4)	5 (1.2)
COVID-19 pneumonia	1 (0.3)	1 (0.3)	1 (0.2)
Pneumonia bacterial	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary sepsis	1 (0.3)	1 (0.3)	1 (0.2)
General disorders and administration site conditions			
Disease progression	2 (0.6)	2 (0.6)	2 (0.5)
Multiple organ dysfunction syndrome	2 (0.6)	2 (0.6)	2 (0.5)
Death	1 (0.3)	1 (0.3)	1 (0.2)
Generalised oedema	1 (0.3)	1 (0.3)	1 (0.2)
Cardiac disorders			
Cardiac arrest	2 (0.6)	2 (0.6)	2 (0.5)
Cardiac failure	1 (0.3)	1 (0.3)	1 (0.2)
Cardiopulmonary failure	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	1 (0.3)	2 (0.6)	2 (0.5)
Hydrothorax	1 (0.3)	1 (0.3)	1 (0.2)
Interstitial lung disease	0	0	1 (0.2)
Respiratory failure	1 (0.3)	1 (0.3)	1 (0.2)
Gastrointestinal disorders			
Ileus	0	1 (0.3)	1 (0.2)
Intestinal perforation	0	1 (0.3)	1 (0.2)
Hepatobiliary disorders			
Hepatic failure	1 (0.3)	1 (0.3)	1 (0.2)

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Hepatic function abnormal	1 (0.3)	1 (0.3)	1 (0.2)
Nervous system disorders			
Cerebral haemorrhage	1 (0.3)	1 (0.3)	1 (0.2)
Vascular disorders			
Hypotension	1 (0.3)	1 (0.3)	1 (0.2)

Abbreviations:N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.1.7.1

The Applicant's Position:

In the 600 mg QD group, 30.4% of participants died from all causes, regardless of the number of days after the last dose of taletrectinib (**Table 39**). On-study deaths (death within 30 days after the last dose of treatment) occurred in 9.1% of participants. The majority of deaths occurred more than 30 days after the last dose of study drug. Regardless of the timing of death in relation to the last dose of treatment, the most common reason of death was disease progression.

TEAEs of pneumonia, cardiac arrest, disease progression, dyspnea, and multiple organ dysfunction syndrome were the only events that led to death in more than 1 participant in the 600 mg QD group (**Table 40**).

Overall, there were 4 participants with treatment-related TEAEs leading to death; 3 participants in the 600 mg QD group had treatment-related TEAEs leading to death. There were no treatment-related TEAEs leading to death reported in more than 1 participant in any group.

Three TEAEs leading to death in the 600 mg QD group were considered by the investigators to be related to taletrectinib: hepatic failure, hepatic function abnormal, and pneumonia (1 [0.3%] participant each). Two of 3 fatal cases (hepatic failure and pneumonia) were considered not treatment-related per the sponsor's assessment as well as that of an independent adjudicator.

A fourth fatal TEAE of interstitial lung disease (ILD) occurred in a participant who received 400 mg QD taletrectinib. This case was assessed as treatment-related by the investigator and possibly related by the sponsor, but unlikely related by an independent adjudicator; this participant had confounding factors such as PD and prior treatment with a PD-L1 inhibitor, but causal relationship with taletrectinib treatment could not be entirely ruled out.

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of deaths by primary reason. FDA's analysis focuses on deaths within 30 days after the last dose of treatment, which is aligned with the Applicant's definition of "on study" deaths. All death narratives provided in this NDA submission were reviewed.

Among patients with *ROS1*-positive NSCLC who received 600 mg QD (n=337), 102 patients (30%) died from all causes, with 61 deaths (18%) considered due to disease progression, 22 (7%) due to AE, 10 (3%) due to unknown causes, 7 (2.1%) due to others, and 2 (0.6%) due to disease related complications without disease progression. At the time of the DCO, 30 patients (9%) had died within 30 days of the last dose of taletrectinib. The causes of death were reported as due to AE (n=20, 6%), disease progression (n=6, 1.8%), other (n=2, 0.6%) and unknown (n=2, 0.6%). In the analysis of TEAEs leading to death, five cases with the primary cause of death reported as disease progression, other and unknown were included in the "TEAEs leading to death" group, contributing to a total of 25 TEAEs leading to death. In FDA's assessment, four deaths reported as due to TEAE were determined to be due to disease progression (Study G208, Patient IDs (b) (6) and Study C203, Patient ID (b) (6)). One death (Study G208, Patient ID (b) (6)) was due to a clear procedure-related complication. We agree with the Applicant that the two deaths in Study G208, Patient IDs (b) (6) were due to progressive disease. Based on FDA's assessment, TEAEs with fatal outcomes occurred in 18 patients (5%) including pneumonia (n=8, 2.4%), multiple organ dysfunction syndrome (n=2, 0.6%), hepatotoxicity (n=2, 0.6%), cardiac arrest (n=2, 0.6%), cardiac failure (n=1, 0.3%), cardiopulmonary failure (n=1, 0.3%), respiratory failure (n=1, 0.3%), and death not otherwise specified (n=1, 0.3%). Note that in FDA's analysis of TEAEs with fatal outcomes, "pneumonia" included events of "pneumonia," "pneumonia bacterial," "pulmonary sepsis" and "COVID-19 pneumonia;" "hepatotoxicity" included events of "hepatic failure" and "hepatic function abnormal."

FDA assessed the causes of death in the reported TEAEs of "generalized edema," "cerebral hemorrhage" and "hypotension" likely to be related to the underlying progressive disease. A brief summary of these three events is as follows:

Study G208, Patient ID (b) (6) cause of death: "generalized edema:" This was a 53-year-old White male with stage IV NSCLC, with metastatic lesions in the brain, lymph node and pleura, who received taletrectinib 600 mg QD. On Day 47 and Day 130, an overall response assessment revealed progressive disease with new lesion in the right retropectoral lymph node; however, study treatment was continued. The patient received radiotherapy to the brain lesions and subaortic lymph node from Day 200 to Day 204. An SAE of generalized edema was reported on Day 235. An echocardiogram showed severe pericardial effusion and ECG showed cardiorespiratory arrest. The patient died on Day 236 due to an SAE of Grade 5 generalized edema and disease progression.

Assessment: FDA considers the patient's death, with generalized edema and pericardial effusion, was likely a sequalae of disease progression with possible contribution of radiotherapy.

Study C203, Patient ID (b) (6) **cause of death: "cerebral hemorrhage:"** This was a 51-year-old Asian male with stage IV NSCLC, with metastatic lesions in the brain (lesions in the right basal ganglia and anterior horn of the left lateral ventricle), liver, bone, and bilateral pulmonary nodules, who received taletrectinib 600 mg QD. On Day 34 and Day 82, an overall response assessment revealed progressive disease with new bone lesions; however, study treatment was continued. On Day 121, the patient presented with limb weakness. A head CT scan showed an approximately 0.4 cm, round high-density shadow in the right thalamic region, suggesting a hemorrhagic focus with midline structure in the middle. Despite medical treatment for cerebral hemorrhage, on Day 123, the patient had sudden dyspnea and confusion with no response and subsequently died due to SAE of Grade 5 cerebral hemorrhage. The investigator assessed the event of cerebral hemorrhage as possibly related to brain tumor progression.

Assessment: FDA agrees with the investigator's assessment that the event of "cerebral hemorrhage" was likely due to metastatic tumor progression in the brain.

Study G208, Patient ID (b) (6) **cause of death: "hypotension:"** This was a 42-year-old Asian male with stage IV NSCLC who received taletrectinib 600 mg QD. On Day 33, the patient experienced an AE of Grade 2 cough. On Day 41, a chest CT scan showed Grade 2 pneumonia and progressive disease with multiple new ground-glass opacities and small nodules in both lungs. On Day 48, his condition was worsened to an SAE of Grade 3 pneumonia requiring hospitalization. Infection work-up was negative. Despite treatment with oxygen, antibiotics and methylprednisolone, his condition was worsening. His guardians did not agree with further lifesaving treatment. On Day 66, the patient's blood pressure and oxygen saturation decreased significantly. He subsequently died due to an SAE of Grade 5 hypotension. The investigator assessed both events of pneumonia and hypotension as related to disease progression.

Assessment: FDA considers the cause of death in this patient was likely due to the underlying disease progression.

There were two patients who received taletrectinib 600 mg QD in Study C205 (Patient IDs (b) (6)) with reported TEAEs of "ileus" and "intestinal perforation" with fatal outcomes. Note that Study C205 enrolled patients with advanced solid tumors with *NTRK* fusions. In both cases, the patients experienced disease progression with extensive abdominal tumors (sarcoma and colorectal carcinoma). FDA considers that these fatal events were related to the underlying disease progression.

Select patient narratives, including those for patients with "unknown" and "other" causes of death within 30 days of the last dose of study treatment, are summarized below:

Study G208, Patient ID (b) (6) **"unknown" cause of death:** This was a 56-year-old Asian female with stage IV NSCLC, with metastatic lesions in the brain and lymph node, who received taletrectinib 600 mg QD. On Day 83, an overall response assessment revealed progressive disease. On Day 230, a head MRI scan showed slightly larger multiple metastases in the brain and a new lesion in the frontal lobe. However, since patient had no

symptoms, treatment was continued. On Day 306, patient experienced an SAE of Grade 4 intracranial hemorrhage. A brain CT scan showed metastatic tumors with suspected bleeding within the tumor. Study treatment was discontinued due to progressive disease. Lorlatinib was started on Day 307. On Day 310, patient died due to an SAE of Grade 5 death (unexplained) after a report of slurred speech and bilateral limb weakness one day prior to her death.
Assessment: FDA considers the event of death likely related to disease progression, based on the report of brain metastatic lesion enlargement, development of new brain lesions and the SAE of intracranial hemorrhage. Post-progression treatment with lorlatinib could be a confounding factor.

Study C203, Patient ID (b) (6) **"unknown" cause of death:** This was a 39-year-old Asian female with stage IIIc NSCLC who received taletrectinib 600mg QD. On Day 278, the patient had sudden onset of illness with no specific reported symptoms. The patient did not visit the hospital. On the same day, the patient died (Grade 5; unexplained death). An autopsy was not performed. FDA requested additional information, but no other information was available.
Assessment: FDA considers it challenging to determine the cause of death as well as relatedness to study treatment due to the lack of information.

Study G208, Patient ID (b) (6) **"other" cause of death:** This was a 68-year-old White female with stage IV NSCLC, with metastatic lesions in the brain, liver, and bone, who received taletrectinib 600 mg QD. On Day 41, the patient was reported to have an SAE of Grade 2 pleural effusion. After improving from thoracentesis and pleural fluid drainage, patient was discharged on Day 42. Study treatment was interrupted and subsequently discontinued due to consent withdrawal. On Day 48, patient was readmitted due to recurrent pleural effusion. On Day 50, a chest/abdomen/pelvis CT revealed a large left pleural effusion, progression of hepatic and adrenal metastatic disease, diffuse peritoneal and retroperitoneal metastatic infiltrative disease, along with new hydronephrosis, bile duct dilatation, and pulmonary features of mild interstitial edema. On Day 57, patient opted for a fully comfort-directed approach and decided to undergo medical assistance in dying (MAID). On Day 62, MAID was completed; and patient died due to an SAE of Grade 5 disease progression. An autopsy was not performed. The primary cause of death was listed as "other".
Assessment: FDA considers the cause of death likely due to disease progression.

Among the patients who received 600 mg QD (n=352), FDA conducted further investigation in the 11 patients with fatal events of "pneumonia," "COVID-19 pneumonia," "pneumonia bacterial," "pulmonary sepsis," "dyspnea" and "respiratory failure" terms, and four patients with fatal events of "cardiac arrest," "cardiac failure" and "cardiopulmonary failure" terms. These events were closely reviewed to assess the presence of underlying confounding factors and potential relatedness of the events to taletrectinib.

Among the 11 patients with respiratory disorder terms, there was no definitive evidence of drug-

induced interstitial lung disease; however, the assessment was challenging due to many confounding factors such as possible diagnosis of pneumonia and progressive disease. A select narrative of a case with a fatal TEAE of "dyspnea" is summarized below.

Study G208, Patient ID (b) (6) **TEAE of "dyspnea" with a fatal outcome:** This was 59-year-old White female with stage IV NSCLC who received taletrectinib 600 mg QD. On Day 228, an overall response assessment revealed progressive disease with new lesion in the left pulmonary parenchyma. Study treatment was continued. On Day 234, the patient was diagnosed with an SAE of respiratory tract infection with lymphangitis on chest XR. There was negative sputum culture, negative PCR influenza vital test and no pulmonary embolism on chest imaging. The patient was discharged on Day 239 after improvement with antibiotics and methylprednisolone, however, was readmitted on Day 245 due to an SAE of dyspnea. A chest XR again showed chest lymphangitis. On Day 248, the patient died due to an SAE of Grade 5 dyspnea and disease progression.
Assessment: FDA considers the event of dyspnea as likely related to the underlying progressive disease given the disease progression with new lesions on Day 228.

Among the four patients with cardiac disorder terms, none had documented QT prolongation at the time of cardiac AE diagnosis. In the case of patient ID (b) (6) the cause of death was listed as "cardiac arrest;" however, FDA assessed that the cause of death in this case could be secondary to multiple factors such as interstitial lung disease, cerebral infarction, and underlying progressive disease.

Study G208, Patient ID (b) (6) **cause of death: "cardiac arrest:"** This was a 38-year-old Asian male with stage IV NSCLC who received taletrectinib 600 mg QD. On Day 12, patient developed Grade 2 dyspnea with a chest CT scan revealing new diffuse ground-glass opacity in both lungs. Blood culture showed no growth. He was hospitalized due to an SAE of Grade 3 ILD and received treatment with antibiotics, and methylprednisolone. Study treatment was interrupted. On Day 22, he was discharged after improvement with treatment. Taletrectinib was restarted at a reduced dose of 400 mg QD. However, on Day 29, the ILD worsened to Grade 2. The patient also presented with aphasia. A brain MRI showed an SAE of Grade 3 cerebral infarction. A chest CT showed newly appeared extensive and diffuse ground-glass opacities in both lungs. The patient required reintubation, high flow oxygen, antibiotics and methylprednisolone. On Day 31, study treatment was discontinued due to progressive disease. On Day 35, the patient refused treatment and received conservative care. On Day 42, he developed an SAE of Grade 5 cardiac arrest and died.
Assessment: FDA assessed that the cause of the patient's fatal cardiac arrest could be multifactorial from ILD, cerebral infarction and underlying progressive disease.

In the 600 mg QD group (n=352), FDA reviewed the narratives for the 6 patients who died within 30 days of the last dose of taletrectinib due to progressive disease. Based on the review of the narratives, FDA agreed with the assessment that death was likely related to progressive

disease.

Four patients were reported to have treatment related TEAEs leading to death, which included three patients who received taletrectinib 600 mg QD with TEAEs of "hepatic failure," "hepatic function abnormal," and "pneumonia" (one patient (0.3%) each), and one patient who received taletrectinib 400 mg QD with an TEAE of "pneumonitis/ILD." Further discussion of liver-related and ILD events with fatal outcomes is included in **Section 8.2.5** Analysis of Submission-Specific Safety Issues.

Serious Adverse Events

Data:

Table 41. Applicant - Frequently Reported (≥2% of Participants in Any Group) Serious Treatment-Emergent Adverse Events

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
At least 1 serious TEAE	103 (30.6)	107 (30.4)	117 (28.4)
Infections and infestations			
Pneumonia	13 (3.9)	14 (4.0)	14 (3.4)
Respiratory, thoracic, and mediastinal disorders			
Pleural effusion	16 (4.7)	16 (4.5)	16 (3.9)
Hepatobiliary disorders			
Hepatic function abnormal	8 (2.4)	8 (2.3)	8 (1.9)

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.1.3.1

Table 42. Applicant - Summary of Serious Treatment-Emergent Adverse Events Related to Taletrectinib

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Number of participants with at least 1 treatment-related serious TEAE	25 (7.4)	27 (7.7)	32 (7.8)
Hepatobiliary disorders			
Hepatic function abnormal	8 (2.4)	8 (2.3)	8 (1.9)
Drug-induced liver injury	1 (0.3)	1 (0.3)	1 (0.2)
Hepatic failure	1 (0.3)	1 (0.3)	1 (0.2)
Liver injury	1 (0.3)	1 (0.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders			
Interstitial lung disease	4 (1.2)	4 (1.1)	5 (1.2)
Haemoptysis	1 (0.3)	1 (0.3)	1 (0.2)
Pulmonary oedema	1 (0.3)	1 (0.3)	1 (0.2)
Nervous system disorders			
Dizziness	2 (0.6)	2 (0.6)	2 (0.5)
Demyelination	1 (0.3)	1 (0.3)	1 (0.2)
Headache	1 (0.3)	1 (0.3)	1 (0.2)
Paraesthesia	1 (0.3)	1 (0.3)	1 (0.2)
Eye disorders			
Retinal detachment	0	0	1 (0.2)
Vitreous floaters	0	0	1 (0.2)
Gastrointestinal disorders			
Diarrhoea	0	0	1 (0.2)
Nausea	1 (0.3)	1 (0.3)	1 (0.2)
Vomiting	1 (0.3)	1 (0.3)	1 (0.2)
General disorders and administration site conditions			
Asthenia	1 (0.3)	2 (0.6)	2 (0.5)
Infections and infestations			
Pneumonia	2 (0.6)	2 (0.6)	2 (0.5)

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Investigations			
Alanine aminotransferase increased	1 (0.3)	1 (0.3)	1 (0.2)
Aspartate aminotransferase increased	1 (0.3)	1 (0.3)	1 (0.2)
Platelet count decreased	1 (0.3)	1 (0.3)	1 (0.2)
Renal and urinary disorders			
Acute kidney injury	1 (0.3)	1 (0.3)	1 (0.2)
Renal failure	0	1 (0.3)	1 (0.2)
Skin and subcutaneous tissue disorders			
Rash	1 (0.3)	1 (0.3)	1 (0.2)
Stevens-Johnson syndrome	1 (0.3)	1 (0.3)	1 (0.2)
Metabolism and nutrition disorders			
Dehydration	0	0	1 (0.2)

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.1.3.2

The Applicant's Position:

A summary of treatment-emergent SAEs (≥2% of participants in any group) is presented in **Table 41**. Treatment-emergent SAEs were reported for approximately 30% of participants in the 600 mg QD group.

The most frequently reported SAEs (in ≥2% of participants) were pleural effusion (4.5%), pneumonia (4.0%), and hepatic function abnormal (2.3%).

A summary of treatment-related SAEs is presented in **Table 42**. Approximately 25% of SAEs were considered to be related to taletrectinib.

In the 600 mg QD group, the only treatment-related SAE reported in ≥2% of participants was hepatic function abnormal (2.3%). Other treatment-related SAEs reported in more than 1 participant included ILD (1.1%), asthenia (0.6%), dizziness (0.6%), and pneumonia (0.6%).

The FDA's Assessment:

While FDA agrees with the Applicant's summary of treatment-emergent SAEs, FDA used grouped terms to calculate the incidence of pneumonia and hepatoxicity. In the *ROS1*-positive

NSCLC 600 mg QD (n=337) and 600 mg QD (n=352) safety populations, treatment-emergent SAEs occurred in 103 patients (31%) and 107 patients (30%), respectively. Among the *ROS1*-positive NSCLC 600 mg QD group (n=337), the most frequent SAEs (in ≥2% of patients) were pneumonia (GT) (n=22, 7 %), pleural effusion (n=16, 4.7%), and hepatotoxicity (GT) (n=8, 2.4%). Note that in FDA's analysis of SAEs, pneumonia (GT) includes pneumonia, bacterial pneumonia, mycoplasma pneumonia and COVID-19 pneumonia.

Dropouts and/or Discontinuations Due to Adverse Effects

Data and the Applicant's Position:

A total of 23 (6.5%) participants in the 600 mg QD group had TEAEs leading to drug discontinuation. Only pneumonia (0.9%), hepatic function abnormal (0.6%), and ILD (0.6%) were reported in more than 1 participant.

Most of the TEAEs were manageable and reversible, and taletrectinib was generally well tolerated. Most of the events did not require dose modification and did not lead to treatment discontinuation.

The FDA's Assessment:

While FDA agrees with the Applicant's summary of treatments discontinuations, FDA used grouped terms to calculate the incidence of pneumonia and hepatoxicity. Among the *ROS1*-positive NSCLC 600 mg QD group (n=337), TEAEs leading to permanent discontinuation of taletrectinib was reported in a total of 22patients (7%). Adverse reactions resulting in permanent discontinuation of taletrectinib in more than one patient were pneumonia (GT) (n=4, 1.2%), ILD/pneumonitis (GT) (n=2, 0.6%), and hepatotoxicity (GT) (n=2, 0.6%).

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data and the Applicant's Position:

ALT and AST increased were the most frequently reported causes of dose interruption and dose reduction.

A total of 143 (40.6%) participants in the 600 mg QD group had TEAEs leading to dose interruption. The most frequently reported (≥2% of participants) TEAEs leading to dose interruption were ALT increased (6.5%), AST increased (6.5%), COVID-19 (4.5%), pyrexia (3.7%), neutrophil count decreased (3.1%), vomiting (3.1%), ECG QT prolonged (2.8%), pneumonia (2.8%), and COVID-19 pneumonia (2.0%).

A total of 102 (29.0%) participants had TEAEs leading to dose reduction. The most frequently reported (≥2% of participants) TEAEs leading to dose reduction were ALT increased (8.5%), AST increased (5.1%), ECG QT prolonged (2.8%), diarrhea (2.3%), and hepatic function abnormal (2.0%).

TEAEs that needed intervention generally resolved with dose interruption and/or dose reduction with/without standard symptomatic measures.

The FDA's Assessment: FDA generally agrees with the Applicant's assessment for dose reduction and dose interruption due to TEAEs.

Among the *ROS1*-positive NSCLC 600 mg QD group (n=337), TEAEs leading to dose interruptions occurred in 137 patients (41%). Adverse events requiring dose interruption in ≥2 % of patients included increased ALT (n=23, 7%), increased AST (n=23, 7%), COVID-19 (n=14, 4.2%), pyrexia (n=11, 3.3%), pneumonia (GT) (n=10, 3%), decreased neutrophil count (n=10, 3%), vomiting (n=10, 3%), ECG QT prolongation (n=10, 3%) and COVID -19 pneumonia (n=7, 2.1%). In FDA's analysis, the following additional adverse events required dose interruption in ≥2 % of patients: hepatotoxicity (GT) (n=10, 3%), rash (GT) (n=7, 2.1%), and diarrhea (GT) (n=7, 2.1%). CPK elevation led to drug interruption in 1.2% of patients.

Among the *ROS1*-positive NSCLC 600 mg QD group (n=337), TEAEs resulting in dose reduction occurred in 97 patients (29%). Adverse reactions requiring dose reduction in ≥2 % of patients were increased ALT (n=29, 9%), increased AST (n=17, 5%), ECG QT prolongation (n=10, 2.8%), diarrhea (GT) (n=8, 2.4%), and hepatotoxicity (GT) (n=8, 2.4%). CPK elevation led to dose reduction in 0.6% of patients.

Significant Adverse Events

TEAEs leading to discontinuation of taletrectinib, TEAEs leading to dose modifications of taletrectinib, and TEAEs leading to death were presented earlier in this section.

One AESI (potential Hy's Law cases) and 7 OSEIs (liver-related events, ILD, QT-related events, gastrointestinal events, neurological events, hyperuricemia, and skeletal fracture) were identified for focused analysis. A detailed discussion is provided in **Section 8.2.5**.

Grade ≥3 TEAEs

Data and the Applicant's Position:

Table 43. Applicant - Frequently Reported (≥2% of Participants in Any Group) Treatment-Emergent Adverse Events of Grade ≥3

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Number of participants with at least 1 TEAE of NCI CTCAE Grade	174 (51.6)	181 (51.4)	220 (53.4)

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Investigations			
Aspartate aminotransferase increased	26 (7.7)	26 (7.4)	31 (7.5)
Alanine aminotransferase increased	34 (10.1)	35 (9.9)	39 (9.5)
Electrocardiogram QT prolonged	12 (3.6)	12 (3.4)	13 (3.2)
Neutrophil count decreased	14 (4.2)	17 (4.8)	18 (4.4)
Blood creatine phosphokinase increased	7 (2.1)	7 (2.0)	7 (1.7)
Gastrointestinal disorders			
Diarrhoea	7 (2.1)	7 (2.0)	11 (2.7)
Infections and infestations			
Pneumonia	14 (4.2)	15 (4.3)	15 (3.6)
Blood and lymphatic system disorders			
Anaemia	12 (3.6)	12 (3.4)	15 (3.6)
Respiratory, thoracic, and mediastinal disorders			
Pleural effusion	10 (3.0)	10 (2.8)	10 (2.4)
Hepatobiliary disorders			
Hepatic function abnormal	15 (4.5)	15 (4.3)	15 (3.6)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, total number of participants; n, subset of total number of participants; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.1.8.1

TEAEs of Grade ≥3 reported in ≥2% of participants are summarized in **Table 43**.

Approximately half of participants reported at least 1 TEAE of Grade ≥3. The most frequently reported (in ≥2% of participants) TEAEs were ALT increased, AST increased, neutrophil count decreased, hepatic function abnormal, pneumonia, anemia, ECG QT prolonged, pleural effusion, and diarrhea.

Approximately one-third of participants reported at least 1 treatment-related TEAE of Grade ≥3 (Module 2.7.4 Table 11). The most frequently reported treatment-related TEAEs (in ≥2% of participants) were ALT increased (8.8%), AST increased (6.3%), neutrophil count decreased (4.5%), hepatic function abnormal (4.3%), ECG QT prolonged (3.4%), anemia (2.6%), and diarrhea (2.0%).

The FDA's Assessment:
In FDA's analysis, among the patients who received taletrectinib 600 mg QD (n=352), TEAEs of Grade ≥3 reported in ≥2% of patients were increased ALT (n=35, 10%), increased AST (n=26, 7%), pneumonia (GT) (n=19, 5%), decreased neutrophil count (n=17, 4.8%), hepatotoxicity (GT) (n=15, 4.3%), anemia (n=12, 3.4%), ECG QT prolongation (n=12, 3.4%), pleural effusion (n=10, 2.8%), increased blood CPK (n=7, 2%), and diarrhea (n=7, 2%). In FDA's review, rash (GT) is also included in this list as it occurred in 7 patients (2%). For the "increased ALT," "increased AST," "decreased neutrophil count," "ECG QT prolongation" and "increased blood CPK" terms in this analysis, FDA used adverse event data instead of laboratory values.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 44. Applicant - Overall Summary of Treatment-Emergent Adverse Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Number of participants with			
Any TEAE	336 (99.7)	351 (99.7)	410 (99.5)
Any treatment-related TEAE	334 (99.1)	349 (99.1)	401 (97.3)
Any AESI	2 (0.6)	2 (0.6)	2 (0.5)
Any treatment-related AESI	2 (0.6)	2 (0.6)	2 (0.5)
Any CTCAE Grade ≥3 TEAE	174 (51.6)	181 (51.4)	220 (53.4)
Any treatment-related CTCAE Grade ≥3 TEAE	110 (32.6)	116 (33.0)	135 (32.8)
Any serious TEAE	103 (30.6)	107 (30.4)	117 (28.4)
Any treatment-related serious TEAE	25 (7.4)	27 (7.7)	32 (7.8)
Any serious AESI	2 (0.6)	2 (0.6)	2 (0.5)
Any treatment-related serious AESI	2 (0.6)	2 (0.6)	2 (0.5)
Any TEAE leading to death	25 (7.4)	28 (8.0)	29 (7.0)
Any treatment-related TEAE leading to death	3 (0.9)	3 (0.9)	4 (1.0)
Any TEAE leading to dose interruption	137 (40.7)	143 (40.6)	174 (42.2)
Any treatment-related TEAE leading to dose interruption	91 (27.0)	96 (27.3)	115 (27.9)
Any TEAE leading to dose reduction	97 (28.8)	102 (29.0)	106 (25.7)
Any treatment-related TEAE leading to dose reduction	93 (27.6)	97 (27.6)	101 (24.5)

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Any TEAE leading to treatment discontinuation	22 (6.5)	23 (6.5)	30 (7.3)
Any treatment-related TEAE leading to treatment discontinuation	8 (2.4)	9 (2.6)	14 (3.4)

Abbreviations: AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.1.1.1

Table 45. Applicant - Frequently Reported (≥10% of Participants in Any Group) Treatment-Emergent Adverse Events

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Number of participants with at least 1 TEAE	336 (99.7)	351 (99.7)	410 (99.5)
Gastrointestinal disorders			
Diarrhoea	213 (63.2)	224 (63.6)	260 (63.1)
Nausea	159 (47.2)	163 (46.3)	197 (47.8)
Vomiting	146 (43.3)	153 (43.5)	179 (43.4)
Constipation	71 (21.1)	73 (20.7)	84 (20.4)
Investigations			
Aspartate aminotransferase increased	243 (72.1)	253 (71.9)	271 (65.8)
Alanine aminotransferase increased	229 (68.0)	238 (67.6)	252 (61.2)
Blood creatinine increased	61 (18.1)	63 (17.9)	73 (17.7)
Electrocardiogram QT prolonged	65 (19.3)	65 (18.5)	68 (16.5)
Blood bilirubin increased	59 (17.5)	65 (18.5)	66 (16.0)
Neutrophil count decreased	56 (16.6)	61 (17.3)	64 (15.5)
Blood creatine phosphokinase increased	56 (16.6)	56 (15.9)	61 (14.8)
White blood cell count decreased	53 (15.7)	59 (16.8)	61 (14.8)
Weight decreased	48 (14.2)	51 (14.5)	58 (14.1)
Weight increased	44 (13.1)	44 (12.5)	44 (10.7)

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Gamma-glutamyltransferase increased	34 (10.1)	34 (9.7)	35 (8.5)
Metabolism and nutrition disorders			
Decreased appetite	53 (15.7)	60 (17.0)	72 (17.5)
Hyperuricaemia	48 (14.2)	50 (14.2)	53 (12.9)
Hypercholesterolaemia	43 (12.8)	44 (12.5)	44 (10.7)
Hypertriglyceridaemia	41 (12.2)	42 (11.9)	42 (10.2)
Nervous system disorders			
Dizziness	71 (21.1)	75 (21.3)	85 (20.6)
Dysgeusia	49 (14.5)	53 (15.1)	67 (16.3)
Headache	35 (10.4)	38 (10.8)	41 (10.0)
Infections and infestations			
COVID-19	47 (13.9)	50 (14.2)	51 (12.4)
Urinary tract infection	38 (11.3)	41 (11.6)	47 (11.4)
Pneumonia	35 (10.4)	37 (10.5)	38 (9.2)
General disorders and administration site conditions			
Fatigue	29 (8.6)	31 (8.8)	50 (12.1)
Asthenia	39 (11.6)	41 (11.6)	45 (10.9)
Pyrexia	38 (11.3)	40 (11.4)	45 (10.9)
Skin and subcutaneous tissue disorders			
Rash	48 (14.2)	49 (13.9)	53 (12.9)
Pruritus	40 (11.9)	41 (11.6)	47 (11.4)
Blood and lymphatic system disorders			
Anaemia	126 (37.4)	129 (36.6)	134 (32.5)
Musculoskeletal and connective tissue disorders			
Arthralgia	33 (9.8)	34 (9.7)	41 (10.0)
Myalgia	32 (9.5)	34 (9.7)	41 (10.0)
Respiratory, thoracic, and mediastinal disorders			
Cough	44 (13.1)	44 (12.5)	50 (12.1)
Renal and urinary disorders			
Proteinuria	41 (12.2)	42 (11.9)	42 (10.2)

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Hepatobiliary disorders			
Hepatic function abnormal	47 (13.9)	50 (14.2)	50 (12.1)

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.1.9.1

Table 46. Applicant - Frequently Reported (≥10% of Participants in Any Group) Treatment-Related Treatment-Emergent Adverse Events

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Number of participants with at least 1 treatment-related TEAE	334 (99.1)	349 (99.1)	401 (97.3)
Gastrointestinal disorders			
Diarrhoea	205 (60.8)	216 (61.4)	242 (58.7)
Nausea	152 (45.1)	156 (44.3)	182 (44.2)
Vomiting	138 (40.9)	145 (41.2)	163 (39.6)
Constipation	47 (13.9)	48 (13.6)	53 (12.9)
Investigations			
Aspartate aminotransferase increased	237 (70.3)	247 (70.2)	261 (63.3)
Alanine aminotransferase increased	225 (66.8)	234 (66.5)	248 (60.2)
Electrocardiogram QT prolonged	63 (18.7)	63 (17.9)	65 (15.8)
Blood bilirubin increased	55 (16.3)	61 (17.3)	61 (14.8)
Neutrophil count decreased	53 (15.7)	58 (16.5)	61 (14.8)
Blood creatinine increased	53 (15.7)	55 (15.6)	60 (14.6)
White blood cell count decreased	51 (15.1)	57 (16.2)	59 (14.3)
Blood creatine phosphokinase increased	50 (14.8)	50 (14.2)	54 (13.1)
Gamma-glutamyltransferase increased	34 (10.1)	34 (9.7)	35 (8.5)
Metabolism and nutrition disorders			
Decreased appetite	49 (14.5)	56 (15.9)	64 (15.5)

System Organ Class Preferred Term	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Hyperuricaemia	38 (11.3)	40 (11.4)	41 (10.0)
Hypercholesterolaemia	37 (11.0)	38 (10.8)	38 (9.2)
Nervous system disorders			
Dysgeusia	49 (14.5)	53 (15.1)	66 (16.0)
Dizziness	51 (15.1)	55 (15.6)	60 (14.6)
Skin and subcutaneous tissue disorders			
Rash	42 (12.5)	42 (11.9)	44 (10.7)
General disorders and administration site conditions			
Asthenia	36 (10.7)	38 (10.8)	40 (9.7)
Blood and lymphatic system disorders			
Anaemia	109 (32.3)	112 (31.8)	112 (27.2)
Hepatobiliary disorders			
Hepatic function abnormal	46 (13.6)	49 (13.9)	49 (11.9)
Renal and urinary disorders			
Proteinuria	38 (11.3)	39 (11.1)	39 (9.5)

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.1.2.2

The Applicant's Position:

An overall summary of TEAEs in the integrated analysis of Phase 1 and 2 studies in participants with solid tumors (Studies AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101) is presented in **Table 44**. AEs were coded using the MedDRA version 27.0.

The majority of TEAEs were reported to be related to study drug. The most frequently reported form of dose modification was dose interruption (40.6%). Less than 7% of participants had TEAEs resulting in study drug discontinuation, and approximately 3% of participants had treatment-related TEAEs leading to discontinuation. Less than 1% of participants had treatment-related TEAEs leading to death.

Treatment-emergent AEs

The TEAEs reported for ≥10% of participants are summarized in **Table 45**. The most frequently reported TEAEs (in ≥30% of participants) were AST increased, ALT increased, diarrhea, nausea, vomiting, and anemia.

Treatment-related AEs

The treatment-related AEs reported for ≥10% of participants are summarized in **Table 46**. The most frequently reported (in ≥30% of participants) treatment-related TEAEs were AST increased, ALT increased, diarrhea, nausea, vomiting, and anemia.

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of common adverse reactions; however, FDA's analysis focused on TEAEs instead of treatment-related AEs (which are provided by the Applicant above in **Table 46**).

Notably, some TEAEs were analyzed using FDA's grouped terms in FDA's analysis of frequent TEAEs (≥10% of patients), including rash, peripheral neuropathy, cough, dysgeusia, pneumonia, urinary tract infection, edema, eye disorders and hemorrhage; refer to **Table 47**, and to **Table 48** for FDA's analysis of TEAEs in the *ROS1*-positive NSCLC group.

Table 47. FDA – Treatment-Emergent Adverse Events (≥10%) in Patients With *ROS1*-Positive NSCLC 600 mg QD and 600 mg QD Groups

Treatment-Emergent Adverse Event[1]	***ROS1*-Positive NSCLC 600mg QD N = 337 n (%)**		**600mg QD N = 352 n (%)**	
	NCI CTCAE All Grades	**NCI CTCAE Grade ≥3**	**NCI CTCAE All Grades**	**NCI CTCAE Grade ≥3**
Rash (GT)	75 (22)	6 (1.8)	78 (22)	7 (2)
Neuropathy peripheral (GT)	57 (17)	1 (0.3)	59 (17)	1 (0.3)
Cough (GT)	55 (16)	0	57 (16)	0
Dysgeusia (GT)	51 (15)	0	55 (16)	0
Pneumonia (GT)	42 (12)	18 (5)	44 (13)	19 (5)
Urinary tract infection (GT)	39 (12)	0	43 (12)	0
Edema (GT)	36 (11)	1 (0.3)	39 (11)	1 (0.3)
Eye disorders (GT)	37 (11)	1 (0.3)	39 (11)	1 (0.3)
Hemorrhage (GT)	34 (10)	4 (1.2)	37 (11)	5 (1.4)

[1] Table based on NCI CTCAE v5.0 and 4.0
Neuropathy peripheral (GT) included dysesthesia, hypoesthesia, neuralgia, peripheral neuropathy, paresthesia, and peripheral sensory neuropathy.

Dysgeusia (GT) included ageusia, and dysgeusia.
Pneumonia (GT) included pneumonia, pneumonia bacterial, pneumonia mycoplasmal, and pneumonia viral.
Cough (GT) included cough and productive cough.
Urinary tract infection (GT) included cystitis, and urinary tract infection.
Edema (GT) included eyelid edema, face edema, generalized edema, localized edema, edema, peripheral edema, and periorbital edema.
Rash (GT) included dermatitis, dermatitis acneiform, drug eruption, eczema, eyelid rash, palmar-plantar erythrodysesthesia syndrome, rash, rash maculo-papular, rash papular, skin exfoliation, and Stevens-Johnson syndrome.
Eye disorders (GT) included cataract, conjunctivitis, diplopia, dry eye, eye pain, photophobia, photosensitivity reaction, vision blurred, visual field defect, visual impairment, and vitreous floaters.
Hemorrhage (GT) included cerebral hemorrhage, epistaxis, gingival bleeding, hematuria, hemoptysis, intracranial tumor hemorrhage, tracheal hemorrhage, and upper gastrointestinal hemorrhage.

Table 48. Adverse Reactions (≥15%) in Patients With *ROS1*-Positive NSCLC Who Received IBTROZI in TRUST-I and TRUST-II

Adverse Reaction[1]	**IBTROZI N=337**	
	All Grades (%)	**Grade 3 or 4 (%)**
Gastrointestinal Disorders		
Diarrhea[a]	64	2.1
Nausea	47	1.5
Vomiting	43	1.5
Constipation	21	0
Nervous System Disorders		
Dizziness[b]	22	0.3
Peripheral neuropathy[c]	17	0.3
Dysgeusia[d]	15	0
Skin and Subcutaneous Tissue		
Rash[e]	22	1.8
General Disorders		
Fatigue[f]	20	0.9
Cardiac		
Electrocardiogram QT prolonged	19	3.6
Metabolism and Nutritional		
Decreased appetite	16	0.3
Respiratory, thoracic and mediastinal disorders		
Cough[g]	16	0

[1] Based on NCI CTCAE version 5.0

[a] Includes enterocolitis

[b] Includes vertigo, and vertigo positional

[c] Includes dysesthesia, hypoesthesia, neuralgia, paresthesia, and peripheral sensory neuropathy

[d] Includes ageusia

[e] Includes dermatitis, dermatitis acneiform, drug eruption, eczema, eyelid rash, palmar-plantar erythrodysesthesia syndrome, rash maculo-papular, rash papular, skin exfoliation, and drug reaction with eosinophilia and systemic symptoms (DRESS)

[f] Includes asthenia

[g] Includes productive cough

While the adverse reaction table in labeling includes those occurring in ≥15% of patients, the following clinically relevant adverse reactions occurring in <15% of patients receiving taletrectinib are included in text in labeling: pneumonia, eye disorders, myalgia, skeletal fractures, ILD/pneumonitis, dermatologic adverse reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) and photosensitivity reactions. Refer to FDA's analysis in **Section 8.2.5**. Analysis of Submission-Specific Safety Issues.

Laboratory Findings

Data:

Table 49. Applicant - Chemistry Laboratory Abnormalities (≥20% of Participants in Any Group) Worsening From Baseline to the Worst On-Study NCI CTCAE Grade

Category[a]	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Albumin (g/L) Low Direction			
All grade	85 (25.2)	90 (25.6)	115 (27.9)
Grade 3 and 4	3 (0.9)	3 (0.9)	4 (1.0)
Alkaline Phosphatase (U/L) High Direction			
All grade	101 (30.0)	103 (29.3)	119 (28.9)
Grade 3 and 4	0	0	0
Alanine Aminotransferase (U/L) High Direction			
All grade	284 (84.3)	296 (84.1)	328 (79.6)
Grade 3 and 4	44 (13.1)	45 (12.8)	49 (11.9)
Aspartate Aminotransferase (U/L) High Direction			
All grade	293 (86.9)	307 (87.2)	349 (84.7)
Grade 3 and 4	34 (10.1)	34 (9.7)	40 (9.7)
Bilirubin (µmol/L) High Direction			
All grade	79 (23.4)	87 (24.7)	92 (22.3)
Grade 3 and 4	2 (0.6)	2 (0.6)	2 (0.5)

Category[a]	**ROS1+ NSCLC 600 mg QD N=337 n (%)**	**600 mg QD N=352 n (%)**	**Overall N=412 n (%)**
Calcium Corrected (mmol/L) Low Direction			
All grade	115 (34.1)	124 (35.2)	136 (33.0)
Grade 3 and 4	5 (1.5)	5 (1.4)	5 (1.2)
Calcium (mmol/L) Low Direction			
All grade	93 (27.6)	100 (28.4)	124 (30.1)
Grade 3 and 4	6 (1.8)	6 (1.7)	6 (1.5)
Cholesterol (mmol/L) High Direction			
All grade	131 (38.9)	134 (38.1)	134 (32.5)
Grade 3 and 4	0	0	0
Creatinine (µmol/L) High Direction			
All grade	131 (38.9)	137 (38.9)	164 (39.8)
Grade 3 and 4	1 (0.3)	3 (0.9)	6 (1.5)
Potassium (mmol/L) High Direction			
All grade	72 (21.4)	74 (21.0)	83 (20.1)
Grade 3 and 4	4 (1.2)	4 (1.1)	4 (1.0)
Triglycerides (mmol/L) High Direction			
All grade	130 (38.6)	134 (38.1)	136 (33.0)
Grade 3 and 4	8 (2.4)	8 (2.3)	8 (1.9)
Urate (µmol/L) High Direction			
All grade	126 (37.4)	130 (36.9)	145 (35.2)
Grade 3 and 4	0	0	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, total number of participants; n, subset of total number of participants; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1.

[a] CTCAE grades are based on the worst on-treatment test.

Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 4.1.2.2

Table 50. Applicant - Hematology Laboratory Abnormalities (≥20% of Participants in Any Group) Worsening From Baseline

Category[a]	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Hemoglobin (g/L) Low Direction			
All CTCAE Grade	161 (47.8)	166 (47.2)	197 (47.8)
CTCAE Grade 3 and 4	12 (3.6)	13 (3.7)	16 (3.9)
Lymphocytes (10^9/L) Low Direction			
All CTCAE Grade	126 (37.4)	129 (36.6)	132 (32.0)
CTCAE Grade 3 and 4	16 (4.7)	17 (4.8)	17 (4.1)
Neutrophils (10^9/L) Low Direction			
All grade	81 (24.0)	86 (24.4)	86 (20.9)
CTCAE Grade 3 and 4	18 (5.3)	21 (6.0)	21 (5.1)
Leukocytes (10^9/L) Low Direction			
All grade	90 (26.7)	96 (27.3)	113 (27.4)
CTCAE Grade 3 and 4	7 (2.1)	8 (2.3)	9 (2.2)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
[a] CTCAE grades are based on the worst on-treatment test.
Source: ISS Table 4.1.3.2

Table 51. Applicant - Summary of Liver Function Abnormalities

Category[a]	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
ALT			
≥3×ULN	123 (36.5)	127 (36.1)	138 (33.5)
≥5×ULN	49 (14.5)	50 (14.2)	55 (13.3)
≥10×ULN	6 (1.8)	6 (1.7)	6 (1.5)
≥20×ULN	1 (0.3)	1 (0.3)	1 (0.2)
AST			
≥3×ULN	108 (32.0)	112 (31.8)	127 (30.8)

Category[a]	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
≥5×ULN	38 (11.3)	40 (11.4)	46 (11.2)
≥10×ULN	6 (1.8)	6 (1.7)	7 (1.7)
≥20×ULN	0	0	0
Transaminases (ALT or AST) and total bilirubin			
ALT/AST ≥3×ULN and bilirubin ≥1.5×ULN	6 (1.8)	7 (2.0)	8 (1.9)
ALT/AST ≥3×ULN and bilirubin ≥2×ULN	4 (1.2)	4 (1.1)	5 (1.2)

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; ULN, upper limit of normal.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
[a] Based on worst on-study value
Source: ISS Table 4.1.1

Table 52. Applicant - Time to Onset and Resolution in Participants With NCI CTCAE Grade 3 or 4 ALT or AST Elevations Based on Laboratory Results

Category	ROS1+ NSCLC 600 mg QD	600 mg QD	Overall
ALT			
Grade ≥3 ALT, n[a]	44	45	49
Time from first dose to first Grade 3 or 4 onset day (days)[b]			
n (%)	44 (100)	45 (100)	49 (100)
Mean (standard deviation)	86.0 (193.97)	85.0 (191.87)	92.2 (201.83)
Median	42.5	42.0	42.0
Q1, Q3	22.0, 62.5	22.0, 62.0	22.0, 62.0
Minimum, Maximum	8, 1217	8, 1217	8, 1217
ALT time to resolution (days)[c]			
n (%)	44 (100)	45 (100)	48 (98.0)
Mean (standard deviation)	14.4 (8.78)	14.6 (8.75)	14.7 (8.55)
Median	13.5	14.0	14.0
Q1, Q3	8.0, 18.5	8.0, 19.0	8.5, 19.0
Minimum, Maximum	4, 51	4, 51	4, 51

Category	ROS1+ NSCLC 600 mg QD	600 mg QD	Overall
AST			
Grade ≥3 AST, n[a]	34	34	40
Time from first dose to first Grade 3 or 4 onset day (days)[b]			
n (%)	34 (100)	34 (100)	40 (100)
Mean (standard deviation)	168.1 (253.79)	168.1 (253.79)	149.4 (238.62)
Median	49.0	49.0	43.0
Q1, Q3	36.0, 169.0	36.0, 169.0	26.0, 153.5
Minimum, Maximum	12, 1217	12, 1217	8, 1217
AST time to resolution (days)[c]			
n (%)	30 (88.2)	30 (88.2)	35 (87.5)
Mean (standard deviation)	19.9 (22.46)	19.9 (22.46)	19.6 (21.46)
Median	11.0	11.0	11.0
Q1, Q3	7.0, 22.0	7.0, 22.0	7.0, 22.0
Minimum, Maximum	3, 92	3, 92	3, 92
ALT/AST			
Grade ≥3 ALT/AST, n[a]	55	56	64
Time from first dose to first Grade 3 or 4 onset day (days)[b]			
n (%)	55 (100)	56 (100)	64 (100)
Mean (standard deviation)	115.0 (209.13)	113.7 (207.45)	113.8 (207.54)
Median	43.0	43.0	43.0
Q1, Q3	22.0, 86.0	23.0, 85.0	22.0, 85.0
Minimum, Maximum	8, 1217	8, 1217	8, 1217
ALT/AST time to resolution (days)[c]			
n (%)	53 (96.4)	54 (96.4)	61 (95.3)
Mean (standard deviation)	18.8 (17.96)	18.9 (17.79)	18.9 (17.16)
Median	14.0	14.0	14.0
Q1, Q3	9.0, 20.0	9.0, 20.0	9.0, 22.0
Minimum, Maximum	4, 92	4, 92	4, 92

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; N, total number of participants; n, subset of total number of participants; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; Q, quartile; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024- 06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.

[a] n is the number of participants with specified treatment-emergent Grade 3 or 4 ALT or AST elevations based on laboratory results, and percentage is based on n.
[b] Defined as the duration from the first dose to the first Grade 3 or 4 onset date and calculated only for participants with the specified event category.
[c] Time to resolution is the first Grade 3 or 4 date to the baseline grade date that in the interview after the first Grade 3 or 4 occurrence, the first occurrence time of the same grade value as baseline or Grade 1.
Source: ISS Table 3.2.7.6

The Applicant's Position:

In the 600 mg QD group, the majority of participants had baseline chemistry parameters of Grade 0 or 1, and few shifts to Grade ≥3 were observed (**Table 49**). The most frequently reported (≥5% of participants) shifts from Grade 0 or 1 at baseline to a worst grade of Grade ≥3 were ALT increased and AST increased.

For hematology evaluation, the majority of participants had baseline values of Grade 0 or 1, and few shifts to Grade ≥3 were observed in hematology parameters (**Table 50**). The most frequently reported (≥3% of participants) shifts from Grade 0 or 1 at baseline to a worst grade of Grade ≥3 were neutrophil count decreased, lymphocyte count decreased, and anemia.

For coagulation evaluation, coagulation abnormalities were infrequent and the majority of cases of worsening from baseline were mild or moderate in severity (Grade <3). There were no shifts from Grade 0 or 1 at baseline to a worst grade of Grade ≥3 reported in more than 1.5% of participants.

Liver function laboratory abnormalities are summarized in **Table 51**.

As shown in **Table 49**, the most frequent hepatic laboratory abnormalities in the 600 mg QD group were increased AST and increased ALT. The hepatic laboratory values were mostly Grade 1 and 2 and outside the range for Hy's Law.

In the 600 mg QD group, 36.1% and 31.8% of participants had increases of ≥3× upper limit of normal (ULN) in ALT and AST, respectively. Most abnormalities observed were <5×ULN. Only 4 participants in the 600 mg QD group had increases of ≥3×ULN in transaminases in conjunction with ≥2×ULN increases in total bilirubin.

Two participants experienced laboratory levels that were consistent with potential Hy's Law cases (ALT, AST >3×ULN]; bilirubin ≥2×ULN; alkaline phosphatase <2×ULN). Please refer to **Section 8.2.5** for the summary for these 2 cases. The TEAEs were deemed related to study drug and led to treatment discontinuation. The LFTs for both cases returned to normal or improved after drug discontinuation.

Liver-related OSEIs are discussed in **Section 8.2.5**.

Time to onset and resolution of NCI CTCAE Grade 3 or 4 aminotransferase elevations based on laboratory results are summarized in **Table 52**. Grade 3 or 4 ALT elevations occurred in 12.8% (45/352) of participants in the 600 mg QD Group with a median time to onset of 42 days. Time to onset and resolution of Grade 3 or 4 transaminase elevations were similar between the *ROS1*+ NSCLC 600 mg QD, 600 mg QD, and Overall Groups. Similar results were observed for ALT,

AST, ALT/AST elevations (**Table 52**).The majority (87.9%) of NCI CTCAE Grade 3 or 4 ALT/AST elevations in participants in the 600 mg QD Group occurred within the first 12 months of treatment (ISS Table 3.2.7.6b). Most (84/91, 92.3%) Grade 3 or 4 transaminase increases were reversible, with a median time to resolution of around 2 weeks (ISS Table 3.2.7.6b).

The FDA's Assessment:
FDA generally agrees with the Applicant's summary of common laboratory abnormalities in the safety analysis population. Refer to **Table 53** for FDA's analysis of laboratory abnormalities. There were slight differences in the incidences of laboratory abnormalities in FDA's analysis since the denominator used to calculate the rate varied from 149 to 336 based on the number of patients with a baseline value and at least one post-treatment value.

For liver function laboratory abnormalities, the median time to first onset of AST or ALT elevation was 15 days (range: 3 days to 20.8 months). Grade 3 or 4 liver function test abnormalities included increased ALT (13%), increased AST (10%), increased GGT (1.8%) and increased bilirubin (0.6%). Among the patients who received taletrectinib 600 mg QD (n=352), two (0.6%) had events which were found to have met Hy's Law criteria. In both cases, the TEAEs were deemed related to study drug and led to treatment discontinuation. Refer to **Section 8.2.5** for discussion of hepatotoxicity in this application.

Table 53. Select Laboratory Abnormalities (≥20%) That Worsened From Baseline in Patients With *ROS1*-Positive NSCLC Who Received IBTROZI in TRUST-I and TRUST-II

Laboratory Abnormality[1]	**IBTROZI[2]**	
	All Grades (%)	**Grade 3 or 4 (%)**
Hematology		
Hemoglobin decreased	48	3.6
Lymphocytes decreased	38	4.8
Neutrophils decreased	25	5
Chemistry		
AST increased	87	10
ALT increased	85	13
Creatine phosphokinase increased	53	5
Cholesterol increased	41	0
Triglycerides increased	41	2.5
Creatinine increased	39	0.3
Uric acid increased	38	0
Gamma glutamyl transferase increased	36	1.8
Alkaline phosphatase increased	30	0
Calcium decreased	28	1.8

Albumin decreased	25	0.9
Bilirubin increased	24	0.6
Potassium increased	21	1.2
Sodium increased	20	0.9

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase

[1] Based on NCI CTCAE version 5.0

[2] The denominator used to calculate the rate varied from 149 to 336 based on the number of patients with a baseline value and at least one post-treatment value.

Vital Signs

The Applicant's Position:

For all vital sign parameters, the majority of participants had Grade 0 or 1 values at baseline, and few shifts to Grade ≥3 were observed. No safety findings were noted as trends in review of vital signs data.

ECG results are discussed in the context of OSEIs in **Section 8.2.5**.

The FDA's Assessment:
FDA agrees with the Applicant's position. In FDA's analysis, among patients who received 600 mg QD (n=352), hypertension (GT) was reported in 21 patients (6%) with five patients (1.4%) experiencing Grade 3 or higher hypertension; hypertension resulted in drug interruption in one patient (0.3%). No SAEs of hypertension were reported.
Hypotension (GT) occurred in 12 patients (3.4%) with one patient (0.3%) experiencing Grade 3 or higher hypotension, and hypotension resulted in drug interruption in one patient (0.3%). SAEs of hypotension were reported in two patients (0.6%). In both cases, hypotension SAEs occurred in the context of pneumonia with progressive disease and dehydration. No dose reduction or drug withdrawal due to hypotension or hypertension was reported.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG results are discussed in the context of OSEIs in **Section 8.2.5**.

The FDA's Assessment:
Refer to FDA's assessment for QT prolongation-related AEs in **Section 8.2.5**. Analysis of Submission-Specific Safety Issues.

QT

Data:

QTcF shifts from baseline are discussed in the context of OSEIs in **Section 8.2.5**, which also includes a brief summary of the concentration-corrected QT interval analysis using PK-matched triplicate ECG assessments.

The FDA's Assessment:
Refer to FDA's assessment for QT prolongation-related AEs in **Section 8.2.5**. Analysis of Submission-Specific Safety Issues.

Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

8.2.5. Analysis of Submission-Specific Safety Issues

AESIs, as defined in the study protocols, and OSEIs for taletrectinib have been identified based on clinical importance of the event, findings in nonclinical studies of taletrectinib, AEs for the same class of drugs approved for ROS1+ NSCLC, and the clinical experience to date with taletrectinib. The categories and criteria that define each category of AESI and OSEI are shown in **Table 54**.

Table 54. Applicant - Adverse Events of Special Interest and Other Safety Events of Interest

Event	Search Strategy
AESIs	
Potential Hy's Law cases	ALT or AST ≥3×ULN and total bilirubin ≥2×ULN and alkaline phosphatase ≤2×ULN (based on laboratory values) Note: total bilirubin elevation has to occur within 7 days after initial elevation of ALT/AST
OSEIs	
Liver-related events	• All liver events: Drug-related hepatic disorders-comprehensive search (SMQ) Broad • Liver function test abnormality:

Event	Search Strategy
	Preferred terms of alanine aminotransferase abnormal, alanine aminotransferase increased, aspartate aminotransferase abnormal, aspartate aminotransferase increased, bilirubin conjugated abnormal, bilirubin conjugated increased, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, gamma-glutamyl transferase abnormal, gamma-glutamyl transferase increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hyperbilirubinemia, hypertransaminasemia, liver function test abnormal, liver function test increased, transaminases abnormal, transaminases increased, blood alkaline phosphatase abnormal, blood alkaline phosphatase increased • ALT/AST increased: Preferred terms of alanine aminotransferase increased/aspartate aminotransferase increased
Interstitial lung disease	Interstitial lung disease SMQ Narrow
QT-related events	Torsade de pointes/QT prolongation SMQ Broad
Gastrointestinal events	Gastrointestinal disorders system organ class
Neurological events	Nervous system disorders system organ class Vestibular disorders SMQ Broad Peripheral neuropathy SMQ Broad HLGT of headache
Hyperuricemia	Preferred term of hyperuricemia and preferred term of blood uric acid increased
Skeletal fracture	Any preferred term containing the term "fracture"

Abbreviations: AESI, adverse event of special interest; ALT, alanineamino transferase; AST, aspartate aminotransferase; HLGT, high level group term; MedDRA, Medical Dictionary for Regulatory Activities; OSEI, other safety event of interest; SMQ, standardized MedDRA query; ULN, upper limit of normal.

The FDA's assessment:

FDA generally agrees with the Applicant's search strategy for AESI and OSEI. FDA conducted a revised analysis including additional drug safety events of interests: myalgia, eye disorders and rash. Refer to the discussion of these events in **Section 8.2.5**. Analysis of Submission Specific-Safety Issues. In FDA's analysis, the following definitions for safety events of interest were used (**Table 55**).

Table 55. FDA - Definition of Safety Events of Interest

Grouped Term	MedDRA Search Terms
Abdominal Pain	Abdominal Discomfort, Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper, Abdominal Tenderness, Epigastric Discomfort, Gastrointestinal Pain, Hepatic Pain
Ataxia	Ataxia, Gait Disturbance, Balance Disorder, Cerebellar Ataxia, And Coordination Abnormal
CNS Toxicity	Somnolence, Insomnia, Hypersomnia, Sleep Disorder, Narcolepsy, Sleep Apnea Syndrome, Snoring, Memory Impairment, Disturbance In Attention, Cognitive

	Disorder, Confusional State, Amnesia, Delirium, Aphasia, Attention Deficit Hyperactivity Disorder, Depressed Level Of Consciousness, Delusion, Hallucinations, Mental Disorder, Mental Status Change, Altered State Of Consciousness, Neurological Decompensation, Affect Lability, Affective Disorder, Aggression, Agitated Depression, Agitation, Anxiety, Anxiety Disorder, Depressed Mood, Depression, Euphoric Mood, Irritability, Mania, Mood Altered, Mood Swings, Persistent Depression Disorder, Personality Change, Personality Disorder, Psychomotor Retardation, Stress, Suicidal Ideation, Dizziness, Vertigo, Dizziness Postural, Dizziness Exertional, Vertigo Positional, Ataxia, Gait Disturbances, Balance Disorder, Cerebellar Ataxia, And Coordination Abnormal
Cognitive Disorders	Memory Impairment, Disturbance in Attention, Cognitive Disorder, Confusional State, Amnesia, Delirium, Aphasia, Attention Deficit Hyperactivity Disorder, Depressed Level Of Consciousness, Delusion, Hallucination, Mental Disorder, Mental Status Changes, Altered State Of Consciousness, And Neurological Decompensation
Dizziness	Dizziness, Dizziness Postural, Dizziness Exertional, Vertigo, Cervicogenic Vertigo, Vertigo Positional, Vertigo CNS Origin, Vertigo Labyrinthine
Diarrhea	Autoimmune Colitis, Colitis, Colitis Microscopic, Diarrhea, Diarrhea Hemorrhagic, Enteritis, Enterocolitis, Frequent Bowel Movements
Eye Disorders	Cataract, Cataract Nuclear, Conjunctivitis, Diplopia, Dry Eye, Eye Pain, Glaucoma, Night Blindness, Photophobia, Photosensitivity Reaction, Vision Blurred, Visual Acuity Reduced, Visual Field Defect, Visual Impairment, Vitreous Floaters
Hyperuricemia	Hyperuricemia, Blood Uric Acid Increased
Mood Disorders	Affect Lability, Affective Disorder, Aggression, Agitated Depression, Agitation, Anxiety, Anxiety Disorder, Depressed Mood, Depression, Euphoric Mood, Irritability, Mania, Mood Altered, Mood Swings, Persistent Depressive Disorder, Personality Change, Personality Disorder, Psychomotor Retardation, Stress, Suicidal Ideation
Myalgia	Myalgia, Musculoskeletal Pain, Myositis, Musculoskeletal Discomfort
Neuropathy peripheral	Neuropathy Peripheral, Peripheral Sensory Neuropathy, Hypoesthesia, Paresthesia, Polyneuropathy, Neuralgia, Peripheral Motor Neuropathy, Hyperesthesia, Autoimmune Neuropathy, Peripheral Sensorimotor Neuropathy, Immune-Mediated Neuropathy, Dysesthesia
Pneumonitis/Interstitial Lung Disease	Interstitial Lung Disease, Pneumonitis, Organizing Pneumonia, Acute Interstitial Pneumonitis, Immune-Mediated Pneumonitis, Radiation Pneumonitis
Rash	Autoimmune Dermatitis, Dermatitis, Dermatitis Acneiform, Dermatitis Bullous, Dermatitis Exfoliative, Dermatitis Exfoliative Generalized, Drug Eruption, Drug Reaction With Eosinophilia And Systemic Symptoms, Dyshidrotic Eczema, Eczema, Eczema Asteatotic, Erythema Multiforme, Exfoliative Rash, Eyelid Rash, Genital Rash, Immune-Mediated Dermatitis, Lichen Planus, Mucocutaneous Rash, Nodular Rash, Palmar-Plantar Erythrodysesthesia Syndrome, Pemphigoid, Penile Rash, Perineal Rash, Perivascular Dermatitis, Rash Erythematous, Rash Follicular, Rash Macular, Rash Maculo-Papular, Rash Maculovesicular, Rash Morbilliform, Rash Papular, Rash Papulosquamous, Rash Pruritic, Rash Pustular, Rash Vesicular, Scrotal Rash, Skin Exfoliation, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Toxic Skin Eruption, Urticarial Dermatitis, Vasculitic Rash, Vulvovaginal Rash

Skeletal Fractures	Fracture: Acetabulum, Ankle, Foot, Rib, Spinal Compression, Sternal
Sleep Disorders	Somnolence, Insomnia, Hypersomnia, Sleep Disorder, Narcolepsy, Sleep Apnea Syndrome, Snoring
Stomatitis	Stomatitis, Aphthous Ulcer, Mouth Ulceration, Cheilitis, Tongue Ulceration, Mucosal Inflammation, Mucositis, Aphthous Ulcer, Glossitis, Mucosal Hyperemia, Oral Mucosal Blistering, Gingival Erosion, Gingival Ulceration, Pharyngeal Inflammation, Oral Mucosal Erythema, Aphthous Stomatitis
Torsades de pointes/QT prolongation	Electrocardiogram QT prolonged, syncope, cardiac arrest, ventricular tachycardia.

AEs of Special Interest

Data and the Applicant's Position:

Potential Hy's Law cases were considered AESIs in the study protocols and for the integrated safety analysis. There were 2 AESIs reported in participants in Study AB-106-C203 who were included in all 3 safety analysis populations, both of these AESIs were considered serious and related to treatment with taletrectinib and resulted in discontinuation of treatment. Detailed narratives and case report forms for these participants are available in the study report (CSR AB-106-C203).

Overall, on review of the 2 cases that met the potential Hy's Law criteria, there was no specific pattern related to time to onset to taletrectinib treatment observed. One case was reported after a month of taletrectinib treatment in a participant with previous history of liver function abnormalities at baseline. The second case was confounded by medical history of hepatic cyst and gallbladder polyps, hepatitis, and cholecystitis (all ongoing at the time of enrollment), with baseline hepatitis B virus DNA of 7.34 E2 IU/mL; at the time of the event, reported after over one year of taletrectinib treatment, hepatitis B virus DNA was 1.646 E3 IU/mL (detection limit: 1.0). Both the participants recovered completely after taletrectinib treatment discontinuation.

The FDA's assessment:

FDA agrees with the Applicant's description of the two cases meeting Hy's Law criteria reported in the 600 mg QD safety analysis dataset (n=352). A summary of each case is provided below.

Study C203, Patient ID (b) (6) **TEAE of "hepatic function abnormal" meeting Hy's Law criteria:** This was a 58-year-old Asian female with stage IV NSCLC who received taletrectinib 600 mg QD. Relevant medical history included hepatitis B and hepatic cyst. At screening, her liver function tests were normal. The patient was reported to have a nonserious AE of Grade 1 increased AST on Day 8 and increased ALT on Day 15. On Day 119, the patient's laboratory tests revealed AST and ALT elevation worsened to Grade 3 with ALT 248.5 U/L (range: 0-32) and AST 313 U/L (range: 8-40). Study treatment was interrupted on Day 119 and resumed at 600 mg QD on Day 141 after AST and ALT improvement. On Day 181, taletrectinib was reduced to 400 mg QD due to a

nonserious AE of diarrhea. On Day 392, lab results showed elevated AST 515 U/L (range: 0 - 40), ALT 403 U/L (range: 0 - 40), GGT 178 U/L (range: 11 - 61), bilirubin 31.6 µmol/L (range: 3.45 - 20) and normal ALP. An ultrasound showed multiple hepatic cysts and abnormal multiple gallbladder polyposis and cholecystitis. On Day 399, study treatment was discontinued due to abnormal hepatic function. The patient received follow-up cancer treatment with crizotinib from Day 458. The patient's AST, ALT and bilirubin were reported to be normal on Day 605. The investigator assessed the event of abnormal hepatic function as possibly related to study treatment.
Assessment: FDA considers the event of hepatotoxicity meeting Hy's Law criteria as possibly related to study treatment although patient's history of chronic hepatitis could be a confounder.

Study C203, Patient ID (b) (6) **TEAE of "hepatic function abnormal" meeting Hy's Law criteria:** This was a 39-year-old Asian female with stage IV NSCLC who received taletrectinib 600 mg QD. At baseline, her liver function test was abnormal with no etiology reported. On Day 14, the patient was diagnosed with Grade 1 abnormal hepatic function (elevated AST, ALT; and normal bilirubin, ALP and GGT). On Day 30, the AE of abnormal hepatic function worsened to a Grade 3 SAE with ALT 206 U/L (range: 7-40), AST 142 U/L (range: 13-35), and normal total bilirubin. Study treatment was interrupted on Day 31 and later resumed at a reduced dose of 400 mg QD on Day 43. Between Day 48 and Day 147, the patient had several AEs of abnormal hepatic function which resulted in drug interruptions on Day 49, Day 83 and Day 128 and dose reduction to 400 mg QD on Day 76 and to 200 mg QD on Day 98 and Day 147. However, on Day 160, the AE of abnormal hepatic function worsened to Grade 3 with ALT 372 U/L (range: 0-40), AST 303 U/L (range: 0-40), and total bilirubin 48.1 µmol/L (range: 0-21); ALP and GGT were normal. On Day 162, study treatment was discontinued. On Day 316, the SAE of abnormal hepatic function was considered resolved. The investigator assessed the event as definitely related to study treatment.
Assessment: FDA considers the event of hepatotoxicity meeting Hy's Law criteria as definitely related to study treatment based on the correlation of the event onset with drug use, improvement with drug interruption, and the event recurrence upon re-exposure.

Upon review of the two cases meeting Hy's Law criteria, and safety data of liver-related AEs, FDA agrees with Applicant's assessment of liver toxicity as a potential risk of the drug. Hepatotoxicity will be included in the Warnings and Precautions section of the product label.

Liver-related Events

Data:

Table 56. Applicant - Overall Summary of Liver-Related Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
All liver events	**295 (87.5)**	**309 (87.8)**	**333 (80.8)**
Treatment related	285 (84.6)	299 (84.9)	317 (76.9)
Serious	13 (3.9)	13 (3.7)	13 (3.2)
Grade 3 or higher	65 (19.3)	66 (18.8)	76 (18.4)
Lead to treatment interruption	42 (12.5)	42 (11.9)	48 (11.7)
Lead to dose reduction	42 (12.5)	43 (12.2)	45 (10.9)
Lead to treatment discontinuation	4 (1.2)	4 (1.1)	6 (1.5)
Lead to death	2 (0.6)	2 (0.6)	2 (0.5)
Liver function test abnormality	**293 (86.9)**	**307 (87.2)**	**330 (80.1)**
Treatment related	283 (84.0)	297 (84.4)	315 (76.5)
Serious	9 (2.7)	9 (2.6)	9 (2.2)
Grade 3 or higher	63 (18.7)	64 (18.2)	74 (18.0)
Lead to treatment interruption	40 (11.9)	40 (11.4)	46 (11.2)
Lead to dose reduction	42 (12.5)	43 (12.2)	45 (10.9)
Lead to treatment discontinuation	3 (0.9)	3 (0.9)	5 (1.2)
Lead to death	1 (0.3)	1 (0.3)	1 (0.2)
ALT/AST increased	**256 (76.0)**	**266 (75.6)**	**284 (68.9)**
Treatment related	250 (74.2)	260 (73.9)	274 (66.5)
Serious	1 (0.3)	1 (0.3)	1 (0.2)
Grade 3 or higher	43 (12.8)	44 (12.5)	52 (12.6)
Lead to treatment interruption	32 (9.5)	32 (9.1)	37 (9.0)
Lead to dose reduction	32 (9.5)	33 (9.4)	35 (8.5)
Lead to treatment discontinuation	1 (0.3)	1 (0.3)	2 (0.5)
Lead to death	0	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.2.1.1, ISS Table 3.2.1.2, ISS Table 3.2.2.2, ISS Table 3.2.3.1, ISS Table 3.2.3.3, ISS Table 3.2.4.1, ISS Table 3.2.5.1, ISS Table 3.2.6.1, ISS Table 3.2.7.1

The Applicant's Position:

An overall summary of liver-related events is presented in **Table 56**. Liver function laboratory abnormalities are presented in **Section 8.2.4** and **Table 51**.

The majority of events were Grade 1 and 2 and nonserious. Most of the liver-related events were transient and reversible in approximately 80% of participants and did not lead to treatment discontinuation. Grade 3 and higher events occurred in 18.8% of the 600 mg QD group, with the most frequently reported Grade 3 events (≥5%) being ALT increased (9.9%) and AST increased (7.4%). Of the 2 participants that met potential Hy's Law criteria, both had liver enzymes that recovered to baseline after treatment discontinuation (refer to **Section 8.2.4** for additional details).

The assessment of hepatic events and abnormal liver function (laboratory values) indicated a potential for hepatotoxicity associated with taletrectinib treatment; most events were LFT abnormalities, specifically AST and ALT elevations. In the majority of the cases, these events were transient, and the majority of patients recovered completely. Most of liver-related events were low grade with few SAEs reported. Few participants discontinued treatment due to liver-related events.

The FDA's Assessment:

FDA generally agrees with the Applicant's position on the description of liver-related events. FDA performed a revised analysis for liver-related TEAEs as listed in **Table 57**.

Table 57. FDA - Liver-Related Treatment Emergent Adverse Events

Liver-related treatment-emergent adverse event[1]	***ROS1*-Positive NSCLC 600mg QD N = 337 n (%)**		**600mg QD N = 352 n (%)**	
	NCI CTCAE All Grades	**NCI CTCAE Grade ≥3**	**NCI CTCAE All Grades**	**NCI CTCAE Grade ≥3**
AST increased	243 (72)	26 (8)	253 (72)	26 (7)
ALT increased	229 (68)	34 (10)	238 (68)	35 (10)
Blood bilirubin increased	59 (18)	4 (1.2)	65 (18)	4 (1.1)
GGT increased	34 (10)	4 (1.2)	34 (10)	4 (1.1)
Blood ALP increased	26 (8)	2 (0.6)	26 (7)	2 (0.6)
Hepatic function abnormal	47 (14)	15 (4.5)	50 (14)	15(4.3)
Cholecystitis	3 (0.9)	0	3 (0.9)	0
Hepatic steatosis	3 (0.9)	0	3 (0.9)	0
Hypertransaminasemia	3 (0.9)	0	3 (0.9)	0
Liver injury	2 (0.6)	0	2 (0.6)	0

Drug-induced liver injury	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Hepatic cytolysis	1 (0.3)	0	1 (0.3)	0
Hyperbilirubinemia	1 (0.3)	0	1 (0.3)	0
Hepatic failure	1 (0.3)	1(0.3)	1 (0.3)	1(0.3)

[1]Based on National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 and 5.0

Among patients who received taletrectinib 600 mg QD (n=352), based on laboratory values, increased AST occurred in 88% of patients, including 10% Grade 3 or 4, while increased ALT occurred in 85% of patients, including 13% Grade 3 or 4. The median time to first onset of AST or ALT elevation was 15 days (range 3 days to 20.8 months).

Given the clinical significance and serious outcomes of liver-related TEAEs, FDA has used the term "hepatotoxicity" to cover the reported terms of "hepatic function abnormal," "liver injury," "hepatic failure" and "drug-induced liver injury" in its assessment of fatal adverse reactions, drug interruptions, dose reductions or drug discontinuations.

Among patients who received taletrectinib 600 mg QD (n=352), liver-related TEAEs leading to drug interruption included increased AST (n=23, 7%), increased ALT (n=23, 7%), hepatotoxicity (GT) (n=10, 2.8%; including "hepatic function abnormal" [n=8], "drug-induced liver injury" [n=1] and "liver injury" [n=1]), increased blood bilirubin (n=3, 0.9%), increased bilirubin conjugated (n=2, 0.6%), and increased GGT (n=1, 0.3%). Liver-related TEAEs leading to dose reduction were increased ALT (n=30, 9%), increased AST (n=18, 5%), hepatotoxicity (GT) (n=8, 2.3%; including "hepatic function abnormal" [n=7] and "drug-induced liver injury" [n=1]), increased GGT (n=2, 0.6%), increased blood bilirubin (n=1, 0.3%), and increased bilirubin conjugated (n=1, 0.3%). Liver-related TEAEs leading to drug discontinuation were hepatotoxicity (GT) (n=2, 0.6%; including "hepatic function abnormal" [n=2. 0.6%]), increased ALT (n=1, 0.3%), increased AST (n=1, 0.3%) and increased blood bilirubin (n=1, 0.3%).

Liver-related SAEs were reported in 12 patients (3.4%). Liver-related TEAEs with a fatal outcome were reported in two patients (0.6%). There were two cases (0.6%) meeting Hy's Law criteria which were discussed under the section entitled "AEs of Special Interest."

The two patients (0.6%) with liver-related TEAEs leading to death are discussed below.

Study C203, Patient ID (b) (6) **SAE of "hepatic failure" with a fatal outcome:**
This was a 36-year-old Asian male with stage IV NSCLC, with metastatic lesions in the bone and both lungs, who received taletrectinib 600 mg QD. The patient had normal liver function test at screening. Between Day 15 to Day 94, the patient was reported to have non-serious AEs of Grade 1-2 of increased blood ALP, increased blood bilirubin, and increased AST. On Day 80, he was hospitalized for a percutaneous vertebroplasty, which occurred on Day 84 but the hospitalization was prolonged due to severe fatigue after surgery. Antibiotics and acetaminophen were reported to be used as pre- and postoperative medications. The patient was also diagnosed with nonserious AEs of Grade

1 abnormal hepatic function, increased bilirubin conjugated and abnormal coagulation test. On Day 95, the patient experienced an SAE of Grade 3 hepatic failure (ALT 490 U/L (range:10-49), AST 602 U/L (range: 0-34), bilirubin 147 µmol/L (range: 5-21), GGT 1149 U/L (range: 0-73)). His previous imaging (date unspecified) showed no liver metastasis. Despite medical treatment, patient's condition did not improve, and his family refused further treatment. On Day 98, the patient died due to the SAE of Grade 5 hepatic failure. An autopsy was not performed. The investigator assessed the event of hepatic failure as possibly related to study treatment.
Assessment: FDA considers the event of Grade 5 hepatic failure as possibly related to the study treatment although patient's preoperative and postoperative medications (antibiotics and acetaminophen) could be confounding factors.

Study C203, Patient ID (b) (6) **SAE of "hepatic function abnormal" with a fatal outcome:** This was a 40-year-old Asian female with stage IV NSCLC, with metastatic lesions in the lymph node and bone, who received taletrectinib 600 mg QD. At screening, patient had abnormal liver function test with ALT, AST, GGT and blood bilirubin elevation, which was considered to be caused by biliary tract compression and cholestasis due to retroperitoneal lymph node metastasis. On Day 7, the patient had worsening liver enzymes. Study treatment was interrupted due to increased AST. On Day 13, the patient developed an SAE of Grade 2 abnormal hepatic function. Laboratory tests revealed AST 228.9 U/L (range: 0-34), bilirubin 105.2 µmol/L (range: 5-31), ALP 446.7 U/L (range: 45-129), and GGT 246.6 U/L (range: 0-38). An ultrasound showed an enlarged and irregular liver with several 7 mm × 9 mm hypoechoic nodules and a 48 mm × 17 mm heterogenous echogenic mass beside the hepatic portal vein. On Day 17, the patient was discharged from the hospital; no further details were available. On Day 25, patient died. An autopsy was not performed. The investigator assessed the event of hepatic function abnormal as possibly related to study treatment and retroperitoneal lymph node metastasis.

Assessment: FDA considers the SAE of abnormal hepatic function as possibly related to the study treatment, although her retroperitoneal lymph node metastasis, liver metastasis and abnormal liver function at baseline could be contributing factors.

The assessment of liver-related TEAEs and liver-related laboratory abnormalities indicates an association of hepatotoxicity with the use of taletrectinib. Hepatotoxicity will be described in the Warnings and Precautions section of the product label.

Interstitial Lung Disease-related Events

Data:

Table 58. Applicant - Overall Summary of Interstitial Lung Disease Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Interstitial lung disease SMQ narrow	**8 (2.4)**	**8 (2.3)**	**9 (2.2)**
Treatment related	6 (1.8)	6 (1.7)	7 (1.7)
Serious	5 (1.5)	5 (1.4)	6 (1.5)
Grade 3 or higher	4 (1.2)	4 (1.1)	5 (1.2)
Lead to treatment interruption	4 (1.2)	4 (1.1)	4 (1.0)
Lead to dose reduction	2 (0.6)	2 (0.6)	2 (0.5)
Lead to treatment discontinuation	2 (0.6)	2 (0.6)	3 (0.7)
Lead to death	0	0	1 (0.2)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; SMQ, standardized MedDRA query.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.2.1.1, ISS Table 3.2.1.2, ISS Table 3.2.2.2, ISS Table 3.2.3.1, ISS Table 3.2.3.3, ISS Table 3.2.4.1, ISS Table 3.2.5.1, ISS Table 3.2.6.1, ISS Table 3.2.7.1

The Applicant's Position:

An overall summary of ILD-related events is presented in **Table 58**.

The rate of the AEs of ILD (narrow search) was 2.3% for the 600 mg QD group. There was no specific timing of onset pattern observed with ILD events, as these events were reported after several months and even years after initiation of taletrectinib treatment.

Although infrequently reported, the assessment of ILD/pneumonitis TEAEs did indicate a potential for its causality. One participant who received 400 mg QD taletrectinib had a fatal outcome reported due to an SAE of ILD. The participant had prior history of use of a PD-L1 inhibitor right before initiation of taletrectinib treatment.

The FDA's Assessment:

FDA agrees with the Applicant's position on the description of ILD/pneumonitis TEAEs. Among patients who received 600 mg QD (n=352), there were 8 patients (2.3%) with ILD/pneumonitis of any Grade. Four patients (1.1%) were noted to have Grade ≥3 ILD/pneumonitis. Five patients (1.4%) were reported to have an SAE of pneumonitis. The AE of ILD/pneumonitis resulted in dose interruption in four patients (1.1%), dose reduction in two patients (0.6 %), and drug discontinuation in two patients (0.6%). The median time to first onset of ILD/pneumonitis was 3.8 months (range: 12 days to 11.8 months).

Among patients who received at least one dose of taletrectinib (n=412), there was one death due to ILD/pneumonitis; this information is included in labeling. The case summary is described below.

Study J102, Patient ID (b) (6) **TEAE of "pneumonitis" with a fatal outcome:** This was a 51-year-old Asian male with stage IV NSCLC who received taletrectinib (DS-6051b) 400 mg QD. Relevant medical history included deep vein thrombosis, hypertension, and pulmonary embolism. His prior cancer treatment included bevacizumab, carboplatin, pemetrexed and avelumab, with the last dose of avelumab approximately 3 months prior to the first dose of taletrectinib. On Day 40, the patient experienced worsening of exertional dyspnea. A chest CT scan showed ground glass opacity in the center of the right lung. Cytology from bronchoalveolar lavage exams showed a few atypical cells and increase in lymphocytes. No signs of infection were reported. He was diagnosed with drug-induced lung injury. Taletrectinib was discontinued. A chest CT scan on Day 81 showed no signs of lung cancer progression. On Day 106, despite multiple courses of steroid treatment, his pneumonitis worsened; the patient died on Day 107. An autopsy was not performed. The investigator considered that the event was related to taletrectinib although it could also be related to the anti-PD-L1 therapy (avelumab) patient received prior to the initiation of taletrectinib.
Assessment: FDA considers the event of ILD/pneumonitis as possibly related to study treatment although recent prior treatment with avelumab could be a confounding factor.

The protocols for Studies G208 and C203 permitted resumption of taletrectinib in patients with Grade 1 or 2 ILD/pneumonitis which resolved within 6 weeks. Among patients who received taletrectinib 600 mg QD (n=352), two patients (Study G208, Patient IDs (b) (6)) who experienced Grade 2 ILD/pneumonitis resumed taletrectinib when the events of ILD/pneumonitis resolved or improved to Grade 1. There was no report of recurrence or worsening of ILD/pneumonitis after study treatment was resumed. FDA agrees with the Applicant's assessment that ILD/pneumonitis is a potential risk of taletrectinib; ILD/Pneumonitis will be included in the Warnings and Precautions section of the product label.

QT Prolongation-related Events

Data:

Table 59. Applicant - Overall Summary of QT Prolongation-Related Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Torsade de pointes/QT prolongation SMQ Broad	**73 (21.7)**	**73 (20.7)**	**79 (19.2)**
Treatment related	65 (19.3)	65 (18.5)	68 (16.5)
Serious	3 (0.9)[a]	3 (0.9)[a]	3 (0.7)[a]
Grade 3 or higher	18 (5.3)	18 (5.1)	21 (5.1)
Lead to dose interruption	10 (3.0)	10 (2.8)	11 (2.7)
Lead to dose reduction	10 (3.0)	10 (2.8)	10 (2.4)
Lead to treatment discontinuation	0	0	0
Lead to death	2 (0.6)[b]	2 (0.6)[b]	2 (0.5)[b]

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; SMQ, standardized MedDRA query; TEAE, treatment-emergent adverse event.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
[a] The serious TEAEs were cardiac arrest (2 cases) and syncope (1 case). None was considered treatment related.
[b] The TEAE leading to death in both cases was cardiac arrest. Neither was considered treatment related.
Source: ISS Table 3.2.1.1, ISS Table 3.2.1.2, ISS Table 3.2.2.2, ISS Table 3.2.3.1, ISS Table 3.2.3.3, ISS Table 3.2.4.1, ISS Table 3.2.5.1, ISS Table 3.2.6.1, ISS Table 3.2.7.1

Table 60. Applicant - ECG Results - Shift Table for Maximum QTcF Increase

Baseline (ms) N=412	Maximum On-treatment Change[a]				Total n (%)
	≤30 ms n (%)	>30 to ≤60 ms n (%)	>60 ms n (%)	Missing n (%)	
≤450 ms	197 (47.8)	158 (38.3)	45 (10.9)	1 (0.2)	401 (97.3)
>450 to ≤480 ms	8 (1.9)	0	1 (0.2)	0	9 (2.2)
>480 to ≤500 ms	1 (0.2)	0	0	0	1 (0.2)
>500 ms	1 (0.2)	0	0	0	1 (0.2)
Missing	0	0	0	0	0
Total	207 (50.2)	158 (38.3)	46 (11.2)	1 (0.2)	412 (100)

Abbreviations: ECG, electrocardiogram; N, total number of participants; n, subset of total number of participants; QTcF, QT interval corrected using Fridericia's formula.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
[a] Maximum change on-treatment value = maximum change after the first dose of study drug and within 30 days after the last dose of study drug.
Source: ISS Table 4.2.1.1

Table 61. Applicant - ECG Results - Shift Table for Maximum QTcF

Baseline (ms) N=412	Maximum On-treatment Value[a]					Total n (%)
	≤450 ms n (%)	>450 to ≤480 ms n (%)	>480 to ≤500 ms n (%)	>500 ms n (%)	Missing n (%)	
≤450 ms	284 (68.9)	91 (22.1)	17 (4.1)	8 (1.9)	1 (0.2)	401 (97.3)
>450 to ≤480 ms	0	4 (1.0)	4 (1.0)	1 (0.2)	0	9 (2.2)
>480 to ≤500 ms	0	0	1 (0.2)	0	0	1 (0.2)
>500 ms	0	0	1 (0.2)	0	0	1 (0.2)
Missing	0	0	0	0	0	0
Total	284 (68.9)	95 (23.1)	23 (5.6)	9 (2.2)	1 (0.2)	412 (100)

Abbreviations: ECG, electrocardiogram; N, total number of participants; n, subset of total number of participants; QTcF, QT interval corrected using Fridericia's formula.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
[a] Maximum change on-treatment value = maximum change after the first dose of study drug and within 30 days after the last dose of study drug.
Source: ISS Table 4.2.1.2

The Applicant's Position:

An overall summary of QT prolongation-related events using the torsade de pointes/QT prolongation SMQ Broad is presented in **Table 59**.

In the 600 mg QD group, QT prolongation-related TEAEs were mostly Grade 1 or 2 and nonserious; 5.1% were considered Grade ≥3.

Three participants experienced QT prolongation-related SAEs, including 2 cases of cardiac arrest and 1 case of syncope. All were considered unrelated to taletrectinib treatment. No participant discontinued treatment due to QT prolongation-related TEAEs, and dose interruptions or reductions were infrequent. None of the reported QT prolongation-related SAEs was associated with evidence of ECG QT prolongation. Of the QT prolongation-related events, all events of QT prolongation were nonserious. In addition, no serious ventricular arrhythmia including Torsades de pointes was reported.

Shift tables for maximum QTcF increases from baseline and maximum QTcF values in the overall group are presented in **Table 60** and **Table 61**, respectively. More than 50% of participants had maximum QTcF interval increase from baseline ≤30 ms, 11.2% of participants had maximum QTcF interval increase from baseline >60 ms with most participants (10.9%) having baseline QTcF ≤450 ms. Nearly all participants had QTcF values <480 ms at baseline and the majority of participants remained in that range throughout treatment. Twenty-three (5.6%) participants had worst QTcF values of >480 to ≤500 ms, 9 (2.2%) participants had worst QTcF values >500 ms.

An analysis of concentration-corrected QT interval analysis using PK-matched triplicate ECG assessments was conducted. The relationship between change in QTcF (ΔQTcF) and plasma concentrations of taletrectinib was modeled using a linear mixed-effects modeling approach. Predicted ΔQTcF at the geometric mean steady-state peak taletrectinib concentration following 600 mg QD administration was 12.76 ms (with an upper bound of 90% confidence interval of 15.43 ms) and 12.11 (with an upper bound of 90% confidence interval of 14.65 ms) based on observed maximum taletrectinib concentrations from Study AB-106-G208 (n=41) and Study AB-106-C203 (n=14), respectively. Therefore, taletrectinib did prolong the QT interval in a concentration-dependent manner but the likelihood of causing a large effect (i.e., >20 ms) at the therapeutic dose is low.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary. Among the patients who received taletrectinib 600 mg QD (n=352), a broad SMQ search for torsades de pointes /QT prolongation AEs generated 73 patients (21%), with 18 patients (5%) having Grade ≥3 AEs. The SMQ-generated AEs included ECG QT prolongation (n=65, 18%), syncope (n=6, 1.7%), cardiac arrest (n=2, 0.6%) and ventricular tachycardia (n=2, 0.6%). No ECG QT prolongation was reported for the two patients that experienced an AE of ventricular tachycardia.

In the pooled safety population, of the 351 patients who underwent at least one post-baseline ECG assessment, 13% experienced an increase in QTcF of >60 msec compared to baseline and 2.6% had an increase in QTcF to >500 msec. Twelve patients (3.4%) experienced a Grade ≥3 ECG QT prolongation event, reported as a TEAE. The median time from the first dose taletrectinib to the onset of ECG QT prolongation was 22 days (range: 1 day to 38.7 months).

There were three (0.9%) SAEs including two events of cardiac arrest and one event of syncope. None of the patients who experienced these SAEs had report of ECG QT prolongation. The two SAEs of cardiac arrest were reviewed under **Section 8.2.4** Safety Results – Deaths. A summary of the SAE of syncope is described below.

> **Study G208, Patient ID** (b) (6) **SAE of "syncope:"** This was a 61-year-old Asian female with NSCLC who received taletrectinib 600 mg QD. Relevant medical history included Vogt-Koyanagi-Harada disease (a rare, autoimmune disorder) and autonomic nervous system imbalance. On Day 59, the patient experienced an SAE of Grade 3 syncope which lasted for about a minute while waiting at the bus stop. The patient's medical evaluation revealed normal electrolytes, normal D-dimer and no significant findings in a head CT scan. A cardiology and a neurology examination determined that the cause of syncope might be neuromodulatory syncope associated with autonomic imbalance. The SAE was considered resolved on Day 62. The patient continued taking taletrectinib with no further report of syncope. On Day 853, study treatment was discontinued due to progressive disease.
>
> Assessment: FDA considers that although the role of taletrectinib in the SAE of Grade 3 syncope could not be excluded, the event was unlikely to be related to taletrectinib. The patient's medical history of autonomic nervous system imbalance could be a potentially contributing factor.

Among patients who received taletrectinib 600 mg QG (n=352), ECG QT prolongation TEAEs resulted in drug interruption in 10 patients (2.8%) and dose reduction in 10 patients (2.8%). No patients required drug discontinuation as a result of ECG QT prolongation TEAEs.

The data indicate ECG QT prolongation is a potential risk of taletrectinib; QT prolongation will be included in the Warnings and Precautions section of the product label.

Gastrointestinal Events

Data:

Table 62. Applicant - Overall Summary of Gastrointestinal Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Gastrointestinal disorders system organ class	**297 (88.1)**	**310 (88.1)**	**363 (88.1)**
Treatment related	287 (85.2)	300 (85.2)	343 (83.3)
Serious	8 (2.4)	11 (3.1)	14 (3.4)
Grade 3 or higher	18 (5.3)	21 (6.0)	31 (7.5)

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Lead to treatment interruption	23 (6.8)	26 (7.4)	38 (9.2)
Lead to dose reduction	14 (4.2)	15 (4.3)	16 (3.9)
Lead to treatment discontinuation	2 (0.6)	2 (0.6)	5 (1.2)
Lead to death	0	2 (0.6)	2 (0.5)

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.2.1.1, ISS Table 3.2.1.2, ISS Table 3.2.2.2, ISS Table 3.2.3.1, ISS Table 3.2.3.3, ISS Table 3.2.4.1, ISS Table 3.2.5.1, ISS Table 3.2.6.1, ISS Table 3.2.7.1

The Applicant's Position:

An overall summary of gastrointestinal events is presented in **Table 62**.

Most of the gastrointestinal-related events reported were Grade 1 or 2 and nonserious. Most participants recovered completely without supportive treatment and infrequently required dose interruption or reduction. Grade 3 and higher events occurred in 6.0% of the 600 mg QD group, with approximately half considered related to taletrectinib by the investigator. Two participants experienced Grade 5 gastrointestinal-related events (ileus and intestinal perforation); both events were considered unrelated to taletrectinib treatment by the investigator and were attributed to background medical conditions and their complications.

The FDA's Assessment:

FDA agrees with the Applicant's summary of gastrointestinal events in the safety analysis dataset. FDA conducted a revised analysis of gastrointestinal events using the definitions of safety events of interest in **Table 55**. Among patients who received taletrectinib 600 mg QD (n=352), diarrhea (GT) was reported in 225 patients (64%) with 7 patients (2%) experiencing a Grade ≥3 AE. The AE of diarrhea resulted in drug interruption in seven patients (2%) and dose reduction in eight patients (2.3%). No drug withdrawal occurred due to the AE of diarrhea.

Vomiting (GT) was reported in 153 patients (43%) with six patients (1.7%) experiencing a Grade ≥3 AE. The AE of vomiting resulted in drug interruption in 11 patients (3.1%) and dose reduction in six patients (1.7%). No drug withdrawal occurred due to the AE of vomiting.

Abdominal pain (GT) was reported in 48 patients (14%) with no patient experiencing a Grade ≥3 AE. The AE of abdominal pain resulted in drug interruption in six patients (1.7%). No dose reduction or drug withdrawal occurred due to the AE of abdominal pain.

Stomatitis (GT) was reported in seven patients (2%) with no patient experiencing a Grade ≥3 AE. No drug interruption, dose reduction and drug withdrawal occurred due to the AE of stomatitis.

Other frequently reported (≥ 10%) gastrointestinal AEs were nausea (n=163, 46%) with five patients (1.4%) having a Grade ≥3 AE and constipation (n=73, 21%) with no patient having a Grade ≥3 AE.

Gastrointestinal related SAEs were reported in 13 patients (3.7%), which included vomiting (n=5, 1.4%), nausea (n=2, 0.6%) and anal fistula, ascites, dysphagia, esophageal obstruction, ileus and intestinal obstruction (n=1, 0.3% for each event). Two patients (0.6%) experienced Grade 5 gastrointestinal related AEs (ileus and intestinal perforation). In both patients, the events occurred in the context of progressive disease with abdominal tumors involved (sarcoma and colorectal carcinoma).

Neurological Events

Data:

Table 63. Applicant - Overall Summary of Neurological Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Nervous system disorders system organ class	**163 (48.4)**	**172 (48.9)**	**205 (49.8)**
Treatment related	128 (38.0)	137 (38.9)	159 (38.6)
Serious	17 (5.0)	17 (4.8)	17 (4.1)
Grade 3 or higher	19 (5.6)	19 (5.4)	22 (5.3)
Lead to treatment interruption	10 (3.0)	10 (2.8)	13 (3.2)
Lead to dose reduction	6 (1.8)	7 (2.0)	7 (1.7)
Lead to treatment discontinuation	2 (0.6)	2 (0.6)	2 (0.5)
Lead to death	1 (0.3)	1 (0.3)	1 (0.2)
Peripheral neuropathy SMQ Broad	**78 (23.1)**	**80 (22.7)**	**98 (23.8)**
Treatment related	63 (18.7)	65 (18.5)	77 (18.7)
Serious	2 (0.6)	2 (0.6)	2 (0.5)
Grade 3 or higher	2 (0.6)	2 (0.6)	2 (0.5)
Lead to treatment interruption	4 (1.2)	4 (1.1)	5 (1.2)
Lead to dose reduction	3 (0.9)	4 (1.1)	4 (1.0)
Lead to treatment discontinuation	0	0	0
Lead to death	0	0	0

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Vestibular disorders SMQ Broad	**75 (22.3)**	**79 (22.4)**	**91 (22.1)**
Treatment related	53 (15.7)	57 (16.2)	63 (15.3)
Serious	2 (0.6)	2 (0.6)	2 (0.5)
Grade 3 or higher	1 (0.3)	1 (0.3)	1 (0.2)
Lead to treatment interruption	3 (0.9)	3 (0.9)	4 (1.0)
Lead to dose reduction	1 (0.3)	1 (0.3)	1 (0.2)
Lead to treatment discontinuation	0	0	0
Lead to death	0	0	0
High level group term of headache	**35 (10.4)**	**38 (10.8)**	**41 (10.0)**
Treatment related	18 (5.3)	21 (6.0)	22 (5.3)
Serious	3 (0.9)	3 (0.9)	3 (0.7)
Grade 3 or higher	3 (0.9)	3 (0.9)	4 (1.0)
Lead to treatment interruption	1 (0.3)	1 (0.3)	1 (0.2)
Lead to dose reduction	0	0	0
Lead to treatment discontinuation	0	0	0
Lead to death	0	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1; SMQ, standardized MedDRA query.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
Source: ISS Table 3.2.1.1, ISS Table 3.2.1.2, ISS Table 3.2.2.2, ISS Table 3.2.3.1, ISS Table 3.2.3.3, ISS Table 3.2.4.1, ISS Table 3.2.5.1, ISS Table 3.2.6.1, ISS Table 3.2.7.1

The Applicant's Position:

An overall summary of neurological events using the nervous system disorders SOC is presented in **Table 63**.

The majority of the reported neurological events were nonserious, Grade 1 or 2, and transient.

The most frequently reported neurological TEAEs (≥5% of participants) were dizziness, dysgeusia, headache, muscular weakness, and hypoesthesia.

Nineteen (5.4%) participants experienced TEAEs of Grade 3 or higher severity (5/19 were considered related to taletrectinib by the investigator's evaluation: demyelination, dizziness, headache, hypoesthesia, syncope). One participant experienced a Grade 4 TEAE (IC tumor hemorrhage, unrelated) and 1 participant experienced a Grade 5 TEAE (cerebral hemorrhage,

assessed per the investigator's evaluation as unrelated to treatment and due to background medical conditions and their complications). Overall, 2 participants discontinued treatment due to neurological-related TEAEs (cerebral hemorrhage and dysarthria, considered unrelated to treatment by the investigators). Few dose reductions (2.0%), dose interruptions (2.8%), or serious (4.8%) neurological TEAEs were reported.

The FDA's Assessment:

FDA agrees with the Applicant's summary of neurological disorder TEAEs. FDA conducted a revised analysis of neurological toxicities using the definitions of safety events of interest in **Table 55**. Among patients who received taletrectinib 600 mg QD (n=352), CNS AEs (GT) occurred in 101 patients (29%) all Grades, with 2 patients (0.6%) experiencing Grade ≥3 AEs. Dizziness (GT) occurred in 79 patients (22%), with 71 patients (20%) experiencing Grade 1, seven patients (2%) experiencing Grade 2 and one patient (0.3%) experiencing a Grade ≥3 AEs. Cognitive disorders (GT) were reported in six patients (1.7%) and were all Grade 1 events. Sleep disorders (GT) occurred in 22 patients (6%), with one patient (0.3%) experiencing a Grade ≥3 AE. Mood disorders (GT) occurred in 10 patients (2.8%) with no patient experiencing Grade ≥3 AE. Headache (GT) occurred in 38 patients (11%), with three patients (0.9%) experiencing Grade ≥3 AEs.

Peripheral neuropathy (GT) occurred in 59 patients (17%), with one patient (0.3%) experiencing a Grade ≥3 AE.

A total of 17 patients (4.8%) were reported to have SAEs of neurological disorders. One patient (0.3%) experienced a Grade 5 neurological disorder TEAE (cerebral hemorrhage) in the context of brain metastasis and progressive disease from NSCLC.

Drug interruption due to neurological disorder TEAEs was reported in a total of 11 patients (3.1%), including nervous system disorders (n=4, 1.1%), epilepsy (n=2, 0.6%), peripheral neuropathy (n=2, 0.6%), headache (n=1, 0.3%), demyelination (n=1, 0.3%) and dysgeusia (n=1, 0.3%). Dose reduction due to neurological disorder TEAEs occurred in eight patients (2.3%), including peripheral neuropathy (n=3, 0.9%), nervous system disorders (n=2, 0.6%), demyelination (n=1, 0.3%), dizziness (n=1, 0.3%) and dysgeusia (n=1, 0.3%). Two patients (0.6%) discontinued treatment due to neurological disorder TEAEs including one patient with cerebral hemorrhage and one patient with dysarthria; both patients were experiencing progressive disease in the brain. Given the limited incidence of serious or severe neurologic events or events which prompted treatment interruption or discontinuation, FDA concluded that CNS toxicity did not warrant inclusion as a Warning and Precaution in product labeling.

Hyperuricemia

Data:

Table 64. Applicant - Overall Summary of Hyperuricemia-Related Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Hyperuricemia	**49 (14.5)**	**51 (14.5)**	**55 (13.3)**
Treatment related	39 (11.6)	41 (11.6)	43 (10.4)
Serious	0	0	0
Grade 3 or higher	0	1 (0.3)	3 (0.7)
Lead to treatment interruption	1 (0.3)	1 (0.3)	1 (0.2)
Lead to dose reduction	0	0	0
Lead to treatment discontinuation	0	0	0
Lead to death	0	0	0

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.
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The Applicant's Position:

An overall summary of hyperuricemia events is presented in **Table 64**.

All hyperuricemia events were nonserious and the majority were Grade 1 or 2 and were reversible. One participant in the 600 mg QD group experienced Grade 3 or higher hyperuricemia. None of the hyperuricemia-related TEAEs were considered SAEs or led to treatment discontinuation. Most participants did not require dose modification or intervention for recovery.

Furthermore, the incidence of hyperuricemia and serum uric acid and urate elevations are comparable to what has been reported within a normal healthy population or in patients with NSCLC, suggesting no increased risk of hyperuricemia for patients treated with taletrectinib.

The FDA's Assessment:

FDA agrees with the Applicant's description of hyperuricemia TEAEs; however, FDA does not agree with the statement that there is no increased risk of hyperuricemia for patients treated with taletrectinib. Among patients who received 600 mg QD (n=352), 51 patients (14%) were

reported to have TEAEs of hyperuricemia (GT). The median time to onset of hyperuricemia (GT) was 2.1 months (range: 7 days to 35.8 months).

Among the 51 patients with hyperuricemia TEAEs (GT), 10 patients (20%) required urate-lowering medication, including 8 patients (16%) without preexisting gout or elevated uric acid at screening. Most patients (8/10) did not report hyperuricemia-related symptoms. Two patients experienced non-specific symptoms such as back pain and fatigue.

One patient (0.3%) experienced a Grade ≥3 hyperuricemia (GT). Hyperuricemia TEAEs led to drug interruption in one patient (0.3%). There were no hyperuricemia TEAEs reported as SAE or resulting in treatment discontinuation. There was no report of gout flare or tumor lysis syndrome.

A review of hyperuricemia was also performed based on the laboratory dataset. Among patients who received 600 mg QD (n=352), increased urate levels occurred in 130/347 (37%) evaluable patients. None of the patients had Grade 3 to 4 hyperuricemia laboratory abnormalities.

Based on the incidence of hyperuricemia TEAE observed and reports of patients with normal uric acid at baseline who required urate lowering medications due to hyperuricemia while taking taletrectinib, FDA considers it appropriate to include hyperuricemia in the Warnings section of the drug label.

Skeletal Fractures

Data:

Table 65. Applicant - Overall Summary of Fracture Events

Category	ROS1+ NSCLC 600 mg QD N=337 n (%)	600 mg QD N=352 n (%)	Overall N=412 n (%)
Fractures	**12 (3.6)**	**12 (3.4)**	**13 (3.2)**
Treatment related	1 (0.3)	1 (0.3)	1 (0.2)
Serious	5 (1.5)	5 (1.4)	5 (1.2)
Grade 3 or higher	5 (1.5)	5 (1.4)	5 (1.2)
Lead to treatment interruption	1 (0.3)	1 (0.3)	1 (0.2)
Lead to dose reduction	0	0	0
Lead to treatment discontinuation	0	0	0
Lead to death	0	0	0

Abbreviations: N, total number of participants; n, subset of total number of participants; NSCLC, non-small cell lung cancer; QD, once daily; ROS1, c-ros oncogene 1.
Integrated studies include AB-106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102, and DS6051-A-U101.
Cutoff date: C203: 2024-06-07, C205: 2024-06-07, G208: 2024-06-07, J102: 2021-12-28, U101: 2021-09-16.

Source: ISS Table 3.2.1.1, ISS Table 3.2.1.2, ISS Table 3.2.2.2, ISS Table 3.2.3.1, ISS Table 3.2.3.3, ISS Table 3.2.4.1, ISS Table 3.2.5.1, ISS Table 3.2.6.1, ISS Table 3.2.7.1

The Applicant's Position:

An overall summary of skeletal fracture-related events is presented in **Table 65**.

The majority of fracture-related events occurred months after initiating treatment, with no clear correlation between taletrectinib treatment initiation and the fracture events. There were no dose reductions or discontinuations reported as a result of these events. Multiple factors were reported as potential confounders for these events (i.e., osteoporosis, bone metastases, degenerative disease). Importantly, no CNS adverse effects (e.g., dizziness, ataxia, peripheral neuropathy) were reported in any of the participants who experienced skeletal fractures suggesting taletrectinib did not cause the accidental falls. Data from nonclinical repeat-dose toxicity studies further supports the Applicant's assessment of risk for skeletal fractures as no skeletal fractures or bone findings were observed in studies of rat or monkey up to 12 weeks.

Overall, the fracture AEs were more likely related to the participants' background medical conditions and medical histories rather than the treatment with taletrectinib. Available data does not support an increased risk in skeletal fracture associated with taletrectinib treatment.

The FDA's Assessment:

FDA agrees with the Applicant's summary of skeletal fracture-related TEAEs. In FDA's revised analysis of skeletal fracture-related TEAEs, one patient (Study G208, Patient ID (b) (6)) with a non-serious AE of rib fracture did not have an assigned AE toxicity grade in the dataset.

Among patients who received 600 mg QD (n=352), a total of 12 patients (3.4%) with AEs of fractures were reported. Fractures involved the ribs (1.4%), spine (0.9%), femur (0.6%), humerus (0.3%), and acetabulum (0.3%). The median time to first onset of skeletal fractures was 10.7 months (range: 26 days to 29.1 months). There was no clear pattern between taletrectinib treatment initiation and the onset of skeletal fracture-related events.

A total of five patients (1.4%) had SAEs of fractures. Five patients (1.4%) had a Grade ≥3 AE. Drug interruption as a result of the AE of fractures occurred in one patient (0.3%). No dose reductions or discontinuations were reported as a result of a skeletal fracture-related TEAE.

FDA reviewed the case narratives for all five cases with SAEs. Predisposing factors for fractures such as sex (all females), age (range: 59 to 78 years of age), and race (4 Asian, 1 White) were identified. Multiple confounding and potential contributing factors including bone metastasis, fall, osteoporosis, and degenerative bone diseases were present.

When the data from the 90-day safety update was included, among patients who received taletrectinib 600 mg QD (n=364), there were a total of 14 patients (3.8%) with reported AEs of fractures. In addition to the 11 AEs of fractures identified in the original NDA application, three

additional AEs of fractures, including 2 SAEs, were reported in the 90-day safety update. They were pathological fracture (n=1, 0.3%), humerus fracture (n=1, 0.3%), and spinal fracture (n=1, 0.3%). In the two patients with SAEs of fractures, predisposing factors and potential contributing factors such as age, sex, race and medical history (osteopenia and previous history of fracture) were present.

Select narratives for SAEs of fractures are discussed below.

Study C203, Patient ID (b) (6) **SAE of "femur fracture:"** This was a 71-year-old Asian female with stage IV NSCLC, with metastatic lesions in the brain, live and bone, who received taletrectinib 600 mg QD. On Day 29, the patient fell in the bathroom and experienced an SAE of Grade 3 femur fracture. The patient reported no dizziness or paresthesia at the time of the event. A CT scan revealed uneven density in multiple ribs and the thoracic vertebral body, possible metastatic lesions, pathological fracture beneath the left femur, possible metastatic lesions, degeneration of both hips, and osteoporosis. On Day 34, patient underwent an open reduction of fracture of the left femur and internal fixation with intramedullary needle. Study treatment was interrupted as a result of femur fracture. On Day 35, study treatment was resumed at a dose of 600 mg QD. The SAE was considered resolved on Day 95. The investigator assessed the event of femur fracture as possibly unrelated to study treatment.
Assessment: FDA considers although the role of taletrectinib in the SAE of femur fracture could not excluded, there were multiple confounding factors such as patient's age, sex, race, underlying bone metastasis, osteoporosis and fall.

Study G208, Patient ID (b) (6) **SAE of "humerus fracture:"** This was a 61-year-old male with stage IV NSCLC, with metastatic lesions in the lymph node, liver, adrenal gland, pleura, bone, spleen, and kidney, who received taletrectinib 600 mg QD. Relevant medical history included history of fracture and prostate cancer. On Day 40, an overall response assessment revealed progressive disease; however, study treatment was continued. On Day 325, the patient was reported to have an SAE of Grade 3 humerus fracture. No presenting symptoms or further details were reported. Study treatment was interrupted as a result of the humerus fracture. On Day 329, the patient underwent surgical intervention to repair the humerus fracture. The SAE of humerus fracture was considered resolved. On Day 331, study treatment was resumed at a dose of 600 mg QD. The investigator assessed the event of humerus fracture as unrelated to study treatment.
Assessment: FDA considers although the role of taletrectinib in the SAE of humerus fracture could not be excluded, patient also had predisposing factors such as age and history of fracture.

Given the occurrence of Grade 3 fractures and known association of this risk with other in-class drugs, FDA considers it is appropriate to include Skeletal fractures in the Warnings of the drug label.

Myalgia with CPK elevation

FDA conducted a pooled term analysis of myalgia given the observation of a high incidence of increased creatine phosphokinase (CPK) in patients treated with taletrectinib and the inclusion of myalgia with CPK increase in labeling for another in-class product (i.e., repotrectinib).

Among patients who received 600 mg QD (n=352), myalgia (GT) with or without blood CPK elevation was observed. The AE of myalgia (GT) was reported in 35 patients (10%, all grades), with no patient experiencing Grade ≥3 AE. The median time to first onset of myalgia (GT) was 11 days (range: 2 days to 10 months).

Drug interruption occurred in one patient (0.3%) with myalgia, who also presented with concurrent CPK elevation. No dose reduction or drug withdrawal occurred as a result of an AE of myalgia. No myalgia-related SAEs and no cases of myositis or rhabdomyolysis were reported.

Of the 150 patients with CPK laboratory data available, elevated CPK occurred in 53% of patients, including 5% Grade 3 or 4. The median time to first onset of CPK elevation was 1.4 months (range: 7 days to 15.2 months). CPK elevation led to drug interruption in 1.1% and dose reduction in 0.6% of patients.

Concurrent myalgia with increased CPK within a 7-day time period was observed in 0.9% of patients. Taletrectinib was interrupted in one patient (0.3%) with myalgia and concurrent CPK elevation.

Given the non-clinical signal for potential muscle toxicity, the need to specifically monitor patients for CPK increase and be aware of the association between taletrectinib and myalgia, FDA considers it is appropriate to include myalgia with CPK increase in the Warnings of the drug label.

Eye disorders

FDA conducted a pooled term analysis of TEAE of eye disorders, given the occurrence of visual disorders with other in-class products (i.e., crizotinib and entrectinib).

Among patients who received 600 mg QD (n=352), AEs of eye disorders (GT) were reported in 39 patients (11%) all Grades, with one patient (0.3%) experiencing a Grade ≥3 AE. Eye exams were included at the screening phases in both Studies G208 and C203 and as a scheduled assessment in Study C203. The incidence rates of eye disorder AEs were similar between study G208 and C203: 10% all Grades and 0.6% Grade ≥3 in G208 and 12% all Grades with no Grade ≥3 eye disorder AEs in C203. Eye disorder AEs reported in ≥1% of patients included vision blurred (n=20, 6%), photosensitivity reaction (n=6, 1.7%), conjunctivitis (n=5, 1.4%), and cataract (n=4, 1.1%).

In the one patient (0.3%) who experienced a Grade ≥3 eye disorder AE, the event was also reported as an SAE. The same patient required drug interruption and drug dose reduction. No patients had drug discontinuation as a result of the AEs of eye disorders.
The case summary of the one patient (0.3%) who experienced SAE of Grade 3 macular hole and required drug interruption and dose reduction is described below.

Study G208, Patient ID (b) (6) **SAE of "macular hole:"** This was a 57-year-old female with stage 4 NSCLC who received taletrectinib 600mg QD. Relevant medical history included dyslipidemia, hypertension, thrombophlebitis, folate deficiency, bilateral cataracts and anemia. At screening, the patient had eye dryness in both eyes. An eye exam by ophthalmology revealed normal assessment. On Day 254, the patient reported having ocular pain and blurry vision that limited daily life. On Day 301, the AE of blurred vision worsened, and the patient experienced an SAE of Grade 3 macular hole (right eye); study treatment was interrupted on Day 333. On Day 364, a vitrectomy was performed. On the same day, the SAE of macular hole was considered resolved. On Day 372, study treatment was resumed at a reduced dose of 200 mg. The event of vision blurred improved to Grade 1 on Day 421, and at the time of reporting, was considered resolving. The investigator assessed the event of macular hole as unrelated to study treatment.
Assessment: FDA considers that although the role of taletrectinib in the SAE of macular hole could not be excluded, the event was confounded by other predisposing factors such as the patient's age and female sex.

Given that most eye disorders TEAEs were Grade 1 and 2, with a low incidence of SAEs, drug interruption and dose reduction, FDA does not consider a Warning in the drug label for eye disorders as necessary. However, given the overall incidence rate, clinical significance, and the association of eye disorders with other in-class drugs, we consider it is appropriate to include eye disorder as an adverse reaction with clinical relevance in the drug label.

Rash and Photosensitivity

During the review process, FDA identified "rash" as an additional safety event of interest. FDA's analysis of rash is included in **Table 66**.

Table 66. FDA - Rash-related Treatment Emergent Adverse Events

Rash	*ROS1*-Positive NSCLC 600mg QD N = 337 n (%)		600mg QD N = 352 n (%)	
	NCI CTCAE All Grades	NCI CTCAE Grade ≥3	NCI CTCAE All Grades	NCI CTCAE Grade ≥3
Rash (GT)	**75 (22)**	**6 (1.8)**	**78 (22)**	**7 (2)**
Rash	48 (14)	4 (1.2)	49 (14)	4 (1.1)
Rash maculo-papular	8 (2.4)	2 (0.6)	8 (2.3)	2 (0.6)
Dermatitis acneiform	6 (1.8)	0	6 (1.7)	0
Eczema	5 (1.5)	0	5 (1.4)	0
Skin exfoliation	4 (1.2)	1 (0.3)	4 (1.1)	1 (0.3)

Dermatitis	4 (1.2)	0	6 (1.7)	1 (0.3)
Palmar-plantar erythrodysaesthesia syndrome	4 (1.2)	0	4 (1.1)	0
Drug eruption	2 (0.6)	0	2 (0.6)	0
Stevens-Johnson syndrome	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Eyelid rash	1 (0.3)	0	1 (0.3)	0
Rash papular	1 (0.3)	0	1 (0.3)	0

Among patients who received 600 mg QD (n=352), rash-related TEAEs resulted in dose interruption in eight patients (2.3%), dose reduction in five patients (1.4%) and drug discontinuation in one patient (0.3%).

Rash-related SAEs occurred in 3/352 patients (0.9%), including Stevens-Johnson Syndrome (SJS)/drug rash with eosinophilia and systemic symptoms (DRESS) (n=1, 0.3%), rash (n=1, 0.3%), and rash maculo-papular (n=1, 0.3%). A summary of the case with DRESS is presented below.

Study G208, patient ID (b) (6) **SAE of SJS/DRESS**: This was a 46-year-old Asian female with stage IV NSCLC who received taletrectinib 600mg QD. Relevant medical history included drug eruption (crizotinib induced dermatitis). On Day 1, the patient developed non-serious AEs of nausea, vomiting and diarrhea for which metoclopramide, olanzapine, prochlorperazine maleate and loperamide hydrochloride were prescribed. On Day 9, the patient experienced a nonserious AE of Grade 1 rash maculo-papular and was prescribed bilastine. On Day 10, the rash maculo-papular worsened to Grade 3. Study treatment was interrupted. On Day 11, the patient was reported to have an SAE of Grade 3 Stevens-Johnson Syndrome (SJS) with oral mucositis, fever, eye and skin problems including bulbar conjunctivitis, blepharoconjunctivitis conjunctival hyperemia of the eyelids, painful skin breaks of the face and scalp, erythema, itchy scalp, facial edema, and erosion of the lips and corners of the mouth. There was no report of other mucosal involvement, or blisters or sheet-like skin detachment. Laboratory tests showed eosinophil count was $0.7x10^9$/L (range:0.04-$0.4x10^9$/L). The event was diagnosed as SJS by local team. Skin biopsy was not performed given clinical improvement with systemic steroids, topical steroids and bilastine. On Day 18, patient's oral erosion and erythema had improved. Study treatment was discontinued due to SJS. The investigator assessed the event of SJS as related to study treatment. An external adjudication review of this event (provided by the Applicant) indicated that the lack of other mucosal involvement, lack of blisters, lack of severely painful skin and lack of sheet-like skin detachment were not typical for SJS. Her presentation, including her elevated eosinophils and elevated transaminases favor drug reaction with eosinophilia and systemic symptoms (DRESS) rather than SJS.

Assessment: FDA considers the event as a severe cutaneous adverse reaction to the drug, with a diagnosis compatible with DRESS, rather than SJS. This event of DRESS was possibly related to taletrectinib; however, recent use of metoclopramide, olanzapine, loperamide and prochlorperazine prior to the event onset were confounding factors.

Based on the detailed information provided, FDA determined that the event described above was consistent with DRESS rather than SJS. Given the confounding factors associated with the case of DRESS and the overall low incidence of Grade ≥3 dermatologic adverse events and dermatologic events reported as SAE or resulting in modification of the dose of taletrectinib, FDA considers it is appropriate to include DRESS an adverse reaction of clinical relevance in the drug label rather than including dermatologic toxicities in the Warnings and Precautions section.

FDA also evaluated events of photosensitivity in the pooled safety database. Notably, nonclinical studies suggest the potential for phototoxicity associated with taletrectinib (refer to **Section 5.5.5**). Six patients experienced photosensitivity reactions in the pooled safety population, with a maximum Grade of 2 (defined as tender erythema covering 10 – 30% of body surface area), and one drug interruption. Both the C203 and G208 protocols advised that patients receiving taletrectinib avoid prolonged sun exposure and use sun protection for at least 5 days after stopping taletrectinib. Although very few clinical cases were reported, the severity and incidence of photosensitivity may have been limited by the advice to take preventative measures described in the protocol. Therefore, FDA considers it appropriate for this information to be included in labeling as a clinically relevant adverse reaction and for the product labeling to advise that patients use sun protective measures.

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

The Applicant's Position:

Not applicable as this application did not include Clinical Outcome Assessment analyses informing the safety or tolerability of taletrectinib.

The FDA's Assessment: This application did not include Clinical Outcome Assessment analyses informing the safety or tolerability of taletrectinib.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

In general, the overall TEAE profile was similar and frequencies of individual TEAEs were comparable between all subgroups analyzed including:

- Participant age at baseline (<65, ≥65 to <75, and ≥75)
- Sex (male, female)

- Race (Asian, White, Other)
- Geographic region (Asia versus Western, China versus non-China, and US versus Asia versus Other)

The FDA's Assessment:
FDA agrees with the Applicant's position on safety analyses by demographic subgroups. FDA performed a descriptive analysis to assess TEAEs by sex, age, and race (**Table 67**). Overall, TEAEs distributions did not appear to have significant differences among different sex and race subgroups. Among patients ≥65 years old compared to patients <65 years old, there was a higher incidence of Grade 3 or greater AEs, SAEs, and AEs leading to treatment interruption; this trend is typically observed in clinical studies in patients with lung cancer.

Table 67. FDA -Treatment-Emergent Adverse Events by Sex, Age and Race in the 600 mg QD Group

600 mg QD N=352	Sex		Age (years of age)			Race		
	Female N=197 n (%)	Male N=155 n (%)	< 65 N = 264 n (%)	≥ 65 to < 75 N = 74 n (%)	≥ 75 N = 14 n (%)	Asian N = 272 n (%)	White N = 52 n (%)	Other N = 28 n (%)
All-Grade TEAEs	197 (100)	154 (99)	263 (100)	74 (100)	14 (100)	272 (100)	51 (98)	28 (100)
≥ Grade 3 TEAEs	107 (54)	74 (48)	124 (47)	49 (66)	8 (57)	138 (51)	25 (48)	18 (64)
SAEs	58 (29)	49 (32)	72 (27)	30 (41)	5 (36)	86 (32)	12 (23)	9 (32)
TEAEs leading to Drug Interruption	85 (43)	58 (37)	102 (39)	34 (46)	7 (50)	109 (40)	25 (48)	9 (32)
TEAEs leading to dose reduction	68 (35)	34 (22)	71 (27)	23 (31)	8 (57)	71 (26)	20 (38)	11 (39)
TEAEs leading to drug withdrawal	11 (6)	12 (8)	18 (7)	3 (4.1)	2 (14)	18 (7)	2 (3.8)	3 (11)

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not applicable. No human carcinogenicity study has been performed with taletrectinib.

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

Human Reproduction and Pregnancy

Data and the Applicant's Position:

The safety of taletrectinib has not been formally evaluated in pregnant or lactating women. Two cases of pregnancy and 1 case of pregnancy of the female partner of a male study participant were reported in the clinical studies of taletrectinib as of the data cutoff date. None was associated with any AE or abnormal pregnancy outcome. Brief summaries for these 3 cases are presented below.

- A 39-year-old Chinese female participant became pregnant during the treatment. The participant received taletrectinib 600 mg QD. The pregnancy was discovered after 186 days of treatment, and taletrectinib treatment was discontinued immediately. At the gestational age of 33 W+6, the participant gave birth to a male neonate, with a height of 40 cm and weight of 1880 g. No abnormality of the neonate was found.
- A 35-year-old Chinese female became pregnant during treatment. The participant received taletrectinib 600 mg QD. The participant was estimated to be pregnant approximately 370 days after initiation of taletrectinib treatment. The pregnancy was discovered on Day 412 via transvaginal ultrasound and taletrectinib treatment was discontinued immediately with the last dose of taletrectinib taken on Day 411. The gestational age was 8 weeks. On Day 423, an elective abortion was performed which terminated the pregnancy. No AE or complication was associated with the pregnancy or termination.
- The spouse of a 30-year-old Chinese male participant receiving taletrectinib 600 mg QD was discovered to be pregnant 126 days after the participant's first dose of taletrectinib. The gestational age at the time of discovery was 40 days, as confirmed by ultrasound. The pregnancy was terminated by taking mifepristone and misoprostol. No AE or complication was associated with the pregnancy or termination.

The FDA's Assessment:

FDA agrees that the safety of taletrectinib has not been formally evaluated in pregnant or lactating women. Limited data from case reports with IBTROZI used in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. Based on literature reports in humans with congenital mutations leading to changes in tropomyosin receptor kinase signaling, findings from animal studies and its mechanism of action, taletrectinib can cause fetal harm when administered to a pregnant woman. Therefore, embryo-fetal toxicity will be included as a Warning in the product label.

Pediatrics and Assessment of Effects on Growth

Data and the Applicant's Position:

Not applicable as taletrectinib has not been studied in pediatric patients.

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

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

As of the data cutoff date, no overdoses were reported in the safety populations. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the participant.

No systematic examination of the abuse potential of taletrectinib was performed in the nonclinical and clinical studies included in this submission. There is no information regarding the dependence potential in animals or humans. Evaluation of AEs does not reveal evidence of euphoria, sedation, or mood alteration.

No studies or systematic analyses to evaluate the potential withdrawal and rebound effects of taletrectinib have been conducted. No TEAEs related to withdrawal or rebound effects were reported in the clinical studies of taletrectinib.

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Taletrectinib has not been marketed anywhere in the world.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety of taletrectinib in the postmarket setting is not expected to differ significantly from that observed in Studies G208 and C203 as assessed during safety review of this NDA submission.

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

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Taletrectinib exposure was similar across the 3 safety analysis populations. In the 600 mg QD group, a total of 352 participants received at least 1 dose of taletrectinib. As of the data cutoff, 42.9% of participants remained on study. The median duration of exposure was 11.14 months, the median dose intensity was 592.09 mg/day, and the relative dose intensity was 98.73%. Two hundred and thirty-eight participants (67.6%) had been treated for more than 6 months and 164 participants (46.6%) had been treated for more than 12 months.

The safety profile of taletrectinib was highly comparable across the 3 safety analysis populations.

The most frequently reported TEAEs were in the investigations SOC (with AST increased and ALT increased being the most frequently reported of these events) or the gastrointestinal disorders SOC (with diarrhea, nausea, vomiting, and diarrhea being the most frequently reported of events). The majority of these TEAEs were Grade 1 or 2 events and nonserious. The TEAEs reported were manageable and reversible. Most of the events did not need dose modification and did not lead to treatment discontinuation. Events that needed intervention generally resolved with dose interruption, dose reduction, and/or standard symptomatic measures. Results over time indicated that prolonged treatment with taletrectinib was well tolerated with no evidence of cumulative toxicity.

The most frequently reported Grade ≥3 TEAEs in the 600 mg QD group were AST increased (7.4%) and ALT increased (9.9%). In the 600 mg QD group, no participant experienced Grade 4 AST increased and only 1 (0.3%) experienced Grade 4 ALT increased.

Pneumonia, pleural effusion, and hepatic function abnormal were the most frequently reported treatment-emergent SAEs.

TEAEs leading to death (NCI CTCAE Grade 5) that were reported in more than 1 participant were pneumonia, cardiac arrest, disease progression, dyspnea, and multiple organ dysfunction syndrome. Grade 5 pneumonia, which occurred in 5 participants across the taletrectinib development program, was the most frequently reported. In the overall group, 4 participants had

AEs leading to death that were considered by the investigator to be treatment related; 2 of these were considered by the sponsor to be treatment related, and after the sponsor's further assessment, the other 2 were considered not related to taletrectinib and more likely to be associated with underlying disease and other confounding factors. The reported events were comparable across the 3 safety analysis populations. On-study deaths (deaths within 30 days after last dose of treatment) occurred in 32 (9.1%) of participants in the 600 mg QD group. Of these, 22 (6.3%) were attributed to AEs.

Two potential Hy's Law cases were the only AESIs reported, both of which were considered serious and related to treatment with taletrectinib and resulted in discontinuation of treatment. Both events resolved after discontinuation of treatment.

Of all liver events reported, the most frequent were low-grade LFT abnormalities, of which a majority were ALT and/or AST increased and were not accompanied by symptoms such as ascites or jaundice. Most events were reversible, resolved completely, and did not require dose modification or discontinuation.

A majority of the events reported in the torsade de pointes/QT prolongation SMQ were QT prolongation, and all were nonserious and not associated with symptomatic presentation, such as syncope, or serious ventricular arrhythmia, such as torsade de pointes.

The most frequently reported gastrointestinal events were diarrhea, nausea, and vomiting (mostly NCI CTCAE Grade 1 and 2). Most participants with these OSEIs recovered completely without supportive treatment and infrequently required dose interruption or reduction.

Dizziness, dysgeusia, and headache were the most commonly reported neurological events; most were NCI CTCAE Grade 1 and did not require dose reduction or discontinuation.

ILD occurred in 2.4% of participants and 1 event resulted in a fatal outcome.

The safety profile of taletrectinib at 600 mg QD was supported by the data from the ROS1+ NSCLC 600 mg QD group and overall group. The overall safety profile was consistent across age, sex, race, and geographic region. TEAEs were consistent and generally expected based on nonclinical and early clinical studies with taletrectinib.

A comparison of the safety profiles of approved ROS1 TKIs is presented in **Table 68**. Compared with approved ROS1 TKIs, taletrectinib demonstrated a more favorable safety profile, with a low rate of neurological AEs.

Table 68. Applicant - Safety Comparison of ROS1 Inhibitors Approved for ROS1+ NSCLC

	Crizotinib[a] (N=171)	Entrectinib[b] (N=355)	Repotrectinib[c] (N=264)
SAEs	34%	39%	33%
Dose reduction	6%	29%	35%
Treatment discontinuation	8%	9%	8%
Common CNS side effects (≥15%)	Dysgeusia: 26% Headache: 22% Dizziness: 18%	Dysgeusia: 44% Dizziness: 38% Dysesthesia: 34% Cognitive impairment: 27% Peripheral sensory neuropathy: 18% Headache: 18% Ataxia: 17%	Dizziness: 63% Dysgeusia: 48% Peripheral neuropathy: 47% Ataxia: 28% Cognitive disorders: 23% Headache: 19%
Other notable common all grade AEs (>20%)	Vision disorder: 71% Diarrhea: 61% Edema: 49% Vomiting: 46% Constipation: 43% Upper respiratory infection: 32% Abdominal pain: 26%	Fatigue: 48% Constipation: 46% Edema: 40% Diarrhea: 35% Nausea: 34% Dyspnea: 30% Myalgia: 28% Increased weight: 25% Cough: 24% Vomiting: 24% Arthralgia: 21% Pyrexia: 21% Vision disorders: 21%	Constipation: 36% Dyspnea: 30% Fatigue: 24% Muscular weakness: 21%

	Crizotinib[a] (N=171)	**Entrectinib[b] (N=355)**	**Repotrectinib[c] (N=264)**
Laboratory abnormalities (≥50%)	Increased ALT: 79% Increased AST: 66% Neutropenia: 52%	Increased creatinine: 73% Anemia: 67% Hyperuricemia: 52%	Decreased hemoglobin: 73% Increased creatine phosphokinase: 57%

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; GGT, Gamma Glutamyl Transferase; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tropomyosin receptor kinase; ROS1, c-ros oncogene 1; SAE, serious adverse event.

a (XALKORI® (crizotinib), 2022). Data are based on a study in previously untreated ALK+ NSCLC.

b (ROZLYTREK™ (entrectinib), 2024). Data are based on studies in both ROS1+ or NTRK+ solid tumors.

c (AUGTYRO™ (repotrectinib), 2023). Data are based on a study in ROS1+ NSCLC.

The FDA's Assessment:
The safety analysis population for taletrectinib 600 mg QD included 352 patients treated with at least one dose of taletrectinib 600 mg QD with pooled data from five studies. Overall, an analysis of the adverse reactions observed in the 600 mg QD group indicated some findings consistent other drug products in the same class. With respect to the Applicant's comparison of the safety profile of taletrectinib and other drugs in the same class (**Table 68**), FDA notes that cross-trial comparisons should be interpreted with caution given the potential for differences in patient populations, safety assessments, and safety reporting.

The primary serious risks related to taletrectinib are hepatotoxicity, ILD/pneumonitis, QTc prolongation, hyperuricemia, myalgia with CPK elevation, skeletal fractures, and embryo-fetal toxicity. These serious risks, which are described in detail in sections above, are adequately addressed in the Warnings and Precautions and Dose Modifications sections of the taletrectinib product labeling.

Among patients in the 600 mg QD safety analysis population (n=352), the most common (≥20%) adverse reactions were diarrhea (64%), nausea (46%), vomiting (43%), dizziness (22%), rash (22%), constipation (21%), and fatigue (20%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased ALT, increased AST, decreased neutrophils, increased creatine phosphokinase, decreased lymphocytes, increased magnesium, decreased hemoglobin, and increased triglycerides.

Among patients with *ROS1*-positive NSCLC 600 mg QD safety analysis population (n=337), the most common adverse reactions (≥15%) were diarrhea, nausea, vomiting, dizziness, rash, constipation, fatigue, QTc prolongation, peripheral neuropathy, decreased appetite, cough and dysgeusia. The most common (≥5%) Grade 3 or 4 laboratory abnormalities were increased ALT, increased AST, decreased neutrophils, and increased creatinine phosphokinase.

The review team considers the safety profile of taletrectinib to be acceptable when assessed in the context of a life-threatening disease. In addition, although taletrectinib can cause serious and severe toxicities, the safety concerns are described in product labeling; taletrectinib will be prescribed by oncologists who are trained to monitor and treat serious treatment-related toxicities. There were no significant safety concerns identified during the NDA review requiring additional risk management tools such as a Risk Evaluation and Mitigation Strategy (REMS).

Although the safety profile of taletrectinib 600 mg QD is acceptable in the indicated population of patients with locally advanced or metastatic NSCLC, preliminary evidence from a randomized dose-optimization study suggests that a lower dose in combination with food may provide similar efficacy results, particularly in patients with TKI-naïve disease, with an improved safety profile. Further, administration with food may result in improved tolerability. A multicenter trial to further characterize known serious risks with taletrectinib and evaluate the safety and activity of a lower daily dosage of 400 mg daily taken with standard meals in patients with advanced or metastatic *ROS1*-positive NSCLC who are TKI-naïve and TKI-pretreated with one prior ROS1

TKI will be conducted as a post-marketing requirement to further evaluate the optimal dose of taletrectinib.

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues noted in the review of this application.

The primary review of efficacy for this application focused on two single arm studies. Study G208 was a global, multicenter, open-label, single-arm study, including six cohorts. Cohort 1 (ROS TKI-naïve) and Cohort 2 (previously treated with ROS TKI) were designed to support a marketing application for taletrectinib for the treatment of patients with locally advanced or metastatic *ROS1*-positive NSCLC.

Study C203 was a multicenter, single-arm, open-label study conducted in single country (China). The study enrolled adult patients with *ROS1* fusion gene positive, locally advanced, or metastatic NSCLC who had either not received any ROS1-TKI treatment or were previously treated with crizotinib.

The primary endpoint in both of these trials was confirmed ORR assessed by BICR per RECIST v1.1, supported by the secondary endpoint of DOR.

Given differences in patients baseline demographics and follow up duration across these trials, FDA's analysis of the primary efficacy outcomes (i.e., ORR and DOR) were also evaluated per individual study, and only individual study results were included in the label.

Among the 103 patients in Study C203 and 54 patients in Study G208 (157 patients total) with NSCLC who were ROS1 TKI-naïve, the ORR per RECIST v1.1 by BICR was 90% (95% CI: 83, 95) and 85% (95% CI: 73, 93), respectively. The median DOR was not reached in either Study C203 or Study G208. (b) (4)

However, responses were considered durable with 72% of responders in Study C203 and 63% of responders in Study G208 exhibiting DOR of at least 12 months.

Among the 66 patients in Study C203 and 47 patients in Study G208 (113 patients total) with NSCLC who were ROS1 TKI-pretreated, the ORR per RECIST v1.1 by BICR was 52% (95% CI: 39, 64) and 62% (95% CI: 46, 75), respectively. The median DOR in Study C203 was 13.2 months (95% CI: 7.7, 24.9). (b) (4)

Durability of response was noted with 74% of responders in Study C203 and 83% of responders in Study G208 exhibiting DOR ≥ 6 months and 44% of responders in Study C203 and 45% of responders in Study G208 exhibiting DOR ≥ 12 months.

In summary, the primary efficacy data of confirmed ORR and DOR from Studies G2O8 and C203 demonstrate clinically meaningful, durable anti-tumor activity of taletrectinib in the treatment of adult patients with *ROS1*-positive locally advanced or metastatic NSCLC.

8.4. Conclusions and Recommendations

The FDA's Assessment:

FDA recommends traditional approval of taletrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC. This recommendation is based on a favorable benefit-risk assessment, with efficacy results based on ORR and DOR in patients with *ROS1*-positive NSCLC (both previously treated with a ROS1-TKI and those naïve to a ROS1-TKI) from Studies C203 and G208 and safety results based on pooled data from five studies (Studies AB106-C203, AB-106-C205, AB-106-G208, DS6051-A-J102 and DS6051-A-U101).

Current standard of care for patients with *ROS1*-positive NSCLC includes treatment with an approved ROS1 inhibitor (crizotinib, entrectinib or repotrectinib). Response rates reported in the US product labels in patients who were ROS TKI naïve in clinical trials range from 66% to 79%. The response rate in patients who were ROS TKI-pretreated without prior chemotherapy reported in the repotrectinib product label is 38% (95% CI: 25, 52).

The primary evidence of effectiveness for this application is derived from two single-arm studies (Studies G208 and C203). Study C203 was a single-country (China only) study. Study G208 was a global multi-regional study including clinical sites from the US, Canada, Europe and Asia. Patients with *ROS1*-positive NSCLC with or without prior chemotherapy who had received a prior ROS1 TKI or were ROS1 TKI-naïve and received at least one dose of taletrectinib 600 mg QD as the starting dose, with a DCO of October 28, 2024, were included in the primary efficacy population. In both studies, patients were required to have histologically confirmed, locally advanced or metastatic, *ROS1*-positive NSCLC, ECOG performance status of 0 or 1, and measurable disease per RECIST v1.1. Identification of ROS1 gene fusions in tumor specimens was determined by a validated assay as performed in Clinical Laboratory Improvement Amendments (CLIA)-certified or locally equivalent diagnostic laboratories. Patients received taletrectinib as a single agent at 600 mg orally QD until disease progression or unacceptable toxicity.

Among the 103 patients in Study C203 and 54 patients in Study G208 (157 patients in total) with NSCLC who were ROS1 TKI-naïve, the ORRs were 90% (95% CI: 83, 95) and 85% (95% CI: 73, 93), respectively. The median DOR was not reached (NR) (95% CI: 30.4 months, NR) in Study C203. The median DOR in Study G208 was also not reached (b) (4)

In the ROS1 TKI-naïve cohort, 72% of responders in Study C203 and 63% of responders in Study G208 had an observed DOR ≥ 12 months. In addition, 15 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation

therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 as assessed by BICR were observed in 11 patients.

Among the 66 patients in Study C203 and 47 patients in Study G208 (113 patients in total) with NSCLC who had received prior treatment with a ROS1 TKI, the ORRs were 52% (95% CI: 39, 64) and 62% (95% CI: 46, 75), respectively. The median DOR in Study C203 was 13.2 months (95% CI: 7.7, 24.9). (b) (4)

In the TKI-pretreated cohort, 74% of responders in Study C203 and 83% of responders in Study G208 had an observed DOR ≥ 6 months; 44% of responders in Study C203 and 45% of responders in Study G208 had a DOR ≥ 12 months. In addition, 24 patients had measurable CNS metastases at baseline as assessed by BICR and had not received radiation therapy to the brain within 2 months prior to study entry; responses in intracranial lesions per modified RECIST v1.1 as assessed by BICR were observed in 15 patients.

Among 32 patients who had re-biopsied samples tested by next-generation sequencing after failure of a prior ROS1 TKI in Studies G208 and C203, 15 had resistance mutations. Responses were observed in 8 of these 15 patients; all responding patients had tumors with solvent front mutation G2032R.

The effectiveness of taletrectinib was consistent across prespecified subgroups (including in patients with CNS metastasis and resistance mutations) and supported by sustained durability of responses, providing substantial evidence of antitumor activity over time.

A companion diagnostic for taletrectinib was not available at the time of approval, but it is under development. Given the availability of standard of care tests to identify *ROS1* fusions and the availability of FDA approved CDx *ROS1* fusion tests for use with other approved ROS1 TKIs, in the context of the magnitude and durability of the responses observed with taletrectinib, the review team considers it appropriate to approve taletrectinib in the absence of a companion diagnostic, with the Applicant's commitment to develop such a test. The final product labeling will reflect the lack of an approved companion diagnostic for the selection of patients for treatment with taletrectinib.

Taletrectinib has an acceptable safety profile when assessed in the context of a life-threatening disease. The pooled safety population included 352 patients with solid tumors who received at least one dose of taletrectinib 600 mg QD, including 337 patients comprising the *ROS1*-positive NSCLC 600 mg QD safety population (patients with *ROS1*-positive NSCLC who received at least one dose taletrectinib with a dosage of 600 mg QD).

Among patients in the pooled safety population (n=352), serious adverse reactions occurred in 30% of patients. The most common (≥20%) adverse reactions were diarrhea (64%), nausea (46%), vomiting (43%), dizziness (22%), rash (22%), constipation (21%), and fatigue (20%).The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased ALT (13%),

increased AST (10%), decreased neutrophils (6%), increased creatinine phosphokinase (5%), decreased lymphocytes (4.9%), increased magnesium (4.4%), decreased hemoglobin (3.7%), and increased triglycerides (2.4%).

Among patients with *ROS1*-positive NSCLC in the 600 mg QD safety population (n=337), serious adverse reactions occurred in 31% of patients. Serious adverse reactions occurring in ≥2% of patients included pneumonia (6.5%), pleural effusion (4.7%), and hepatotoxicity (2.4%). Fatal adverse reactions occurred in 18 (5%) patients who received taletrectinib, including pneumonia (2.4%), multiple organ dysfunction syndrome (0.6%), hepatotoxicity (0.6%), cardiac arrest (0.6%), cardiac failure (0.3%), cardiopulmonary failure (0.3%), respiratory failure (0.3%), and death not otherwise specified (0.3%). Permanent discontinuation of taletrectinib was required in 7% of patients due to adverse reactions; adverse reactions resulting in permanent discontinuation in ≥2 patients were pneumonia, ILD, and hepatotoxicity. Dosage interruptions due to an adverse reaction occurred in 41% of patients; adverse reactions which required dosage interruption in ≥5% of patients included increased AST and increased ALT. Dose reductions due to an adverse reaction occurred in 29% of patients; adverse reactions that required dosage reductions in ≥5% of patients included increased ALT and increased AST. The most common adverse reactions (≥15%) were diarrhea (64%), nausea (47%), vomiting (43%), dizziness (22%), rash (22%), constipation (21%), fatigue (20%), QTc prolongation (19%), peripheral neuropathy (17%), decreased appetite (16%), cough (16%) and dysgeusia (15%). The most common (≥2%) Grade 3 or 4 laboratory abnormalities were increased ALT (13%), increased AST (10%), decreased neutrophils (5%), increased creatine phosphokinase (5%), decreased lymphocytes (4.8%), increased magnesium (4.4%), decreased hemoglobin (3.6%), and increased triglycerides (2.5%).

Safety risks identified as significant and serious enough to warrant inclusion in the Warnings and Precautions section of labeling for taletrectinib are hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, QTc prolongation, hyperuricemia, myalgia with creatine phosphokinase elevation, skeletal fractures, and embryo-fetal toxicity. These safety concerns are adequately addressed in the Warnings and Precautions section and dose modification recommendations included in the product label. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Taletrectinib will be prescribed by oncologists who are familiar with monitoring, identifying, and managing the toxicities described in the USPI.

The recommended dosage is 600 mg orally once daily on empty stomach (no food intake at least 2 hours before and 2 hours after taking IBTROZI). Although the safety profile of taletrectinib 600 mg QD is acceptable in the indicated population of patients with locally advanced or metastatic NSCLC in the context of the observed efficacy, preliminary evidence from a randomized dose-optimization study suggests that a lower dose in combination with food may provide similar efficacy results, particularly in patients with TKI-naïve disease, with an improved safety profile. Further, administration with food may result in improved tolerability. A multicenter trial to further characterize known serious risks with taletrectinib and evaluate the safety and activity of a lower daily dosage of 400 mg daily taken with standard meals in patients with advanced or metastatic *ROS1*-positive NSCLC who are TKI-naïve and TKI-pretreated with one prior ROS1 TKI will be conducted as a post-marketing requirement to further evaluate the optimal dose of taletrectinib.

This submitted evidence for this NDA meets the statutory standard for demonstration of substantial evidence of effectiveness. FDA considers the substantial evidence standard to be met based on the evidence of effectiveness provided by two adequate and well-controlled trials. The clinically meaningful magnitude of ORR and demonstration of durable responses observed in the efficacy populations across these two trials provide evidence of a clinically meaningful benefit of taletrectinib in the rare, genetically defined subgroup of patients with locally advanced or metastatic *ROS1*-positive NSCLC. Subgroup analyses support taletrectinib's antitumor activity in patients with CNS metastases and in patients with resistance mutations following prior ROS1 TKI therapy. The magnitude and duration of responses observed with taletrectinib are considered to reflect clinically meaningful benefit in the indicated patient population; these results, coupled with the rarity of *ROS1*-positive NSCLC, render the conduct of a randomized trial challenging.

Based on the favorable risk-benefit assessment for this population with a serious, life-threatening disease, traditional approval is recommended for the following indication:

> Taletrectinib is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication *(enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response)*:

   > Taletrectinib is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR
   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[1,2,3]

      OR
   c. ☐ Evidence that supported SEE from a prior approval *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)*[2]

3. Complete response, if applicable
   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X X

Primary Statistical Reviewer Statistical Team Leader

X X

Primary Clinical Reviewer Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10 Pediatrics

The Applicant's Position:

The Applicant reached an agreement with the FDA on the initial Pediatric Study Plan (iPSP) on 03 May 2024.

The FDA's Assessment:

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

11 Labeling Recommendations

Data:

This is an original application. Please see annotated label in Module 1 for proposed labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1 INDICATIONS AND USAGE		FDA agrees with the Applicant's proposed indication statement: *IBTROZI™ (taletrectinib) is indicated for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC).*
2 DOSAGE AND ADMINISTRATION Subsection 2.2		For consistency with the Guidance for Industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format, FDA revised (b) (4) to *Recommended Testing and Evaluation Before Initiating IBTROZI. Information about concomitant use with strong or moderate CYP3A inhibitors is provided in Section 7, Drug Interactions.*
2.3 Recommended Dosage and Administration		FDA provided editorial revisions and included a statement to avoid food or drink containing grapefruit during treatment with IBTROZI.
2.4 Dosage Modifications for Adverse Reactions		FDA revised the dosage modification table to include advice for hyperuricemia and myalgia and creatinine phosphokinase elevation and revised the text for clarity.
3 DOSAGE FORMS AND STRENGTHS		For consistency with the Guidance for Industry *Naming of Drug Products Containing Salt Drug Substances* FDA added: *Each capsule contains 272 mg of taletrectinib adipate equivalent to 200 mg of taletrectinib.*

5 WARNINGS AND PRECAUTIONS		FDA added three new warnings to reflect the safety observed in the pooled safety population: hyperuricemia, myalgia and creatinine phosphokinase elevations, and skeletal fractures.
6.1 Clinical Trials Experience		FDA revised the text for consistent content and format across oncology labeling.
7 DRUG INTERACTIONS		FDA revised the text for consistent content and format across oncology labeling. FDA removed (b) (4)
8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy		FDA added detailed information from the rabbit embryo-fetal development study.
8.6 Renal Impairment 8.7 Hepatic Impairment		FDA removed these subsections for consistency with 21 CFR 201.56(d)(4), as they do not contain actionable advice.
11 DESCRIPTION		FDA revised the text for consistent content and format across oncology labeling.
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action		FDA revised the text to present the mechanism of action consistent with the indication statement.
12.2 Pharmacodynamics		FDA revised the text for consistency with 21 CFR 201.57(c)(13)(i)(B).
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility		FDA added details from the male and female rat fertility and early embryonic development.
14 CLINICAL STUDIES 14.1 Locally Advanced or Metastatic ROS1-Positive NSCLC		FDA revised the text for consistent content and format across oncology labeling. FDA separated the presentation of ROS1 TKI-Naïve and ROS1 TKI-pretreated efficacy data and moved

		intracranial responses from table format to text.
16 HOW SUPPLIED/STORAGE AND HANDLING		FDA revised the text for consistent content and format across oncology labeling.
17 PATIENT COUNSELING INFORMATION		FDA revised the text to reflect important safety data in Section 5 and for consistent content and format across oncology labeling.
PATIENT INFORMATION		Reviewed and revised by Office of Prescription Drug Promotion (OPDP) and Division of Medical Policy Programs (DMPP)

The Applicant's Position:

The draft US prescribing information is provided with this submission.

The FDA's Assessment:

The Applicant's proposed text was reviewed and revised by FDA for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
There were no significant safety concerns identified during the NDA review requiring risk management beyond labeling or warranting a consideration for a REMS. Taletrectinib will be prescribed by oncologists who are trained in monitoring, diagnosing, and managing serious toxicities caused by antineoplastic drugs, including tyrosine kinase inhibitors. The safe use of taletrectinib can be adequately implemented in the post-marketing setting as safety concerns are adequately addressed in the Warnings and Precautions and Dosage and Administration sections of product labeling.

13 Postmarketing Requirements and Commitment

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

Postmarketing requirements:

4856-1

Conduct a molecularly targeted pediatric cancer investigation to assess dosing, pharmacokinetics, safety and preliminary efficacy of taletrectinib in pediatric patients with advanced or metastatic solid tumors with *NTRK* or *ROS1* alterations.

4856-2

Conduct a multicenter trial to further characterize known serious risks with taletrectinib including severe hepatotoxicity, interstitial lung disease, other serious adverse reactions, and the risk of gastrointestinal toxicity, by evaluating the safety, activity, and pharmacokinetics of taletrectinib 400 mg daily taken with standard meals, in patients with advanced or metastatic ROS1 positive non-small cell lung cancer who are naïve to prior ROS1 tyrosine kinase inhibitors (TKIs) and in patients who have received one prior ROS1 TKI. Include an adequate number of patients from each subgroup (i.e., ROS1 TKI-naïve and previously treated with ROS1 TKI).

4856-3

Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dosage of taletrectinib in patients with moderate and severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

4856-4

Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A, CYP2D6, BCRP, OATP1B1, and OATP1B3 to evaluate the magnitude of exposure change of these substrates and serious potential risk of increased drug toxicity, and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP and transporter substrates. This study should be designed and conducted in accordance with "M12 Drug Interaction Studies."

Postmarketing commitments:

4856-5

Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A and CYP1A2 in healthy subjects to

evaluate the magnitude of decreased drug exposure and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP substrates. This study should be designed and conducted in accordance with "M12 Drug Interaction Studies."

4856-6

Conduct a clinical trial to evaluate if staggered administration of an H2-receptor antagonist decreases the exposure of taletrectinib and to inform instructions for taking taletrectinib with H2-receptor antagonists. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications."

4856-7

Complete a clinical trial to further characterize the clinical benefit of taletrectinib for the treatment of adult patients with *ROS1* fusion-positive metastatic NSCLC by providing a more precise estimation of the BICR-assessed overall response rate (ORR) and duration of response (DOR) in the ROS1 TKI-naive patients with *ROS1*-positive NSCLC and ROS1 TKI-pretreated patients enrolled in TRUST-I and TRUST-II studies. Include updated DOR results for the 139 responders in the response evaluable population of 157 ROS1 TKI-naïve patients and for the 63 responders in the response evaluable population of 113 ROS1 TKI-pretreated patients, after all responders have been followed for at least 18 months from the date of initial response.

4856-8

Conduct an appropriate analytical and clinical validation study to support the development of an in vitro diagnostic device using clinical trial data that demonstrates that the device is essential to the safe and effective use of taletrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive NSCLC.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _x _ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes x _No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _x No

14 Division Director (DHOT) (NME ONLY)

X _____

15 Division Director (OCP)

X _____

16 Division Director (OB)

X _____

17 Division Director (Clinical)

X _____

18 Office Director (or Designated Signatory Authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

The Applicant's References:

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19.2. Financial Disclosure

The Applicant's Position:

A total of 665 Investigators were participating Investigators in Study AB-106-G208 entitled "*A Single-Arm, Open-Label, Multicenter Phase 2 Study to Evaluate the Efficacy And Safety of Taletrectinib in Patients With Advanced Or Metastatic ROS1 Positive NSLC And Other Solid Tumors (TRUST-II)*".

A total of 258 Investigators were participating Investigators in Study AB-106-C203 entitled "A Phase II, Multi- center, Single-arm, Open-label Study of AB-106 in the Treatment of Locally Advanced or Systemic Metastatic Advanced NSCLC with ROS1 Fusion (TRUST-I)".

Tables of participating Investigators for each study were provided. These include tables of Investigators with disclosable financial interests and tables of Sub-Investigators where financial disclosures were not collected. If an Investigator reported disclosable financial interest, an assessment of bias was provided. If a financial disclosure was not collected, the due diligence to collect the financial disclosure was described.

A summary of the financial interests and arrangements with clinical investigators is described in the summary table below.

Covered Clinical Study (Name and/or Number):* Study G208

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 665		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: 1 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

Covered Clinical Study (Name and/or Number):* Study C203

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 258		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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

The FDA's Assessment:

FDA agrees with the Applicant's position. The financial disclosure forms were reviewed and summarized. As of the DCO date of June 7, 2024, financial disclosure information was submitted for 665 investigators in Study G208 and 258 investigators in Study C203. Financial Disclosure Forms for 6 sub-PIs in Study G208 and 6 sub-PIs in C203 were not submitted with the application. There was one sub-PI (b) (6) who held a significant equity interest, as defined in 21 CFR 54.2(b); and one investigator who served as a PI (b) (6) with significant payments of other sorts, as defined in 21 CFR 54.2(f).

(b) (6) disclosed financial information. (b) (6) was a sub-PI at Site (b) (6)

(b) (6) FDA considers any potential bias related to the conflict would be mitigated.

(b) (6) was a PI at Site (b) (6) FDA considers any potential bias related to the conflict would be mitigated. These two sites were included in FDA clinical site inspection which did not find significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice, or regulatory compliance.

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

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Not applicable. All data are presented in **Section 5**, Nonclinical Pharmacology/Toxicology.

The FDA's Assessment:

Refer to **Section 5**.

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Bioanalytical Review

The FDA's Assessment:

Plasma concentrations of taletrectinib were measured using validated turbo ion spray liquid chromatography-tandem mass spectrometry (LC-MS/MS). The bioanalytical method validation results and performance in the pivotal clinical studies G208 and C203 are summarized in **Table 69** and **Table 70**. Note that the section and table numbers in the following summaries of bioanalytical method refer to the corresponding sections and tables in the bioanalytical method

validation reports, rather than the current review. The precision and accuracy of quality controls (QC) and standards (STD) were within the pre-specified acceptance limits. The Applicant also adequately validated the selectivity, matrix effect, and stability. The long-term stability was validated to 991 days at -60°C to -80°C, which covered the longest period of PK sample storge of 795 days in Study G208 and 876 days in Study C203 at the same temperature.

The bioanalytical method validation and performance in early phase clinical trials DS6051-A-U101 and DS6051-A-J102 and clinical pharmacology studies AB-106-C110, AB-106-U112, AB-106-U113, and AB-106-U114 are not included in the current review. However, FDA has determined that the bioanalytical method validation and performance for these studies are acceptable.

Overall, FDA finds the Applicant's bioanalytical method validation and performance acceptable to determine the concentrations of taletrectinib in plasma samples collected from patients in the clinical studies.

Table 69. Summary of Bioanalytical Method Validation and Performance in Pivotal Clinical Studies AB-106-G208 and AB-106-C203

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of AB-106 in Human Plasma using Liquid Chromatography with Tandem Mass Spectrometric Detection Final Report: 8420-241		
Method description	A validated LC-MS/MS method for the determination of taletrectinib in human plasma		
Materials used for standard calibration curve and concentration	Taletrectinib in human K_2EDTA plasma at 1.00, 2.00, 5.00, 20.0, 100, 500, 900, and1000 ng/mL		
Validated assay range	1.00 ng/mL to 1000 ng/mL		
Material used for quality controls (QCs) and concentration	Taletrectinib in human K_2EDTA plasma at 1.00, 3.00, 40.0, 400, and 800 ng/mL Dilution QC at 8000 ng/mL		
Minimum required dilutions	NA		
Source and lot of reagents	NA		
Regression model and weighting	Linear with $1/x^2$ weighting		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	3	Table 7.2 of 8420-241
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.9% to 2.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤5.1%	
	Number of standard calibrators from LLOQ to ULOQ	4	Table 7.3 of 8420-241
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.5% to 2.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤6.3%	

Validation parameters	Method validation summary		Source location
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	4	Table 8.2 Addendum No.1 of 8420-241
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.3% to 3.0%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤6.6%	
	Number of standard calibrators from LLOQ to ULOQ	2	Table 8.2 Addendum No.2 of 8420-241
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.8% to 1.4%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤5.6%	
Performance QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 5 QC levels	-0.5% to 10.0%	Table 7.6 of 8420-241
	Inter-batch %CV in 5 QC	≤5.6%	
	Total error (TE)	NA	
	Cumulative accuracy (%bias) in 5 QC levels	-3.3% to 0.3%	Table 8.4 Addendum No.1 of 8420-241
	Inter-batch %CV in 5 QC	≤6.7%	
	Total error (TE)	NA	
	Cumulative accuracy (%bias) in 4 QC levels	0.1% to 6.3%	Table 8.4 Addendum No.2 of 8420-241
	Inter-batch %CV in 5 QC	≤4.0%	
	Total error (TE)	NA	
Selectivity & matrix effect	6 lots tested, all passed		Figure 8.5 to Figure 8.13 of 8420-241
	Mean %CV of normalized matrix factor ≤3.7%		Table 7.12 of 8420-241

Validation parameters	Method validation summary	Source location
Interference & specificity	<20.0% LLOQ analyte response and <5% lowest IS response	Figure 8.3 to Figure 8.4 of 8420-241
	Blank human Plasma in the presence of itraconazole or rifampin have <20.0% LLOQ analyte response and <5% lowest IS response	Figure 9.1 to Figure 9.2 Addendum No.1 of 8420-241
	Blank human Plasma in presence of the Omeprazole have <20.0% LLOQ analyte response and <5% lowest IS response	Figure 9.1 Addendum No.2 of 8420-241
Hemolysis effect	1 lot, bias -11.0% to -1.0% (3.00 ng/mL) and -1.6% to 4.6% (800 ng/mL)	Table 7.14 of 8420-241
Lipemic effect	1 lot, bias -5.0% to 11.3% (3.00 ng/mL) and 4.0% to 12.6% (800 ng/mL)	Table 7.15 of 8420-241
Dilution linearity & hook effect	8000 ng/mL 20-fold dilution, bias -1.1% to 2.9%	Table 7.9 of 8420-241
Bench-top/process stability	Benchtop 71 hours at room temperature, bias -7.3% to 1.7% (3.00 ng/mL) and -6.9% to 5.1% (800 mg/mL)	Table 8.5 Addendum No.1 of 8420-241
	Processed 191 hours at 2°C to 8°C bias 3.7% to 13.3% (3.00 ng/mL) and 0.8% to 6.9% (800 mg/mL)	Table 7.23 of 8420-241
Freeze-thaw stability	5 cycles (-10°C to -30°C/RT), bias 1.3% to 14.3% (3.00 ng/mL) and 3.0% to 6.0% (800 mg/mL)	Table 7.21 of 8420-241
	5 cycles (-60°C to -80°C/RT), bias 6.7% to 13.0% (3.00 ng/mL) and 4.1% to 7.8% (800 mg/mL)	

Validation parameters	Method validation summary	Source location
Long-term storage	502 days in plasma at -10°C to -30°C °C, bias -4.3% to 6.3% (3.00 ng/mL) and -0.1% to 2.3% (800 mg/mL) 991 days in plasma at -60°C to -80°C, bias -4.7% to 3.3% (3.00 ng/mL) and -5.4% to -1.5% (800 mg/mL) 296 days in plasma spiked with itraconazole at -60°C to -80°C, bias 2.7% to 17.7% (3.00 ng/mL) and -5.8% to 4.4% (800 mg/mL) 296 days in plasma spiked with rifampin at -60°C to - 80°C, bias 4.7% to 7.3% (3.00 ng/mL) and -3.1% to 4.0% (800 mg/mL) 133 days in plasma spiked with omeprazole at -60°C to -80°C, bias -1.0% to 5.7% (3.00 ng/mL) and -6.4% to -0.4% (800 mg/mL	Table 8.6 Addendum No.1 of 8420-241 Table 8.6 Addendum No.2 of 8420-241 Table 8.7 to Table 8.8 Addendum No.2 of 8420-241 Table 8.10 Addendum No.2 of 8420-241
Parallelism	NA	NA
Carryover	Carryover <20.0% LLOQ analyte response and <5% lowest IS response	Figure 8.7 of 8420-241
Method Performance in AB-106-G208 Study; Report 8472-629		
Assay passing rate	1469 study samples were analyzed, and the final concentration values of 1469/1469 (100%) samples were accepted Therein, 120/1469 (8.2%) study samples were repeated due to mistaken re-assay and anomalous result, and 120/120 (100%) were confirmed original results.	Table 9.2 of 8472-629 Table 9.6 of 8472-629
Standard curve performance	Cumulative bias range: -0.6% to 1.0% Cumulative precision (%CV): ≤3.8%	Table 9.3 of 8472-629
QC performance	Cumulative bias range: 0.0% to 1.7% Cumulative precision (%CV): ≤3.9%	Table 9.5 of 8472-629
Method reproducibility	Incurred sample re-analysis was performed in 129/1469 (8.8%) of study samples, and 129/129 (100%) of the samples met the pre-specified criteria	Table 9.7 of 8472-629
Study sample analysis/stability	Longest period from sample collection to analysis was 795 days, and study samples were analyzed within the established stability time of 991 days at -60 to -80°C	NA

Method Performance in AB-106-C203 Study; Report 8420-242		
Assay passing rate	1428 study samples were analyzed, and the final concentration values of 1428/1428 (100%) samples were accepted, Therein 1/1428 (0.07%) study samples were repeated due to original concentration >ULOQ	Table 9.2 of 8420-242 Table 9.7 of 8420-242
Standard curve performance	Cumulative bias range: -1.4% to 1.0% Cumulative precision (%CV): ≤4.7%	Table 9.3 of 8420-242
QC performance	Cumulative bias range: 1.6% to 2.3% Cumulative precision (%CV): ≤4.5%	Table 9.5 of 8420-242
Method reproducibility	Incurred sample re-analysis was performed in 125/1428 (8.8%) of study samples, and 125/125 (100%) of the samples met the pre-specified criteria	Table 9.6 of 8420-242
Study sample analysis/stability	Longest period from sample collection to analysis was 876 days, and study samples were analyzed within the established stability time of 991 days at -60 to -80°C	NA

Source: Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 70. Cross Validation Summary for Taletrectinib

Bioanalytical method validation report name and hyperlink	Cross Validation of a Method for the Determination of AB-106 in Human Plasma by HPLC with MS/MS Detection Final Report: 8480279		
Changes in method	NA		
New validated assay range if any	NA		
Validation parameters	**Cross-validation performance**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (% bias) in standard calibrators from LLOQ to ULOQ	-4.5% to 9.0%	Table 7.2 of 8480279
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 4 QCs	-3.3% to 3.8%	Table 7.4 of 8480279
Cross-validation	6 replicates at concentrations near the Low QC, Low-medium QC, Medium QC, and High QC sample concentrations. Precision (%CV) are 1.2% to 5.8% and %bias are -0.6% to -5.0%		Table 7.5 of 8480279
	6 replicates of thirty pooled incurred samples, %bias are -7.5% to 14.3%		Table 7.6 of 8480279
List other parameters	NA		NA

Source: Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods

19.4.2. Overview of population PK and E-R Analysis

The pharmacometrics analyses were focused on assessing the appropriateness of dosing in patients with advanced or metastatic *ROS1* positive NSCLC, especially in the presence of high rate of hepatotoxicity that is exposure dependent where PK variability is substantial due to food status (e.g., 10-hour fast, 2-hour fast, standard meals, high-fat meals) and race effect (Asian vs non-Asian) (**Table 71**).

Table 71. FDA - Assessment of Model Risk

Question of interest	Is the proposed dosage appropriate for all *ROS1* positive NSCLC patients under the following conditions: 1) taken 2 hours before or after a meal, 2) no dosage adjustment for Asian patients?
Context of use	PopPK was used to evaluate the patient factors (food effect, Asian race) on exposure, and generate individual exposure for E-R analyses. E-R analyses were conducted to understand exposure dependent changes in efficacy and safety in patients.
Decision consequence	Medium • Clinical trial was conducted at the dosage of 600 mg taken 2 hours before or after a meal, with no additional dosage adjustment for Asian patients. The current labeling decision on dosage is driven by clinical evidence. • Given the high rate of hepatotoxicity, high PK variability based on popPK, and a positive relationship between exposure and Grade≥3 AST/ALT elevation, additional PMR study is recommended to study 400 mg taken with standard meals (with added benefit for mitigating GI toxicities).
Model influence	Low: current labeling dosage is driven by clinical observation only. Low-medium: analyses driven proposal for the alternative dosage in the PMR study.
Model risk	Medium

The overall model risk is considered medium. In line with the determined model risk and specific objectives, following model evaluation/additional analysis was conducted for the respective methodologies as outlined in **Table 72**.

Table 72. FDA - Model Evaluation/Additional Analysis

Methodology	Objective	Model evaluation	Section
PopPK	• Characterize PK profile of taletrectinib • Evaluate patient factors (i.e., food status, race) substantially impact PK • Predict individual exposure for subsequent E-R analysis	Standard model evaluation Sensitivity analysis for food effect (considering different sources of data contributing to effect estimation) in covariate analysis	19.4.3
Exposure-efficacy	• Characterize E-R relationship • Evaluate if a lower dose (i.e., 400 mg) is appropriate	Standard model evaluation for ORR and decrease in tumor size at nadir	19.4.4.1-19.4.4.2
Exposure-safety	• Characterize E-R relationship • Evaluate risk in subgroup (i.e., Asian race) that is likely overexposed	• Standard model evaluation for general AEs (SAE, Gr>=3 TEAEs, dose modifications due to AEs), and AEs of interest (Gr>=2 GI AE, Gr>=3 AST/ALT increase) • Independent analysis to assess safety risk in Asian patients with a 30% increase in exposure	19.4.4.3-19.4.4.6

The pharmacometrics findings in relation to the clinical pharmacology questions are summarized in **Section 6.2.2.1**. In short, the proposed dosage of 600 mg QD taken 2 hours before or after a meal with no dose adjustment for Asian patients is generally acceptable. Nevertheless, given high incidence of hepatotoxicity, we consider the dosage could be further optimized based on a flat E-R relationship for efficacy and positive E-R relationships for various safety endpoints including Grade>=3 AST/ALT elevation where a 50% increase in Cavgss is predicted to result in ~50% greater risk for experiencing those AEs. Taking drug with food may improve safety by reducing PK variability and exposure-dependent hepatotoxicity as well as add benefit of mitigating GI toxicity via altering physiological attributes. Dosage optimization study in Study G208 cohort 5 (400 mg and 600 mg taken 2 hours before or after a meal) with limited patients (n=~20) provided preliminary evidence for tolerability improvement, and possible efficacy

maintenance with uncertainties in TKI experienced patients. Taken together, in the dosage randomization PMR study, the FDA recommends 400 mg QD with standard meals to be evaluated based on preliminary clinical data, expected smaller PK variability, observed flat exposure-efficacy and positive exposure-safety relationships where limited data of 400 mg QD from G208 cohort 5 were included in the analyses. (b) (4)

In a patient subgroup (i.e., Asian race), a 30% exposure increase was observed which may increase safety risk. The increase in exposure in Asian patients is described in product labeling. Based on independent evaluation, FDA does not consider specific instructions for this subgroup to be necessary due to the similarity between Asian and White patients in AE profile and proportion of dose reductions related to hepatotoxicity (the main clinically relevant adverse event), especially under frequent AST/ALT monitoring as proposed in the labeling.

19.4.3. Population PK Analysis

19.4.3.1. Executive Summary

The FDA's Assessment:

The PK of taletrectinib in adult population was characterized by a linear 3-compartment model with first-order absorption followed by first-order elimination. The final population PK (popPK) model provided by the Applicant described the observed data reasonably well and is considered as the final model.

Given the large PK variability observed in patients taking 600 mg taletrectinib 2 hours before or after a meal, further sensitivity analysis was conducted by FDA to evaluate the PK difference between standard meals and 2-hour fast, given potential benefit in reducing PK variability and the exposure dependent hepatotoxicity of taking the drug with food, as well as added benefit of mitigating GI toxicity.

The proposed dosage of 600 mg QD taken 2 hours before or after a meal could be optimized for the proposed patient population, and the fed condition should also be considered to reduce PK variability and ameliorate GI toxicity. FDA recommended 400 mg QD taken with standard meals to be further studied in the dosage optimization study considering that this dosage will have smaller PK variability and improve GI tolerability with AUC not exceeding that of 600 mg QD taken 2 hours before or after a meal.

19.4.3.2. PPK Assessment Summary

The Applicant's Position:

The PK of taletrectinib following oral administration was adequately described by a linear 3-compartment model with first-order absorption with a lag time and first-order elimination. Food status had a marked effect on taletrectinib absorption. Bioavailability was higher under fed and 2 hour fasted conditions relative to 10 hour-fasted condition by approximately 58% and 55%, respectively. Absorption rate was approximately 83% and 77% lower, respectively, under fed

and 2 hour-fasted conditions relative to a 10 hour-fasted condition. Additionally, body weight and race were found to be statistically significant covariates for clearance (CL). Body weight and type of the participant (participants with cancer vs healthy participants) were significant covariates for the central volume of distribution (Vc).

General Information		
Objectives of PPK Analysis		• To characterize the PK of taletrectinib following oral administration in healthy participants and participants with solid tumors • To quantify the effects of intrinsic and extrinsic factors on taletrectinib PK and exposure • Predict individual exposure for E-R assessment
Study Included		DS6051-A-U101, DS6051-A-J102, AB-106-C110, AB-106-U113, AB-106-C114, AB-106-C203, AB-106-C205, AB-106-G208
Dose(s) Included		50 mg to 1200 mg
Population Included		Healthy participants and participants with solid tumors
Population Characteristics (Table 5 of the popPK report)	General	Age median (range): 52 yr (20, 83), 21% participants ≥65 yr, 3.5% participants ≥75 yr) Weight median (range): 66 kg (38, 125) Male n (%): 284 (55%) White n (%): 100 (19%), Asian n (%): 360 (70%), Black or African American n (%): 28 (5.4%), Missing n (%): 27 (5.2%)
	Organ Impairment	Hepatic (NCI): Normal 423 (82%), Mild 92 (18%) Renal (NKF criteria): Normal 449 (87%), Mild 59 (11%), Moderate 7 (1.4%),
	Pediatrics (if any)	Not included
No. of Patients, PK Samples, and BLQ		515 participants, 6966 PK samples, BLQ 162 (2.3%)
	Rich Sampling	Predose and up to 408 hours postdose

Sampling Schedule	In ITT Population	Rich samples: C1D1 at predose, and up to 24 hr, C1D8 at predose, C1D15 at predose, and up to 24 hr, C2D1 and C3D1 at predose. Sparse samples: C1D1 at predose and 2-7 hr postdose, C1D8 at predose, C1D15 at predose and 2-7 hr postdose, C2D1 at predose, 2-7 hr postdose, and C3D1 at predose
Covariates Evaluated	Static	Baseline age, sex, race, baseline weight, baseline serum albumin, estimated glomerular filtration rate (eGFR), hepatic impairment, participant type, baseline Eastern Cooperative Oncology Group (ECOG) score, prior TKI treatment, and food status
	Time-varying	

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM (version 7.5.1) R (version 4.2.3)	Yes
Model Structure	A linear 3-compartment model with first-order absorption with a lag time and first-order elimination and an allometrically scaled baseline body weight effect on clearances and volume of distribution.	Yes
Model Parameter Estimates	Table 10 of the popPK report	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All fixed-effects were estimated with %RSE below 25%. Most structural model parameters were estimated with good precision (<10% RSE), with the exception of V3 and KA (<20% RSE). Random effects were also well estimated with the % RSE below 20% with the exception of CL (36% RSE).	Yes

	The shrinkages of the random-effects on CL and VC are not directly interpretable as discussed in section 4.1.2.3 section of the report. The precision of the final model parameter estimates was obtained by sampling importance resampling (SIR) analysis with five iterations. 95% CIs of the final parameter estimates were constructed from 1000 samples of the final iteration and overlapped with those of the final model estimates.	
BLQ for Parameter Accuracy	162 (2.3%) BLQ data points were excluded from the model and it has no impact on the objectives of the popPK analysis.	Yes
GOF, VPC	Figure 4, 5 and A-3 of the popPK report	Yes
Significant Covariates and Clinical Relevance	Figure 7 and 8 of the popPK report Food status had a marked effect on taletrectinib absorption. Bioavailability was higher under fed and 2 hour fasted conditions relative to 10 hour-fasted condition by approximately 58% and 55%, respectively. Additionally, body weight and race were found to be statistically significant covariates for clearance (CL). Body weight and type of the participant (participants with cancer vs healthy participants) were significant covariates for the central volume of distribution (Vc). However, effect of body weight, race, and type of the participant on PK are not clinically significant.	Data for estimating the effect of standard meals on bioavailability were limited, therefore, its estimated effect was determined by the category with which it was combined, i.e., high fat meals. Asian patients (race effect and lower body weight distribution) were associated with a 30% increase in Cavgss compared to White patients.

Analysis Based on Simulation (optional)		
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK		Added "A 30% increase in taletrectinib exposure (AUC) was observed in Asian patients compared to White patients. No clinically significant differences in the AUC were observed between White and Black patients."

Table 73. Applicant - Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Participant Type

Characteristic[a]	Healthy N 110[b]	NSCLC N=346[b]	Other Tumor N=59[b]	Overall N=515[b]
Age (yr)				
Mean (SD)	34 (8)	55 (12)	59 (13)	51 (15)
Median (Range)	33 (20, 55)	56 (26, 83)	62 (24, 79)	52 (20, 83)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Age category				
Age <65	110 (100%)	261 (75%)	38 (64%)	409 (79%)
Age ≥65	0 (0%)	85 (25%)	21 (36%)	106 (21%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Characteristic[a]	Healthy N 110[b]	NSCLC N=346[b]	Other Tumor N=59[b]	Overall N=515[b]
Sex				
M	104 (95%)	152 (44%)	28 (47%)	284 (55%)
F	6 (5.5%)	194 (56%)	31 (53%)	231 (45%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Race				
Asian	78 (71%)	268 (77%)	14 (24%)	360 (70%)
Missing	0 (0%)	25 (7.2%)	2 (3.4%)	27 (5.2%)
Caucasian	8 (7.3%)	50 (14%)	42 (71%)	100 (19%)
Black or African American	24 (22%)	3 (0.9%)	1 (1.7%)	28 (5.4%)
Baseline Weight (kg)				
Mean (SD)	69 (10)	65 (14)	75 (20)	67 (14)
Median (Range)	67 (53, 95)	64 (38, 115)	70 (48, 125)	66 (38, 125)
Missing	0 (0%)	3 (0.9%)	0 (0%)	3 (0.6%)
Baseline BMI (kg/m^2)				
Mean (SD)	23.5 (2.3)	24.2 (4.0)	26.6 (6.1)	24.3 (4.1)
Median (Range)	23.3 (19.2, 29.8)	23.8 (15.6, 39.3)	24.5 (18.5, 42.9)	23.7 (15.6, 42.9)
Missing	0 (0%)	6 (1.7%)	0 (0%)	6 (1.2%)
Baseline Serum Albumin (g/L)				
Mean (SD)	46.0 (3.1)	39.5 (5.0)	36.1 (5.9)	40.5 (5.7)
Median (Range)	46.0 (34.5, 53.0)	40.0 (24.0, 51.4)	37.0 (23.0, 48.0)	41.0 (23.0, 53.0)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Baseline ECOG				
0	110 (100%)	113 (33%)	16 (27%)	239 (46%)
1	0 (0%)	233 (67%)	42 (71%)	275 (53%)
2	0 (0%)	0 (0%)	1 (1.7%)	1 (0.2%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ROS1+				
N	110 (100%)	6 (1.7%)	44 (75%)	160 (31%)
Y	0 (0%)	340 (98%)	15 (25%)	355 (69%)

Characteristic[a]	Healthy N 110[b]	NSCLC N=346[b]	Other Tumor N=59[b]	Overall N=515[b]
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prior TKI				
No	110 (100%)	174 (50%)	2 (3.4%)	286 (56%)
Yes	0 (0%)	166 (48%)	11 (19%)	177 (34%)
Missing	0 (0%)	6 (1.7%)	46 (78%)	52 (10%)
Line of Therapy				
0	110 (100%)	134 (39%)	6 (10%)	250 (49%)
1	0 (0%)	124 (36%)	6 (10%)	130 (25%)
2	0 (0%)	53 (15%)	5 (8.5%)	58 (11%)
≥3	0 (0%)	33 (9.5%)	41 (69%)	74 (14%)
Missing	0 (0%)	2 (0.6%)	1 (1.7%)	3 (0.6%)
Hepatic Impairment Status (NCI Criteria)				
Normal	104 (95%)	272 (79%)	47 (80%)	423 (82%)
Mild	6 (5.5%)	74 (21%)	12 (20%)	92 (18%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Baseline eGFR (mL/min/1.73 m^2)				
Mean (SD)	111 (15)	112 (17)	103 (26)	111 (18)
Median (Range)	115 (74, 138)	114 (43, 151)	104 (39, 163)	114 (39, 163)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal Impairment Status (NKF Criteria)				
Normal	97 (88%)	310 (90%)	42 (71%)	449 (87%)
Mild	13 (12%)	33 (9.5%)	13 (22%)	59 (11%)
Moderate	0 (0%)	3 (0.9%)	4 (6.8%)	7 (1.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; F, female; M, male; NCI, National Cancer Institute; NSCLC, non-small cell lung cancer; NKF, National Kidney Foundation; PK, pharmacokinetics; ROS1+, ROS1 fusion positive ; SD, standard deviation; TKI, tyrosine kinase inhibitor.

[a] Unknown is shown as Missing
[b] n (%)
Source: Report ANTX-Proj1-24-0002 Table 5

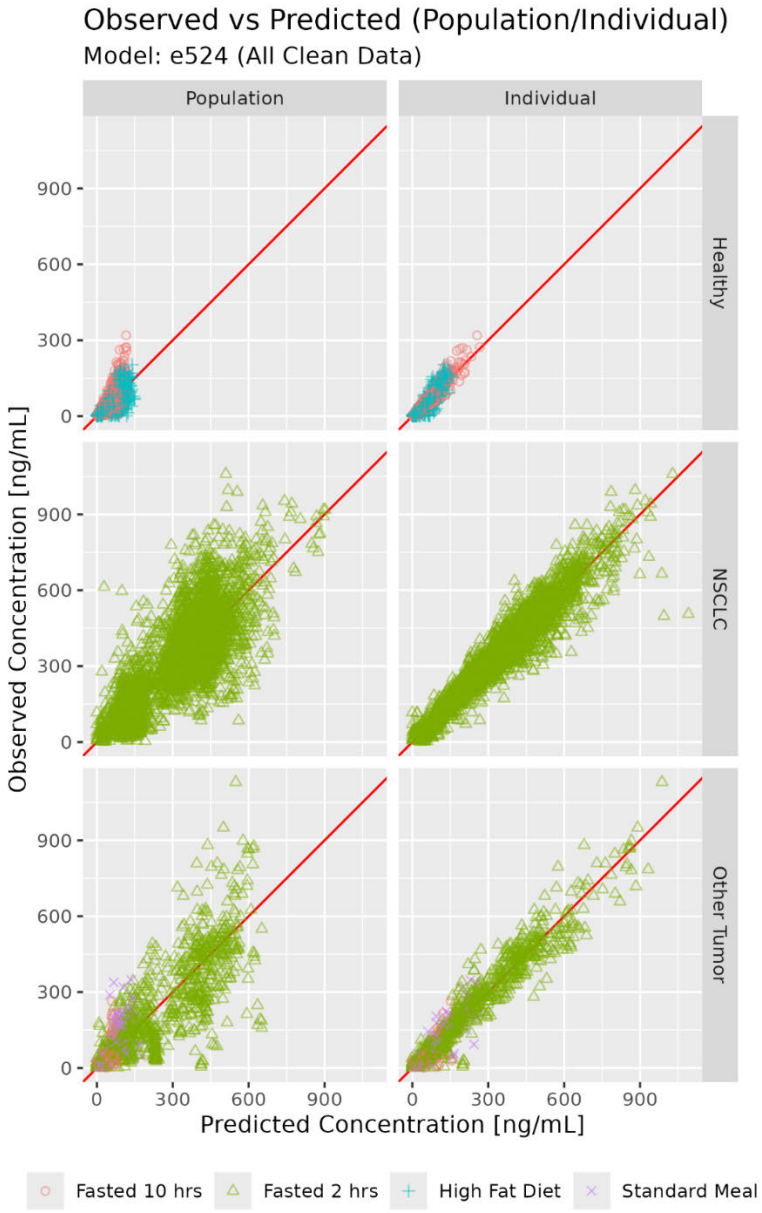
Table 74. Applicant - Parameter Estimates and SE From Final Population PK Model

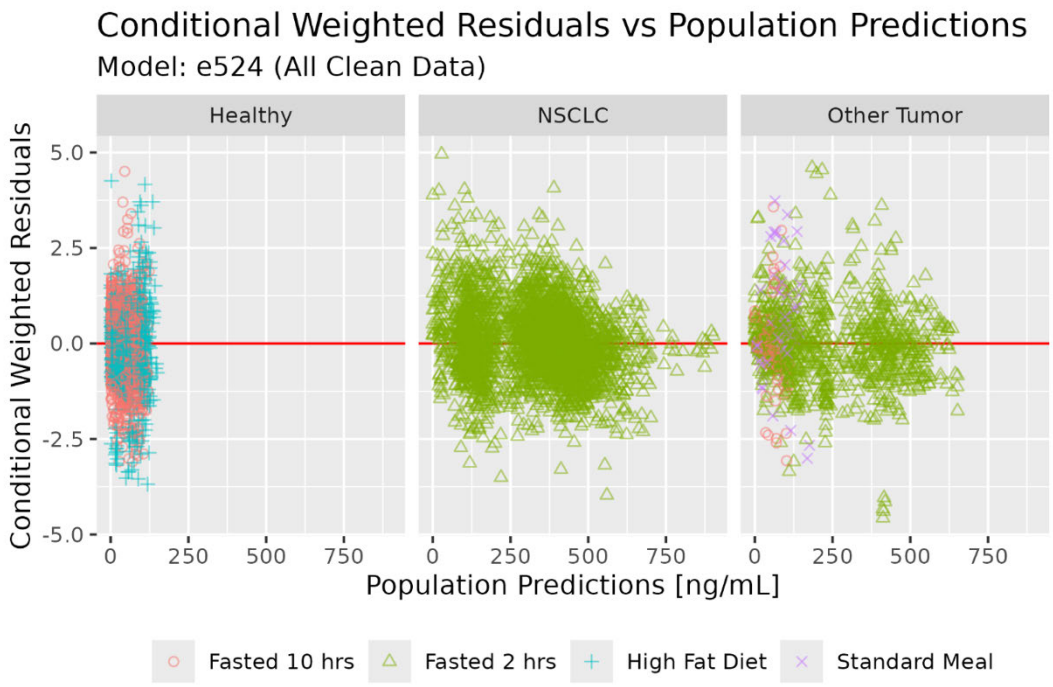
Parameter[a]	Symbol	NONMEM Parameter	Estimate	RSE [%][a]	95% CI[b]	Shrinkage [%]
Apparent Clearance [L/h]	CL	THETA1	94.24	4.4	87.8, 101	NA
Apparent Volume (Central) [L]	VC	THETA2	3,680.27	4.58	3440, 3930	NA
Apparent Intercompartmental Clearance (Cmpt-3) [L/h]	Q3	THETA3	19.06	7.08	16.7, 21.3	NA
Apparent Volume (Cmpt-3) [L]	V3	THETA4	3,650.55	17.71	3070, 4620	NA
Apparent Intercompartmental Clearance (Cmpt-4) [L/h]	Q4	THETA5	133.07	9.3	113, 156	NA
Apparent Volume (Cmpt-4) [L]	V4	THETA6	2,492.92	5.64	2320, 2690	NA
Absorption Rate Constant [1/h]	KA	THETA7	2.25	19.09	1.79, 2.85	NA
Absorption Time Lag [h]	ALAG	THETA8	0.72	5.16	0.677, 0.759	NA
Relative Bioavailability [-]	FREL	THETA9	1[c]	NA	NA	NA
CL ~ WT (power model) [-]	CL_WT	THETA10	0.37	21.21	0.239, 0.51	NA
CL ~ Asian (exponential model) [-]	CL_ASIAN	THETA11	−0.18	18.09	-0.239, -0.126	NA
VC ~ WT (power model) [-]	VC_WT	THETA23	1[c]	NA	NA	NA
VC ~ Cancer Patients (exponential model) [-]	VC_CPAT	THETA24	0.25	20.19	0.167, 0.33	NA
KA ~ Fasted 2hr (exponential model) [-]	KA_FAST2	THETA25	−1.47	11.38	-1.68, -1.25	NA
KA ~ Fed (exponential model) [-]	KA_FED	THETA26	−1.75	16.31	-1.99, -1.53	NA
FREL ~ Fasted 2hr (exponential model) [-]	FREL_FAST2	THETA29	0.44	9.05	0.378, 0.501	NA
FREL ~ Fed (exponential model) [-]	FREL_FED	THETA30	0.46	13.73	0.427, 0.497	NA
standard deviation (proportional error Ph1) [-]	sd(PERR)	THETA32	0.23	6.15	0.225, 0.239	NA

Parameter[a]	**Symbol**	**NONMEM Parameter**	**Estimate**	**RSE [%]**[a]	**95% CI**[b]	**Shrinkage [%]**
standard deviation (additive error Ph2) [-]	sd(AERR2)	THETA33	30.1	12.75	27.1, 32.6	NA
standard deviation (proportional error Ph2) [-]	sd(PERR2)	THETA34	0.14	7.24	0.134, 0.154	NA
variance (CL) [-]	var(CL)	OMEGA11	0.03	35.69	0.0156, 0.0427	41.68
covariance (CL,VC) [-]	cov(CL,VC)	OMEGA21	-0.00012	86,642	-0.0164, 0.017	
variance (VC) [-]	var(VC)	OMEGA22	0.11	17.67	0.0842, 0.143	33.15
variance (KA) [-]	var(KA)	OMEGA77	0.7	15.14	0.582, 0.865	23.16
variance (FREL) [-]	var(FREL)	OMEGA99	0.08	12.05	0.0671, 0.0986	13.35
variance (RUV) [-]	var(RUV)	SIGMA11	1[c]	NA	NA	NA

Abbreviations: 2LL, log-likelihood ratio; CL, clearance; Cmpt, compartment; FREL, relative bioavailability; KA, first-order absorption rate constant; NA, not applicable; RSE, relative standard error; RUV, residual unexplained variability; VC, volume of distribution of central compartment; WT, weight.
Deviance (-2LL): 46170.004
Condition number: 292.235
[a] Relative standard error from NONMEM covariance matrix
[b] 95% confidence interval from sampling importance resampling method
[c] Parameter value was fixed
Source: Report ANTX-Proj1-24-0002 Table 10

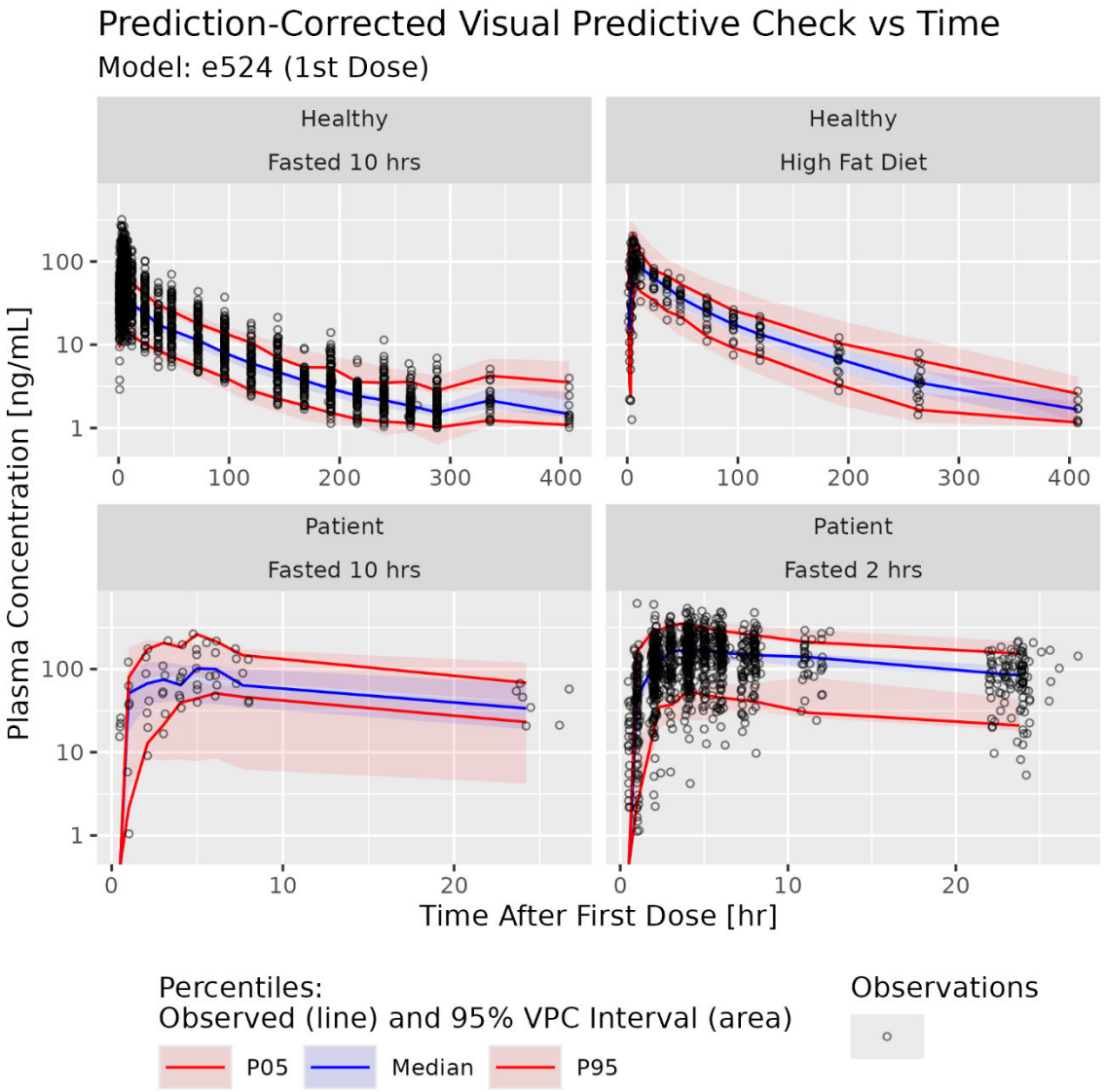
Figure 29. Applicant - Goodness-of-Fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)



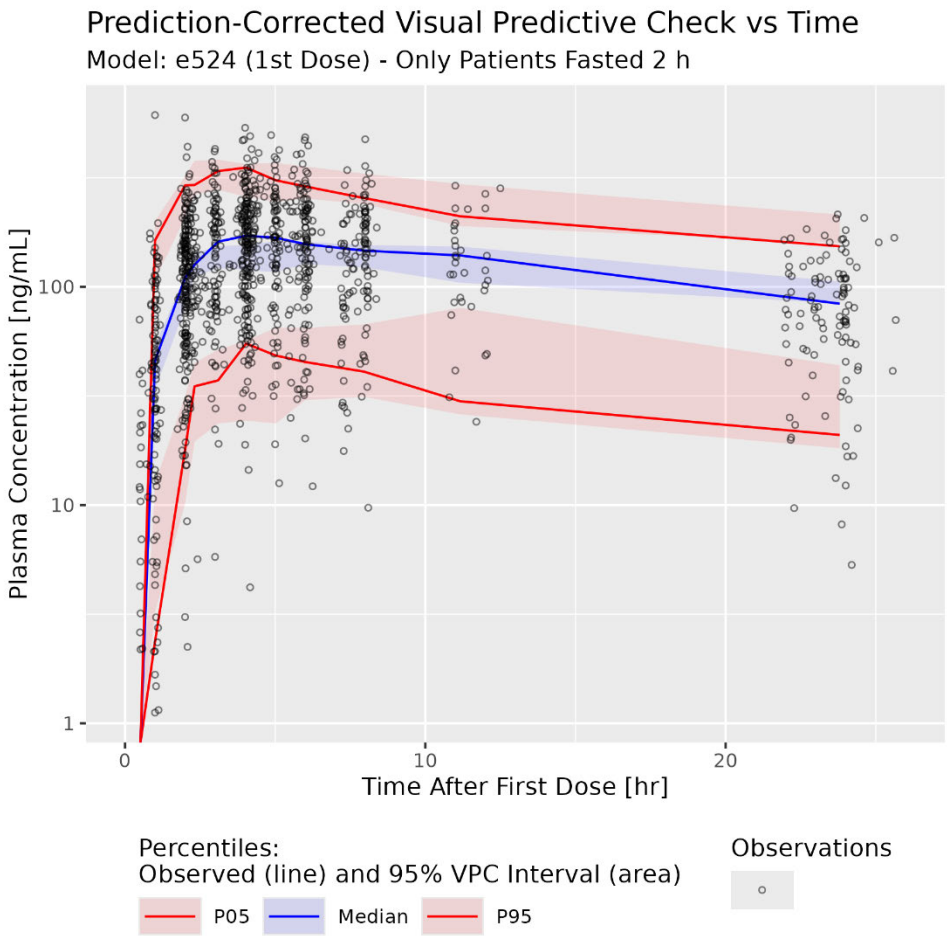


Source: Report ANTX-Proj1-24-0002 Figure A-3

Figure 30. Applicant - VPC of Final Population PK Model, Stratified by Paticipant Type

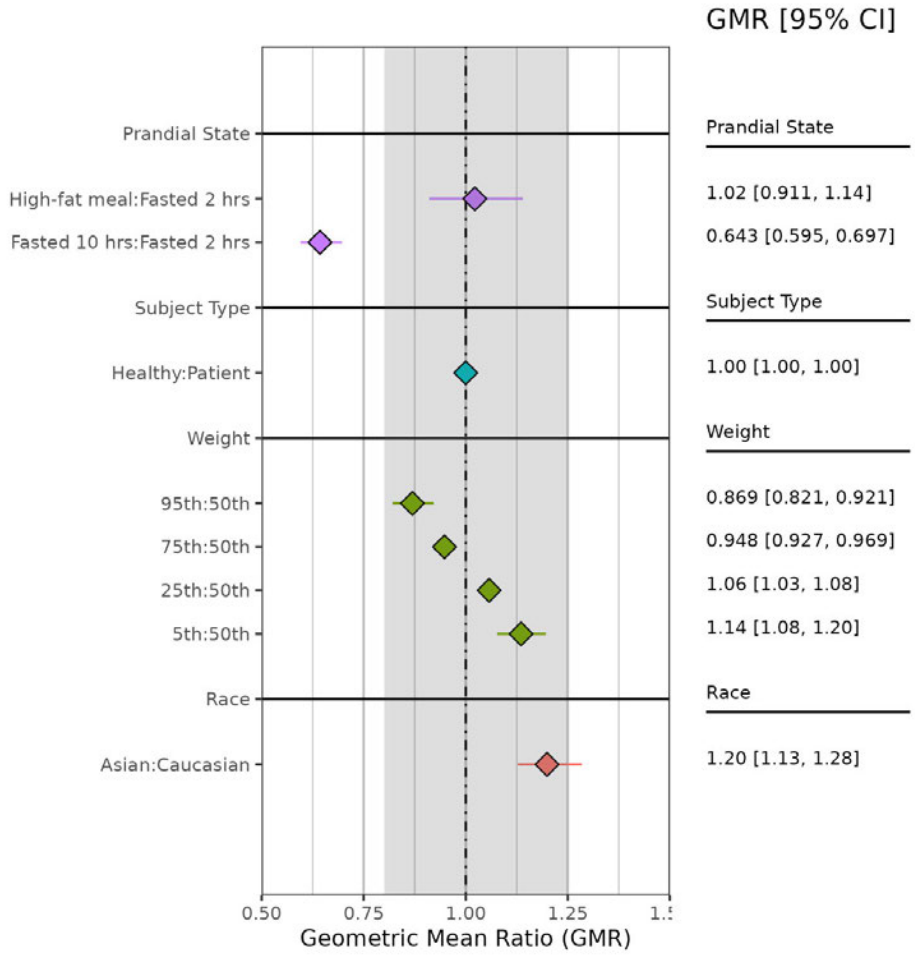


Abbreviations: pcVPC, prediction-corrected visual predictive check; VPC, visual predictive check.
Source: Report ANTX-Proj1-24-0002 Figure 4



Abbreviations: pcVPC, prediction-corrected visual predictive check; VPC, visual predictive check.
Source: Report ANTX-Proj1-24-0002 Figure 5

Figure 31. Applicant - Impact of Significant Covariates on Exposure (C_{avgss})



Abbreviations: C_{avgss}, time-averaged concentration at steady-state; CI, confidence interval; GMR, geometric mean ratio; QD, once daily.
Note: Based on population parameter estimates of final model (e524) with uncertainty. Reference subject is a Caucasian cancer patient of the median body weight fasted 2 hr.
Source: Report ANTX-Proj1-24-0002 Figure 7

The FDA's Assessment:
The population PK analysis is considered adequate.

19.4.3.3. PPK Review Issues

Data for estimating the effect of standard meals on relative bioavailability were limited, therefore, the estimated effect was determined by the covariate category with which it was combined, i.e., high fat meals. The effect of standard meals on relative bioavailability and the

related issues were further discussed in **Section 19.4.3.4**.

19.4.3.4. Reviewer's Independent Analysis

The impact of food effect, especially under fed condition, was determined by the food effect of high-fat meals based on data from Ph1 study in heathy subjects. Fed condition is of interest given a potential benefit in ameliorating GI tolerability and reducing PK variability. Should the magnitude of exposure increase with standard meals compared to the current proposed 2-hour fast be accurately estimated, an alternative dosage taken with standard meals could be subsequently proposed based on exposure matching.

Post hoc relative bioavailability estimates were plotted against food status to visualize food effect across studies. As shown in **Figure 32**, a large variability is observed in patients taking taletrectinib under 2-hour fast. This observation is expected considering that 2-hour fast (taking taletrectinib 2 hours before or after a meal according to study protocol) would have a varying degree of fasting prior to taking the drug, ranging from overnight to 2 hours amongst patients and/or days.

Across different food status, there appears to be an incremental change from 10-hour fast to fed (high fat or standard meals) where the fasting and fed data are mainly contributed by healthy subjects. The number of patients taking drug under 10-hour fast or with standard meals is limited. Therefore, relative to 10-hour fast, the estimated food effect of a 2-hour fast is determined by cross study comparison between patients taking drug under 2-hour fast and healthy subjects taking drug under 10-hour fast, and that of fed condition (high-fat or standard meals) is determined by the data of healthy subjects with high-fat meals, which concluded that there is a comparable magnitude of increase in relative bioavailability between 2-hour fast and standard/high-fat meal. Of note, the relative bioavailability appears to be higher in patients than healthy subjects with corresponding food status.

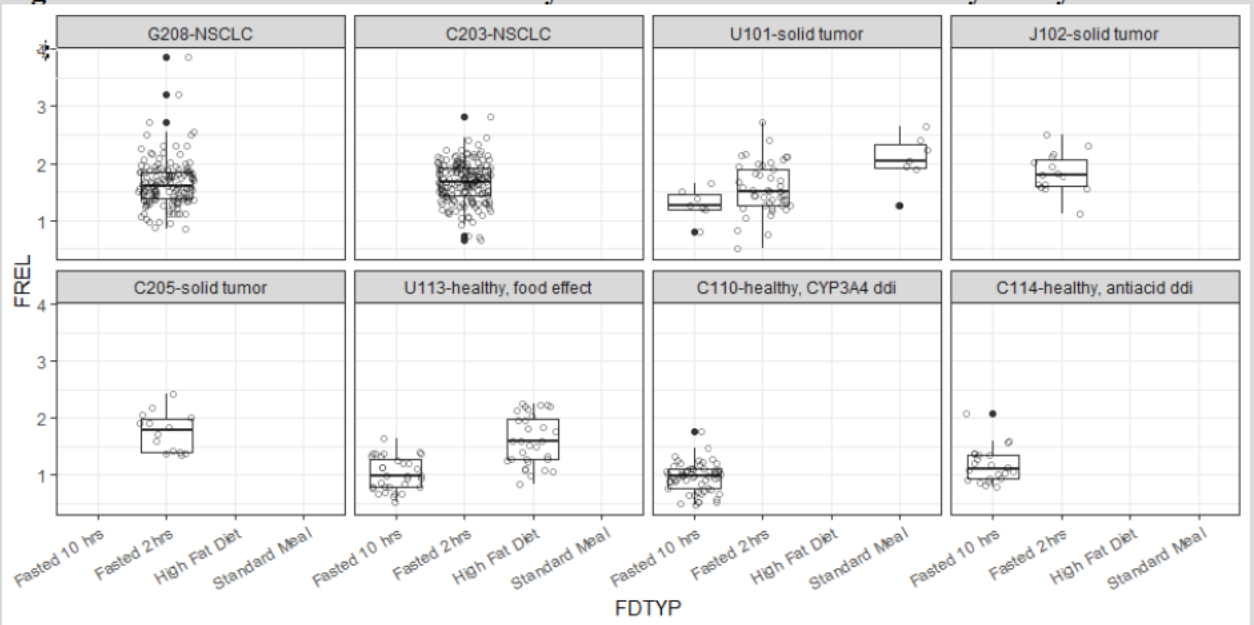
Given that the estimated effect could be confounded by between subject variability, to mitigate such impact, data of the same patients taking taletrectinib under various food status were evaluated. There were 6 patients taking taletrectinib under 3 food statuses (i.e., 10-hour fast, 2-hour fast, standard meals) in Study U101. In this study, the relative bioavailability under 2-hour fast overlapped with that observed under 10-hour fast when analyzing the entire patient cohort. However, amongst the 6 patients who underwent all 3 food statuses, a stepwise elevation in relative bioavailability was observed from 10-hour fast to standard meals (**Figure 33**). This again highlighted the confounding effect due to between subject variability. The distribution of relative bioavailability also clearly showed a larger variability with 2-hour fast compared to 10-hour fast or standard meals.

Due to the limited number of patients under ≥ 2 food statuses and a large variability in bioavailability with 2-hour fast, the increase in exposure from 2-hour fast to standard meals could not be robustly estimated. When subject type was added as a covariate on relative

bioavailability, OFV and condition number were both significantly improved (OFV drop of 15.05 points, and condition number reduced from 450.52 to 45.75). The estimated effect of 2-hour fast compared to 10-hour fast became much smaller—a 15% increase in relative bioavailability compared to 57% estimated with Applicant's final model, and the RSE associated with this estimate is large (74%), suggesting parameter uncertainty. Therefore, the expected increase in exposure from 2-hour fast to standard meals could vary across studies and amongst subjects, making it difficult to identify a dosage taken with standard meals that would match exposure of 600 mg QD taletrectinib taken under 2-hour fast with confidence.

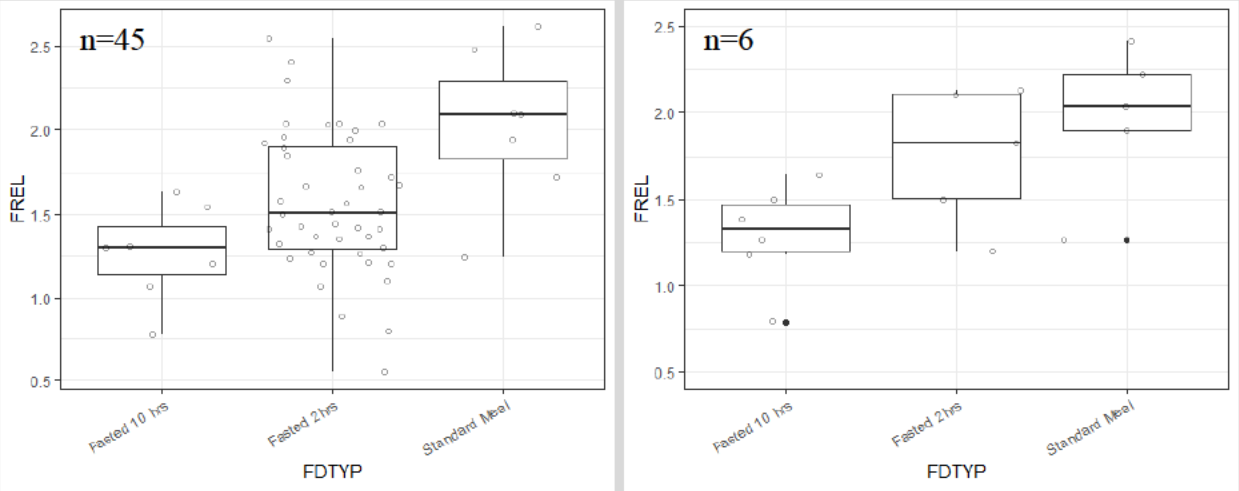
Considering that AUC increased by~50% with high-fat meals compared to 10-hour fast based on Ph1 food effect study AB-106-U113, AUC increase will be <50% with standard meals compared to 2-hour fast. Therefore, we recommend the Applicant to study 400 mg with standard meals instead of 2-hour fast which is expected to achieve AUC between 400 mg and 600 mg under 2-hour fast.

Figure 32. FDA - Relative Bioavailability Under Various Food Status by Study



Source: Reviewer's analysis. A modified model where OCC by Study was added for 2-hour fast.

Figure 33. FDA - Relative Bioavailability Under Various Food Status by Study



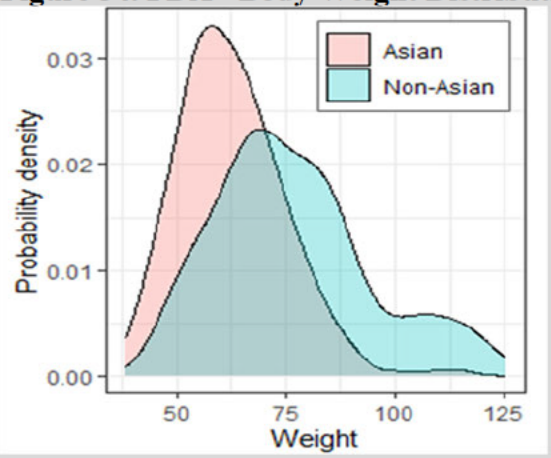
Source: Reviewer's analysis. A modified model where OCC by Study was added for 2-hour fast.

Race effect on exposure

Race and weight were both identified as significant covariates on CL. Based on population parameters with uncertainty demonstrated by **Figure 31**, the estimated effect of Asian race is associated with a 20% increase in Cavgss, and the estimated effect of 5th percentile body weight is associated with a 14% increase in Cavgss.

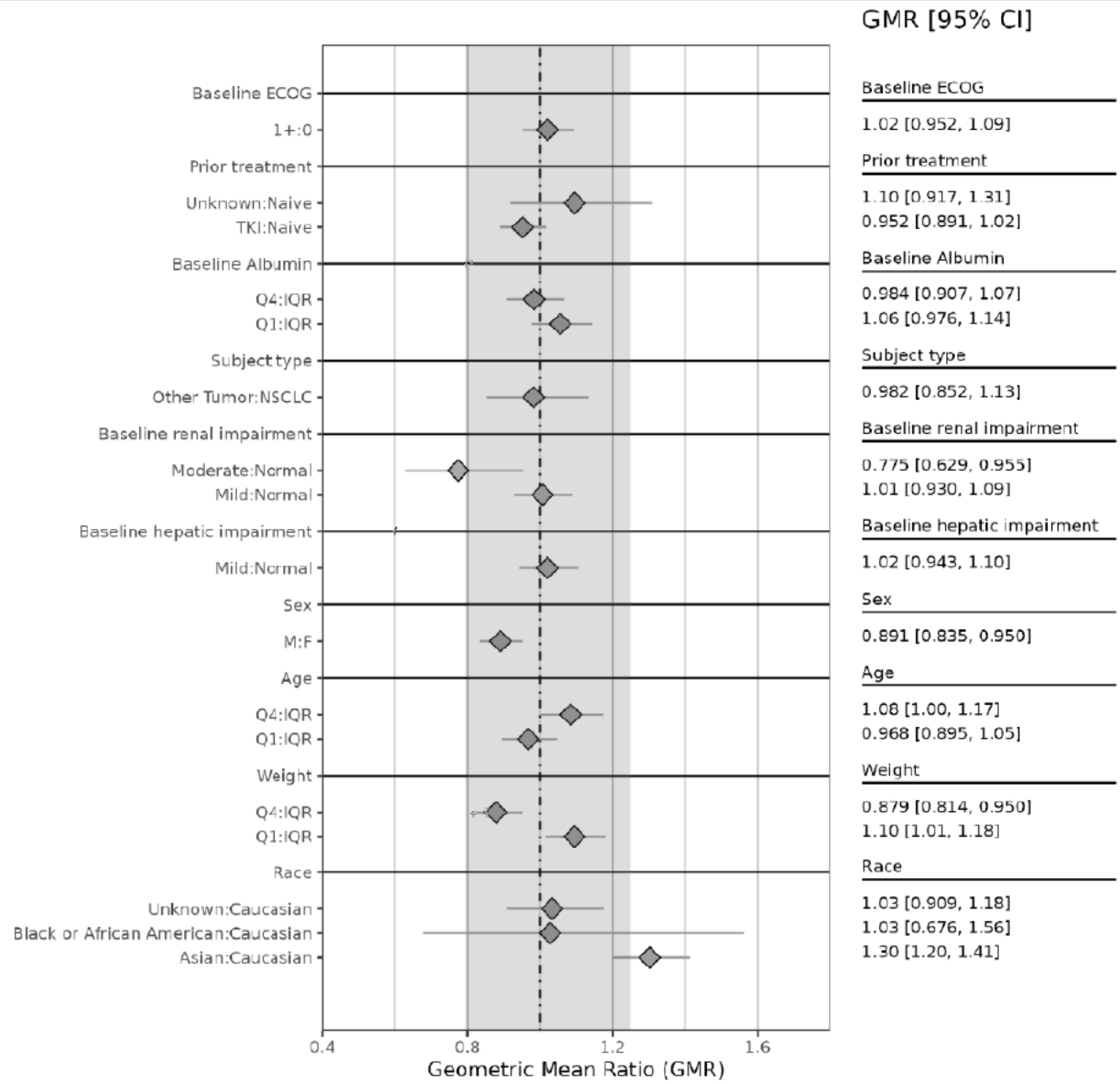
In Asian patients who have a lower weight distribution compared to non-Asian patients (**Figure 34),** post hoc Cavgss exhibits a 30% increase shown by the forest plot (**Figure 35**). The increase in exposure is likely associated with a higher risk for Grade ≥3 AST/ALT increase (refer to **Section 19.4.4.3**).

Figure 34. FDA - Body Weight Distribution in Asian and Non-Asian Patients



Source: Reviewer's analysis. PopPK data excluding healthy subjects were used in the analysis.

Figure 35. Effects of Covariates on Cavgss (600 mg QD) Based on EBEs



Source: Applicant's popPK and ER report (Figure 8). EBE = empirical Bayes estimate; ECOG = Eastern Cooperative Oncology Group; GMR = geometric mean ratio; IQR = interquartile range; NSCLC = Non-small cell lung cancer; Q1 =quartile 1; Q4 = quartile 4.

19.4.4. Exposure-Response Analysis

19.4.4.1. ER (Efficacy) Executive Summary

The FDA's Assessment:

Lack of positive E-R relationships for efficacy endpoints was observed across steady-state exposure with data of mainly 600 mg QD dosage. In the randomized study of small sample size (n=~20/arm), a lower ORR (including confirmed and unconfirmed responses) was observed for the 400 mg QD arm among patients previously treated with ROS1 TKIs, while a difference was not observed in TKI naïve patients. The difference in ORR observed in those with prior TKI treatment may be attributed to an imbalance of patient characteristics in this subgroup (refer to **Section 6**). Integrating the randomized data in the pooled E-R analysis did not alter the flat E-R trend. This suggests the exposure of doses less than 600 mg taken 2 hours before or after a meal (e.g., 400 mg dose taken 2 hours before or after a meal, or with standard meals) may preserve efficacy.

19.4.4.2. ER (Efficacy) Assessment Summary

The Applicant's Position:

For the primary efficacy endpoint objective response, no relationship was identified between taletrectinib exposure measures (Cavg,ss) and probability of achieving objective response in logistic regression model. Prior TKI treatment history was identified as the only significant predictor of ORR. As a supportive analysis, linear regression models utilizing taletrectinib popPK predicted exposure measures (Cavg.ss) as a covariate did not indicate a clear clinically relevant association between best percent change in tumor size and exposure to taletrectinib. Similarly, prior TKI treatment history was identified as a significant predictor of tumor size change.

General Information		
Goal of ER analysis		To characterize taletrectinib E-R relationships of efficacy with respect to the following efficacy measures (ORR and tumor size)
Study Included		AB-106-C203 and AB-106-G208
Endpoint		Primary: Objective response (IRC) Secondary: Decrease in tumor size (nadir of IRC assessed SLD
No. of Patients (total, and with individual PK)		161 TKI-naïve patients and 151 TKI pretreated patients
Population Characteristics	General	Age median (range): 56 yr (26, 83) Weight median (range): 64 kg (38, 115)

(Table 20 of the ER report)		Male n (%): 133 (43%) White n (%): 46 (15%), Asian n (%): 241 (77%), Other n(%): 25 (8.0%)	
	Pediatrics (if any)	Not included	
Dose(s) Included		400 mg and 600 mg	
Exposure Metrics Explored (range)		C_{avgss} (C_{maxss} is highly corrected with C_{avgss} due to very flat PK profile at steady state: R^2= 0.95)	
Covariates Evaluated		Age, Sex, Race, Baseline weight, Baseline serum albumin Brain metastases, Prior TKI treatment, Baseline ECOG	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Primary: logistic regression $\log\left(\frac{P_i}{1-P_i}\right) = \beta_0 + \beta_{Cavgss} \cdot Cavgss_i + \beta_1 x_{i1} + \beta_2 x_{i2} \cdots \beta_j x_{ij}$ where, P_i is the probability of that subject i will achieve an OR, C_{avgssi} is the value of Cavgss in subject i, and β_{Cavgss} is the estimated effect of Cavgss on the log-odds of achieving an OR. Additionally, x_{ij} represents the value of covariate j in subject i, and β_j are estimated parameters that represent log-odds ratios. Secondary: linear regression (nonlinear if necessary) $\min_{t>0} \frac{SLD_{i,t} - SLD_{i,0}}{SLD_{i,0}} = \beta_0 + \beta_{Cavgss} \cdot Cavgss_i + \beta_1 x_{i1} + \beta_2 x_{i2} \cdots \beta_j x_{ij}$ where, $SLD_{i,0}$ is the baseline SLD, $SLD_{i,t}$ is value of SLD at time t,	Yes

	$Cavgss_i$ is the value of C_{avgss} in subject i, and β_{Cavgss} is the estimated effect of C_{avgss} on the nadir of SLD. Additionally, x_{ij} represents the value of covariate j in subject i, and β_j are estimated parameters.	
Model Parameter Estimates	Table 22 and 25 in the ER report (for primary and secondary endpoints)	Yes
Model Evaluation	The visual predictive checks were constructed from simulated datasets (N=1000) containing simulated responses. The observed proportion of responders (overall and stratified by Cavgss quartiles) was compared to the corresponding simulated 90% prediction interval.	Yes
Covariates and Clinical Relevance	TKI-pretreatment status	Albumin was identified as an additional covariate in the updated E-R model.
Simulation for Specific Population	NA	
Visualization of E-R relationships		**Figure 37**
Overall Clinical Relevance for ER	No relationship was identified between taletrectinib exposure measures ($C_{avg,ss}$) and efficacy endpoints	Interpret with caution given narrow exposure range with data mainly contributed by 600 mg QD dosage.
Labeling Language	**Description**	**Acceptability** **[FDA's comments]**

12.2 Pharmacodynamics		Added "Taletrectinib exposure-response relationships for efficacy and the time course of pharmacodynamic response have not been fully characterized."

Table 75. Applicant - Summary of Subject Characteristics (E-R Efficacy Objective Response Dataset)

Characteristic	AB-106-C203 N=167[a]	AB-106-G208 N=145[a]	Overall N=312[a]
Age (yr)			
Mean (SD)	54 (11)	57 (12)	55 (12)
Median (Range)	55 (26, 77)	57 (27, 83)	56 (26, 83)
Sex			
M	71 (43%)	62 (43%)	133 (43%)
F	96 (57%)	83 (57%)	179 (57%)
Race			
Caucasian	0 (0%)	46 (32%)	46 (15%)
Asian	167 (100%)	74 (51%)	241 (77%)
Other	0 (0%)	25 (17%)	25 (8.0%)
Baseline ECOG			
0	38 (23%)	57 (39%)	95 (30%)
1	129 (77%)	88 (61%)	217 (70%)
Baseline Body Weight (kg)			
Mean (SD)	63 (12)	68 (15)	65 (13)
Median (Range)	62 (38, 115)	66 (42, 114)	64 (38, 115)
Baseline Tumor Burden (mm)			
Mean (SD)	40.8 (4.5)	38.1 (5.1)	39.5 (5.0)
Median (Range)	40.9 (28.8, 51.4)	38.0 (24.0, 49.8)	40.0 (24.0, 51.4)

Characteristic	AB-106-C203 N=167[a]	AB-106-G208 N=145[a]	Overall N=312[a]
Baseline Albumin (g/L)			
Mean (SD)	40.8 (4.5)	38.1 (5.1)	39.5 (5.0)
Median (Range)	40.9 (28.8, 51.4)	38.0 (24.0, 49.8)	40.0 (24.0, 51.4)
Prior TKI Therapy Group			
Naive	104 (62%)	57 (39%)	161 (52%)
TKI	63 (38%)	88 (61%)	151 (48%)
Tumor Stage (N)			
3	11 (6.6%)	7 (4.8%)	18 (5.8%)
4	156 (93%)	138 (95%)	294 (94%)
Brain Metastasis at Baseline per IC			
Y	44 (26%)	66 (46%)	110 (35%)
N	123 (74%)	79 (54%)	202 (65%)
Best Overall Response by IRC (RECIST 1.1)			
CR	6 (3.6%)	9 (6.2%)	15 (4.8%)
PR	133 (80%)	83 (57%)	216 (69%)
SD	17 (10%)	33 (23%)	50 (16%)
PD	8 (4.8%)	16 (11%)	24 (7.7%)
NE	3 (1.8%)	4 (2.8%)	7 (2.2%)
Response Flag			
Y	139 (83%)	92 (63%)	231 (74%)
N	28 (17%)	53 (37%)	81 (26%)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; E-R, exposure-response; F, female; IC, inhibitory concentration; IRC, independent review committee; M, male; N, no; NE, not evaluable; PD, progressive disease, PR, partial response; SD =stable disease; TKI, tyrosine kinase inhibitor, Y, yes.
[a] n (%)
Source: Report ANTX-Proj1-24-0002 Table 20

Table 76. Applicant - Summary of Subject Characteristics (E-R Efficacy Tumor Size Change Dataset)

Characteristic	AB-106-C203 N=168[a]	AB-106-G208 N=143[a]	Overall N=311[a]
Age (yr)			

Characteristic	AB-106-C203 N=168[a]	AB-106-G208 N=143[a]	Overall N=311[a]
Mean (SD)	54 (11)	57 (12)	55 (12)
Median (Range)	55 (26, 77)	57 (27, 83)	56 (26, 83)
Sex			
M	72 (43%)	62 (43%)	134 (43%)
F	96 (57%)	81 (57%)	177 (57%)
Race			
Caucasian	0 (0%)	45 (31%)	45 (14%)
Asian	168 (100%)	73 (51%)	241 (77%)
Other	0 (0%)	25 (17%)	25 (8.0%)
Baseline ECOG			
0	38 (23%)	57 (40%)	95 (31%)
1	130 (77%)	86 (60%)	216 (69%)
Baseline Body Weight (kg)			
Mean (SD)	63 (12)	68 (14)	65 (13)
Median (Range)	62 (38, 115)	66 (42, 114)	63 (38, 115)
Missing	1 (0.6%)	2 (1.4%)	3 (1.0%)
Baseline Tumor Burden (mm)			
Mean (SD)	40.8 (4.5)	38.1 (5.2)	39.6 (5.0)
Median (Range)	40.9 (28.8, 51.4)	38.0 (24.0, 49.8)	40.0 (24.0, 51.4)
Baseline Albumin (g/L)			
Mean (SD)	40.8 (4.5)	38.1 (5.2)	39.6 (5.0)
Median (Range)	40.9 (28.8, 51.4)	38.0 (24.0, 49.8)	40.0 (24.0, 51.4)
Prior TKI Therapy Group			
Naive	104 (62%)	57 (40%)	161 (52%)
TKI	64 (38%)	86 (60%)	150 (48%)
Tumor Stage (N)			
3	11 (6.5%)	7 (4.9%)	18 (5.8%)

Characteristic	AB-106-C203 N=168[a]	AB-106-G208 N=143[a]	Overall N=311[a]
4	157 (93%)	136 (95%)	293 (94%)
Brain Metastasis at Baseline per IC			
Y	45 (27%)	64 (45%)	109 (35%)
N	123 (73%)	79 (55%)	202 (65%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; E-R, exposure-response; F, female; IC, inhibitory concentration; M, male; N, no; SD =standard deviation; TKI, tyrosine kinase inhibitor, Y, yes.
[a] n (%)
Source: Report ANTX-Proj1-24-0002 Table 23

Table 77. Applicant - Summary of Subject Characteristics by C_{avgss} Quartile (ng/mL) (E-R Efficacy Objective Response Analysis Dataset)

Characteristic	Q1 N=78[a]	Q2 N=78[a]	Q3 N=78[a]	Q4 N=78[a]	Overall N=312[a]
Age (yr)					
Mean (SD)	56 (13)	52 (12)	55 (12)	59 (10)	55 (12)
Median (Range)	56 (27, 83)	53 (26, 79)	56 (31, 77)	59 (32, 80)	56 (26, 83)
Sex					
M	44 (56%)	36 (46%)	30 (38%)	23 (29%)	133 (43%)
F	34 (44%)	42 (54%)	48 (62%)	55 (71%)	179 (57%)
Race					
Caucasian	23 (29%)	11 (14%)	6 (7.7%)	6 (7.7%)	46 (15%)
Asian	41 (53%)	60 (77%)	70 (90%)	70 (90%)	241 (77%)
Other	14 (18%)	7 (9.0%)	2 (2.6%)	2 (2.6%)	25 (8.0%)
Baseline ECOG					
0	23 (29%)	28 (36%)	23 (29%)	21 (27%)	95 (30%)
1	55 (71%)	50 (64%)	55 (71%)	57 (73%)	217 (70%)
Baseline Body Weight (kg)					
Mean (SD)	70 (15)	67 (12)	63 (13)	60 (11)	65 (13)
Median (Range)	68 (47, 115)	65 (44, 106)	60 (38, 95)	59 (43, 109)	64 (38, 115)
Missing	0 (0%)	1 (1.3%)	0 (0%)	2 (2.6%)	3 (1.0%)
Baseline Albumin (g/L)					

Characteristic	Q1 N=78[a]	Q2 N=78[a]	Q3 N=78[a]	Q4 N=78[a]	Overall N=312[a]
Mean (SD)	40.2 (4.9)	40.0 (5.3)	39.1 (5.1)	38.9 (4.7)	39.5 (5.0)
Median (Range)	40.8 (27.0, 51.4)	40.0 (27.0, 50.0)	38.4 (24.0, 49.0)	39.6 (25.0, 48.5)	40.0 (24.0, 51.4)
Prior TKI Therapy					
Naive	38 (49%)	41 (53%)	35 (45%)	47 (60%)	161 (52%)
TKI	40 (51%)	37 (47%)	43 (55%)	31 (40%)	151 (48%)
Brain Metastasis at Baseline per IC					
Y	30 (38%)	25 (32%)	31 (40%)	24 (31%)	110 (35%)
N	48 (62%)	53 (68%)	47 (60%)	54 (69%)	202 (65%)
Best Overall Response by IRC (RECIST 1.1)					
CR	1 (1.3%)	4 (5.1%)	6 (7.7%)	4 (5.1%)	15 (4.8%)
PR	57 (73%)	52 (67%)	54 (69%)	53 (68%)	216 (69%)
SD	15 (19%)	13 (17%)	11 (14%)	11 (14%)	50 (16%)
PD	5 (6.4%)	7 (9.0%)	5 (6.4%)	7 (9.0%)	24 (7.7%)
NE	0 (0%)	2 (2.6%)	2 (2.6%)	3 (3.8%)	7 (2.2%)
Response Flag					
Y	58 (74%)	56 (72%)	60 (77%)	57 (73%)	231 (74%)
N	20 (26%)	22 (28%)	18 (23%)	21 (27%)	81 (26%)

Abbreviations: C_{avgss}, Time-averaged concentration at steady-state; CR, complete response; ECOG, Eastern Cooperative Oncology Group; E-R, exposure-response; F, female; IC, inhibitory concentration; IRC, independent review committee; M, male; N, no; NE, not evaluable; PD, progressive disease; PR, progressive disease; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, stable disease; TKI, tyrosine kinase inhibitor, Y, yes.
C_{avgss} quartiles [ng/mL]: Q1 = [149, 407], Q2 = (407, 506], Q3 = (506, 616], Q4 = (616, 1430]
[a] n (%)
Source: Report ANTX-Proj1-24-0002 Table 21

Table 78. Applicant - Summary of Subject Characteristics by C_{avgss} Quartile (E-R Efficacy Tumor Size Change Analysis Dataset)

Characteristic	Q1 N=78[a]	Q2 N=78[a]	Q3 N=77[a]	Q4 N=78[a]	Overall N=311[a]
Age (yr)					
Mean (SD)	56 (13)	52 (12)	55 (12)	59 (10)	55 (12)
Median (Range)	56 (27, 83)	53 (26, 79)	55 (31, 77)	59 (32, 80)	56 (26, 83)

Characteristic	Q1 N=78[a]	Q2 N=78[a]	Q3 N=77[a]	Q4 N=78[a]	Overall N=311[a]
Sex					
M	44 (56%)	36 (46%)	31 (40%)	23 (29%)	134 (43%)
F	34 (44%)	42 (54%)	46 (60%)	55 (71%)	177 (57%)
Race					
Caucasian	23 (29%)	11 (14%)	5 (6.5%)	6 (7.7%)	45 (14%)
Asian	41 (53%)	60 (77%)	70 (91%)	70 (90%)	241 (77%)
Other	14 (18%)	7 (9.0%)	2 (2.6%)	2 (2.6%)	25 (8.0%)
Baseline ECOG					
0	23 (29%)	27 (35%)	24 (31%)	21 (27%)	95 (31%)
1	55 (71%)	51 (65%)	53 (69%)	57 (73%)	216 (69%)
Baseline Body Weight (kg)					
Mean (SD)	70 (15)	67 (12)	62 (12)	60 (11)	65 (13)
Median (Range)	68 (47, 115)	65 (44, 106)	60 (38, 92)	59 (43, 109)	63 (38, 115)
Missing	0 (0%)	1 (1.3%)	0 (0%)	2 (2.6%)	3 (1.0%)
Baseline Albumin (g/L)					
Mean (SD)	40.2 (4.9)	40.0 (5.2)	39.2 (5.2)	38.9 (4.7)	39.6 (5.0)
Median (Range)	40.8 (27.0, 51.4)	40.0 (27.0, 50.0)	38.6 (24.0, 49.0)	39.6 (25.0, 48.5)	40.0 (24.0, 51.4)
Prior TKI Therapy					
Naive	38 (49%)	41 (53%)	35 (45%)	47 (60%)	161 (52%)
TKI	40 (51%)	37 (47%)	42 (55%)	31 (40%)	150 (48%)
Brain Metastasis at Baseline per IC					
Y	30 (38%)	26 (33%)	29 (38%)	24 (31%)	109 (35%)
N	48 (62%)	52 (67%)	48 (62%)	54 (69%)	202 (65%)

Abbreviations: C_{avgss}, time-averaged concentration at steady-state; ECOG, Eastern Cooperative Oncology Group; E-R, exposure-response; F, female; IC, inhibitory concentration; M, male; N, no; NE, not evaluable; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation; TKI, tyrosine kinase inhibitor, Y, yes.
C_{avgss} quartiles [ng/mL]: Q1 = [149, 407], Q2 =(407, 505], Q3 = (505, 616], Q4 = (616, 1430]
[a] n (%)
Source: Report ANTX-Proj1-24-0002 Table 24

Table 79. Applicant - Parameter Estimates: E-R of Objective Response

Predictor	Odds Ratio[a]	RSE (%)[b]	95% CI[c]	p value
Intercept	0.88239	55.9	0.33350–2.3358	0.7999
Sex (Female:Male)	1.0221	32.0	0.53658–1.9409	0.9468
Age [yr]	0.98855	1.3	0.96352–1.0138	0.3732
Race (Asian:Caucasian)	0.99873	42.6	0.42746–2.2851	0.9976
Race (Other:Caucasian)	0.75853	75.2	0.24631–2.3363	0.6279
Baseline Weight [kg]	0.99036	1.3	0.96505–1.0162	0.4594
Baseline Albumin [g/L]	1.0525	3.2	0.98631–1.1239	0.1234
Baseline ECOG (1+:0)	1.1108	30.2	0.57272–2.1398	0.7540
C_{avg} at SS [ng/mL]	0.99896	0.1	0.99696–1.0010	0.3073
Prior TKI Treatment (Naive:TKI)	11.825	3.3	5.6861–26.969	0.0000000003657
Brain Metastasis at Baseline (Y:N)	1.0214	30.1	0.56036–1.8781	0.9451

Abbreviations: C_{avg}, time-averaged concentration in a dosing interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; N, no; RSE, relative standard error; SS, steady state; TKI, tyrosine kinase inhibitor; Y, yes.

[a] Estimated odds ratio of comparator:reference (for categorical predictors) or per unit change in value (continuous predictors)

[b] Relative standard error

[c] 95% confidence interval

Source: Report ANTX-Proj1-24-0002 Table 22

Table 80. Applicant - Parameter Estimates: E-R of Change in Tumor Size

Predictor	Estimated Value[a]	RSE (%)[b]	95% CI[c]	p value
Intercept	−23.234	−18.6	−31.761–−14.707	0.0000001644
Sex (Female:Male)	0.57616	461.6	−4.6571–5.8094	0.8286
Age [yr]	0.28270	36.5	0.079734–0.48566	0.006493
Race (Asian:Caucasian)	−1.0369	−363.3	−8.4504–6.3766	0.7833
Race (Other:Caucasian)	5.1832	100.5	−5.0723–15.439	0.3207
Baseline Weight [kg]	0.048903	218.6	−0.16150–0.25931	0.6477

Predictor	Estimated Value[a]	RSE (%)[b]	95% CI[c]	p value
Baseline Albumin [g/L]	−0.015117	−1,698.0	−0.52023–0.48999	0.9531
Baseline ECOG (1+:0)	2.6377	102.3	−2.6699–7.9454	0.3289
Cavg at SS [ng/mL]	0.011080	73.7	−0.004981–0.02714	0.1756
Prior TKI Treatment (Naive:TKI)	−18.280	−14.6	−23.532–−13.028	0.00000000004208
Brain Metastasis at Baseline (Y:N)	0.16810	1,543.2	−4.9369–5.2731	0.9484

Abbreviations: Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; E-R, exposure-response; ECOG, Eastern Cooperative Oncology Group; N, no; RSE, relative standard error; SS, steady state; TKI, tyrosine kinase inhibitor; Y, yes.

[a] Estimated % tumor size change of comparator:reference (for categorical predictors) or per unit change in value (continuous predictors)

[b] Relative standard error

[c] 95% confidence interval

Source: Report ANTX-Proj1-24-0002 Table 25

19.4.4.3. ER (Safety) Executive Summary

The FDA's Assessment:

Positive E-R relationships were observed across steady-state exposures for Grade≥3 TEAEs, AE leading to dose modification, and Grade≥3 AST/ALT elevation. A 50% increase in Cavgss is predicted to result in ~50% greater risk for experiencing those AEs. Integrating the randomized data in the pooled E-R analysis minimally impacted the results. The lower dose (i.e., 400 mg) is predicted to improve safety, reducing the risk of those AEs by ~25%. Refer to overview of popPK and E-R (**19.4.2**) for increased hepatotoxicity risk that is associated with higher exposure considering high PK variability for 2-hour fast, as well as observed increase in exposure in Asian patients, and their respective recommendations.

19.4.5. ER (Safety) Assessment Summary

The Applicant's Position:

For safety endpoints, no apparent trend between taletrectinib exposure and SAE, Grade ≥3 ALT/AST elevations, or Grade ≥2 GI AEs was observed. Although a statistically significant relationship was observed between taletrectinib exposure and AEs leading to dose modification, as well as Grade ≥3 TEAEs, the trend was relatively modest. For both AEs leading to dose modification and Grade ≥3 TEAEs, the hazard ratios (HR) were estimated to be 1.0017, which is a relatively shallow ER relationship.

General Information		
Goal of ER analysis		To characterize taletrectinib E-R relationships of safety with respect to the following adverse events: • Serious AEs • AEs leading to dose interruption/modification/discontinuation • Gr3+ treatment emergent AEs (excluding Covid-19) • Gr3+ AST/ALT increase • Gr2+ GI AEs
Study Included		DS6051-A-U101, DS6051-A-J102, AB-106-C203, AB-106-C205 and AB-106-G208
Population Included		Multiple types of advanced solid tumors with at least 1 post-treatment plasma concentration measurement
Endpoint		• Serious AEs • AEs leading to dose interruption/modification/discontinuation • Gr3+ treatment emergent AEs (excluding Covid-19) • Gr3+ AST/ALT increase • Gr2+ GI AEs
No. of Patients (total, and with individual PK)		405 Participants
Population Characteristics (Table 12 of the ER report)	General	-Age median (range): 56 yr (24, 83) -Weight median (range): 65 kg (38, 125) -Male n (%): 180 (44%) - White n (%): 92 (23%), Asian n (%): 282 (70%), Other n (%): 31 (7.7%)
	Organ impairment	-Hepatic (NCI): Normal 319 (79%), Mild 86 (21%) -Renal (NKF criteria): Normal 352 (87%), Mild 46(11%), Moderate 7 (2%)
	Pediatrics (if any)	Not included

	Geriatrics (if any)	- Age median (range): 56 yr (24, 83), 26% participant ≥65 yr, 4.4% participant ≥75 -Male n (%): 51 (48%) male	
Dose(s) Included		50, 100, 200, 400, 600, 800, and 1200 mg QD or 400 mg BID	
Exposure Metrics Explored (range)		C_{avgss} (C_{maxss} is highly corrected with C_{avgss} due to very flat PK profile at steady state: R^2= 0.95)	
Covariates Evaluated		Age, Sex, Race, Baseline weight, Baseline serum albumin Brain metastases, Prior TKI treatment, Baseline ECOG	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Cox proportional hazards (CPH) model: $h_i = h_0 \cdot \exp(\beta_{Cavgss} \cdot Cavgss_i + \beta_1 x_{i1} + \beta_2 x_{i2} \cdots \beta_j x_{ij})$ where, $Cavgss_i$ is the value of C_{avgss} in subject i, and β_{Cavgss} is the estimated effect of C_{avgss} on the log-hazard of experiencing an event. Additionally, x_{ij} represents the value of covariate j in subject i, and β_j is the estimated log-hazard ratio for the covariate.	Yes
Model Parameter Estimates		Table 15-19 in ER report	Yes
Model Evaluation		The CPH models were evaluated by visual predictive checks (VPC), of the overall dataset as well as by C_{avgss} quartiles. The visual predictive checks were constructed from simulated datasets (N=1000) containing simulated event/censoring times corresponding to the observed event/censoring times.	Yes

Covariates and Clinical Relevance	ECOG status was identified as a predictor of SAE rates, with higher ECOG scores associated with a greater risk of experiencing SAEs. Baseline albumin level was significantly related to the risk of SAEs, Grade ≥3 TEAEs, and Grade ≥2 GI AEs. Participants with lower albumin levels demonstrated a higher risk of experiencing these AEs. Additionally, baseline weight and sex were identified as predictors for Grade ≥3 TEAEs and Grade ≥2 GI AEs, respectively, with lighter participants having a higher risk of experiencing Grade ≥3 TEAEs and female participants having a higher risk of experiencing Grade ≥2 GI AEs.	Yes
Simulation for Specific Population	NA	
Visualization of E-R relationships	Figure 16, 18, 20, 22, 24 in the ER report	Yes
Overall Clinical Relevance for ER	Risk of Grade ≥3 AEs and AEs leading to dose modification (including reduction, interruption, and discontinuation) were higher at higher average concentration at steady state. However, the observed trend is sufficiently mild that reduction in starting dose for safety reasons is not warranted. No apparent correlation was observed between taletrectinib exposure and other safety endpoints, including serious AEs (SAEs), Grade 3 or higher alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations, or Grade 2 or higher gastrointestinal AEs.	Updated E-R analysis (after correction of limited data errors) showed that the risk of Grade ≥3 AST/ALT increase was higher at higher Cavgss. A 50% increase in Cavgss is predicted to result in ~50% greater risk for experiencing those AEs with positive E-R relationships.

Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics		Added "Higher taletrectinib exposure is associated with an increased risk of Grade ≥3 of increased AST/ALT."

Table 81. Applicant - Summary of Baseline Characteristics and Laboratory Values in the Dataset

Characteristic	AB-106-C203 N=173[a]	AB-106-G208 N=158[a]	DS6051-A-U101 N=45[a]	DS6051-A-J102 N=15[a]	AB-106-C205 N=14[a]	Overall N=405[a]
Age (yrs)						
Mean (SD)	54 (12)	57 (13)	59 (14)	53 (12)	60 (14)	56 (12)
Median (Range)	55 (26, 78)	57 (27, 83)	62 (24, 79)	51 (34, 69)	65 (30, 73)	56 (24, 83)
Sex						
M	73 (42%)	70 (44%)	21 (47%)	8 (53%)	8 (57%)	180 (44%)
F	100 (58%)	88 (56%)	24 (53%)	7 (47%)	6 (43%)	225 (56%)
Race						
Caucasian	0 (0%)	52 (33%)	40 (89%)	0 (0%)	0 (0%)	92 (23%)
Asian	173 (100%)	79 (50%)	1 (2.2%)	15 (100%)	14 (100%)	282 (70%)
Other	0 (0%)	27 (17%)	4 (8.9%)	0 (0%)	0 (0%)	31 (7.7%)
Baseline ECOG Status						
0	39 (23%)	65 (41%)	15 (33%)	8 (53%)	2 (14%)	129 (32%)
1	134 (77%)	93 (59%)	30 (67%)	7 (47%)	11 (79%)	275 (68%)
2	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7.1%)	1 (0.2%)
Baseline Body Weight (kg)						
Mean (SD)	63 (12)	69 (15)	78 (19)	61 (13)	64 (15)	67 (15)

Characteristic	AB-106-C203 N=173[a]	AB-106-G208 N=158[a]	DS6051-A-U101 N=45[a]	DS6051-A-J102 N=15[a]	AB-106-C205 N=14[a]	Overall N=405[a]
Median (Range)	62 (38, 115)	67 (42, 115)	76 (48, 125)	62 (39, 89)	61 (47, 110)	65 (38, 125)
Baseline Albumin (g/L)						
Mean (SD)	40.7 (4.5)	38.2 (5.2)	34.8 (5.2)	38.6 (6.0)	40.1 (5.5)	39.0 (5.3)
Median (Range)	40.9 (28.8, 51.4)	38.1 (24.0, 49.8)	35.0 (23.0, 43.0)	39.0 (29.0, 48.0)	41.3 (25.4, 47.6)	39.4 (23.0, 51.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; E-R, exposure-response; SD, standard deviation.
[a] n (%)
Source: Report ANTX-Proj1-24-0002 Table 12

Table 82. Covariate Distribution over C_{avgss} Quartiles for All Subjects Included in the ER Analysis of safety (endpoint).

Characteristic	Q1 N=102[a]	Q2 N=101[a]	Q3 N=101[a]	Q4 N=101[a]	Overall N=405[a]
Age (yrs)					
Mean (SD)	56 (12)	53 (13)	54 (12)	60 (11)	56 (12)
Median (Range)	56 (27, 83)	55 (26, 79)	54 (24, 77)	62 (32, 80)	56 (24, 83)
Sex					
M	58 (57%)	48 (48%)	43 (43%)	31 (31%)	180 (44%)
F	44 (43%)	53 (52%)	58 (57%)	70 (69%)	225 (56%)
Race					
Caucasian	45 (44%)	20 (20%)	11 (11%)	16 (16%)	92 (23%)
Asian	44 (43%)	70 (69%)	85 (84%)	83 (82%)	282 (70%)
Other	13 (13%)	11 (11%)	5 (5.0%)	2 (2.0%)	31 (7.7%)
Baseline ECOG Status					
0	31 (30%)	37 (37%)	31 (31%)	30 (30%)	129 (32%)
1	71 (70%)	64 (63%)	69 (68%)	71 (70%)	275 (68%)
2	0 (0%)	0 (0%)	1 (1.0%)	0 (0%)	1 (0.2%)
Baseline Body Weight (kg)					
Mean (SD)	73 (17)	68 (14)	64 (14)	61 (12)	67 (15)

Characteristic	Q1 N=102[a]	Q2 N=101[a]	Q3 N=101[a]	Q4 N=101[a]	Overall N=405[a]
Median (Range)	70 (47, 125)	65 (39, 110)	63 (38, 116)	60 (43, 109)	65 (38, 125)
Baseline Albumin (g/L)					
Mean (SD)	39.3 (5.0)	39.5 (5.4)	38.6 (5.6)	38.5 (5.2)	39.0 (5.3)
Median (Range)	39.8 (27.0, 51.4)	40.0 (27.0, 50.0)	38.4 (24.0, 49.0)	39.4 (23.0, 48.5)	39.4 (23.0, 51.4)

Abbreviaitons: $C_{avgss.}$ time-averaged concentration at steady-state; ECOG, Eastern Cooperative Oncology Group; E-R, exposure-response; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4; SD, standard deviation.
[a] n (%)
C_{avgss} quartiles [ng/mL]: Q1=[47.9, 399], Q2=(399, 501], Q3=(501, 621], and Q4=(621,1430]
Source: Report ANTX-Proj1-24-0002 Table 13

Table 83. Applicant - Parameter Estimates: E-R of Serious AEs

Predictor	Hazard Ratio[a]	RSE (%)[b]	95% CI[c]	p value
Sex (Female:Male)	0.77150	25.2	0.52685–1.1298	0.1825
Age [yr]	1.0017	0.8	0.98604–1.0176	0.8331
Race (Asian:Caucasian)	1.1533	25.8	0.64341–2.0674	0.6319
Race (Other:Caucasian)	2.1707	17.4	1.0374–4.5422	0.03966
Baseline Weight [kg]	0.99585	0.8	0.98087–1.0111	0.5912
Baseline Albumin [g/L]	0.93589	1.9	0.90382–0.96911	0.0001963
Baseline ECOG (1+:0)	1.8627	12.2	1.1954–2.9026	0.005989
Cavg at SS [ng/mL]	1.0005	0.1	0.99943–1.0017	0.3360

Abbreviations: AE, adverse event; Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; E-R, exposure-response; ECOG, Eastern Cooperative Oncology Group; RSE, relative standard error; SS, steady state.
[a] Estimated hazard ratio of comparator:reference (for categorical predictors) or per unit change in value (continuous predictors)
[b] Relative standard error
[c] 95% confidence interval
Source: Report ANTX-Proj1-24-0002 Table 15

Table 84. Applicant - Parameter Estimates: E-R of AEs Leading to Dose Modification

Predictor	Hazard Ratio[a]	RSE (%)[b]	95% CI[c]	p value
Sex (Female:Male)	1.3931	12.2	0.99718–1.9463	0.05196

Predictor	Hazard Ratio[a]	RSE (%)[b]	95% CI[c]	p value
Age [yr]	1.0075	0.7	0.99433–1.0209	0.2651
Race (Asian:Caucasian)	0.63032	35.3	0.40751–0.97497	0.03809
Race (Other:Caucasian)	1.2380	24.7	0.68003–2.2538	0.4849
Baseline Weight [kg]	0.99413	0.6	0.98163–1.0068	0.3617
Baseline Albumin [g/L]	0.99869	1.5	0.96933–1.0289	0.9314
Baseline ECOG (1+:0)	1.0133	16.8	0.72626–1.4137	0.9382
Cavg at SS [ng/mL]	1.0017	0.1	1.0007–1.0027	0.0009980

Abbreviations: AE, adverse event; Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; E-R, exposure-response; ECOG, Eastern Cooperative Oncology Group; RSE, relative standard error; SS, steady state.
[a] Estimated hazard ratio of comparator:reference (for categorical predictors) or per unit change in value (continuous predictors)
[b] Relative standard error
[c] 95% confidence interval
Source: Report ANTX-Proj1-24-0002 Table 16

Table 85. Applicant - Parameter Estimates: E-R of Grade ≥ 3 TEAE

Predictor	Hazard Ratio[a]	RSE (%)[b]	95% CI[c]	p value
Sex (Female:Male)	1.0688	13.9	0.79966–1.4286	0.6529
Age [yr]	1.0072	0.6	0.99584–1.0187	0.2147
Race (Asian:Caucasian)	0.46788	42.6	0.31662–0.69140	0.0001378
Race (Other:Caucasian)	1.2710	20.2	0.76889–2.1010	0.3497
Baseline Weight [kg]	0.98642	0.6	0.97538–0.99759	0.01726
Baseline Albumin [g/L]	0.96881	1.4	0.94410–0.99417	0.01623
Baseline ECOG (1+:0)	1.1173	13.8	0.82672–1.5101	0.4704
Cavg at SS [ng/mL]	1.0017	0.0	1.0007–1.0026	0.0003880

Abbreviations: Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; E-R, exposure-response; ECOG, Eastern Cooperative Oncology Group; RSE, relative standard error; SS, steady state; TEAE, treatment-emergent adverse event.
[a] Estimated hazard ratio of comparator:reference (for categorical predictors) or per unit change in value (continuous predictors)
[b] Relative standard error
[c] 95% confidence interval
Source: Report ANTX-Proj1-24-0002 Table 17

Table 86. Applicant - Parameter Estimates: E-R of Grade ≥ 3 ALT/AST AE

Predictor	Hazard Ratio[a]	RSE (%)[b]	95% CI[c]	p value
Sex (Female:Male)	1.4617	22.8	0.75962–2.8126	0.2557
Age [yr]	1.0126	1.3	0.98755–1.0383	0.3276
Race (Asian:Caucasian)	1.1349	41.1	0.45475–2.8323	0.7862
Race (Other:Caucasian)	1.7324	36.5	0.50110–5.9892	0.3853
Baseline Weight [kg]	0.98728	1.3	0.96252–1.0127	0.3232
Baseline Albumin [g/L]	1.0014	2.9	0.94622–1.0597	0.9623
Baseline ECOG (1+:0)	1.0616	30.2	0.56676–1.9886	0.8519
Cavg at SS [ng/mL]	1.0014	0.1	0.99976–1.0030	0.09424

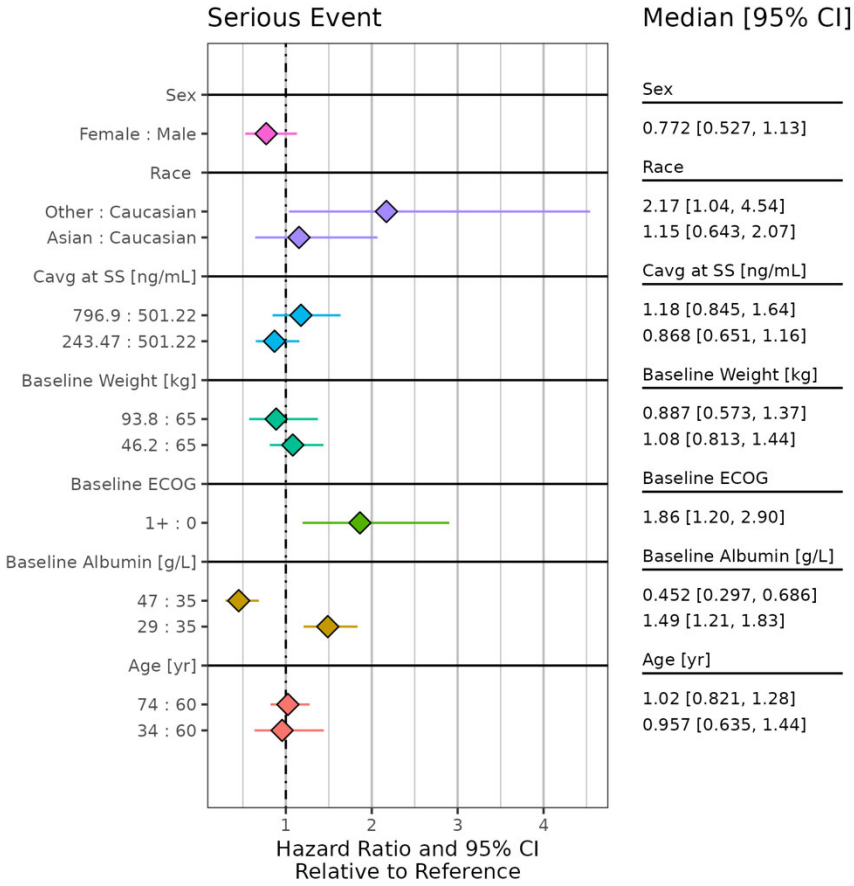
Abbreviations: AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; Cavg = time-averaged concentration in a dosing interval; CI = confidence interval; E-R = exposure-response; ECOG = Eastern Cooperative Oncology Group; RSE = relative standard error; SS = steady state.
[a] Estimated hazard ratio of comparator:reference (for categorical predictors) or per unit change in value (continuous predictors)
[b] Relative standard error
[c] 95% confidence interval
Source: Report ANTX-Proj1-24-0002 Table 18

Table 87. Applicant - Parameter Estimates: E-R of Grade ≥ 2 Gastrointestinal AE

Predictor	Hazard Ratio[a]	RSE (%)[b]	95% CI[c]	p value
Sex (Female:Male)	1.5355	12.8	1.0452–2.2557	0.02887
Age [yr]	1.0090	0.8	0.99410–1.0241	0.2380
Race (Asian:Caucasian)	0.66312	37.4	0.40781–1.0783	0.09768
Race (Other:Caucasian)	1.2782	26.0	0.66694–2.4495	0.4596
Baseline Weight [kg]	1.0013	0.7	0.98786–1.0149	0.8522
Baseline Albumin [g/L]	0.95958	1.8	0.92774–0.99252	0.01656
Baseline ECOG (1+:0)	1.0694	19.0	0.71758–1.5937	0.7417
Cavg at SS [ng/mL]	1.0001	0.1	0.99903–1.0012	0.8134

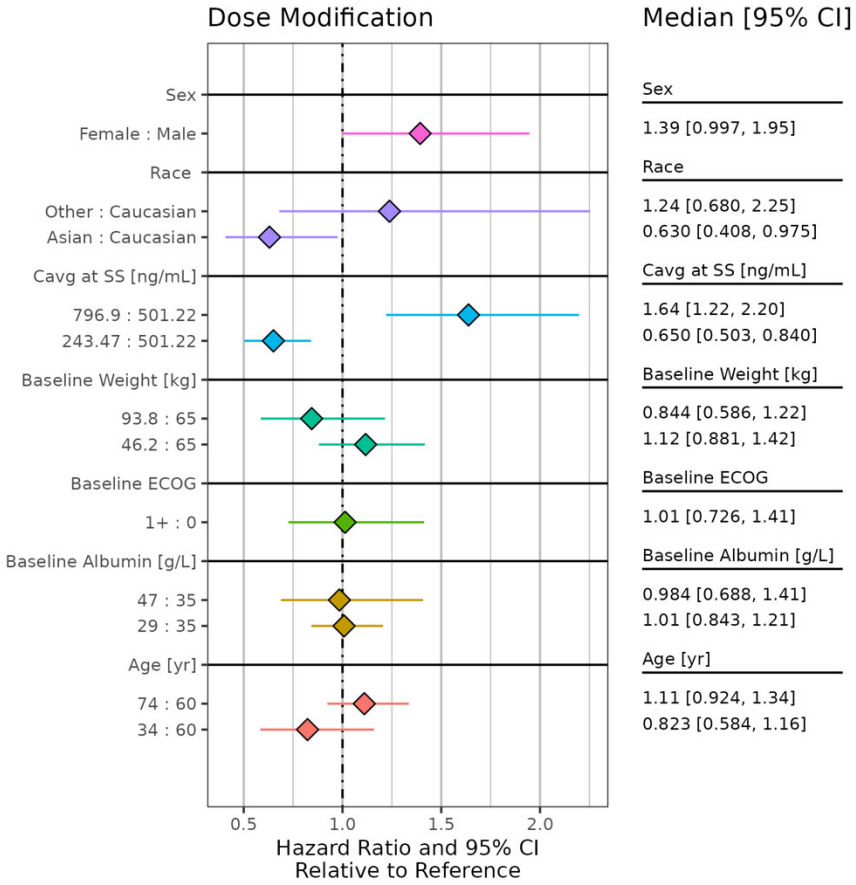
Abbreviations: AE, adverse event; Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; RSE, relative standard error; SS, steady state.
[a] Estimated hazard ratio of comparator:reference (for categorical predictors) or per unit change in value (continuous predictors)
[b] Relative standard error
[c] 95% confidence interval
Source: Report ANTX-Proj1-24-0002 Table 19

Figure 36. Applicant - Hazard Ratio Relative to Reference in 405 Patients Forest Plot of Serious AEs



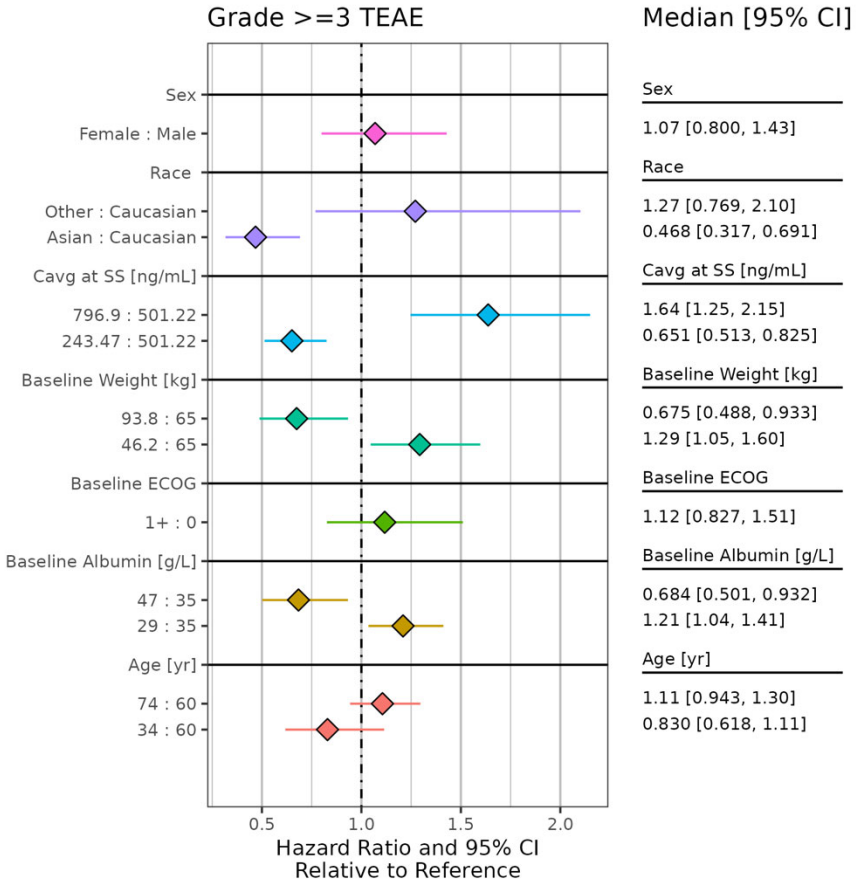
Abbreviations: AE, adverse event; Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SS, steady state.
Source: Report ANTX-Proj1-24-0002 Figure 15.

Forest Plot of AEs Leading to Dose Modification



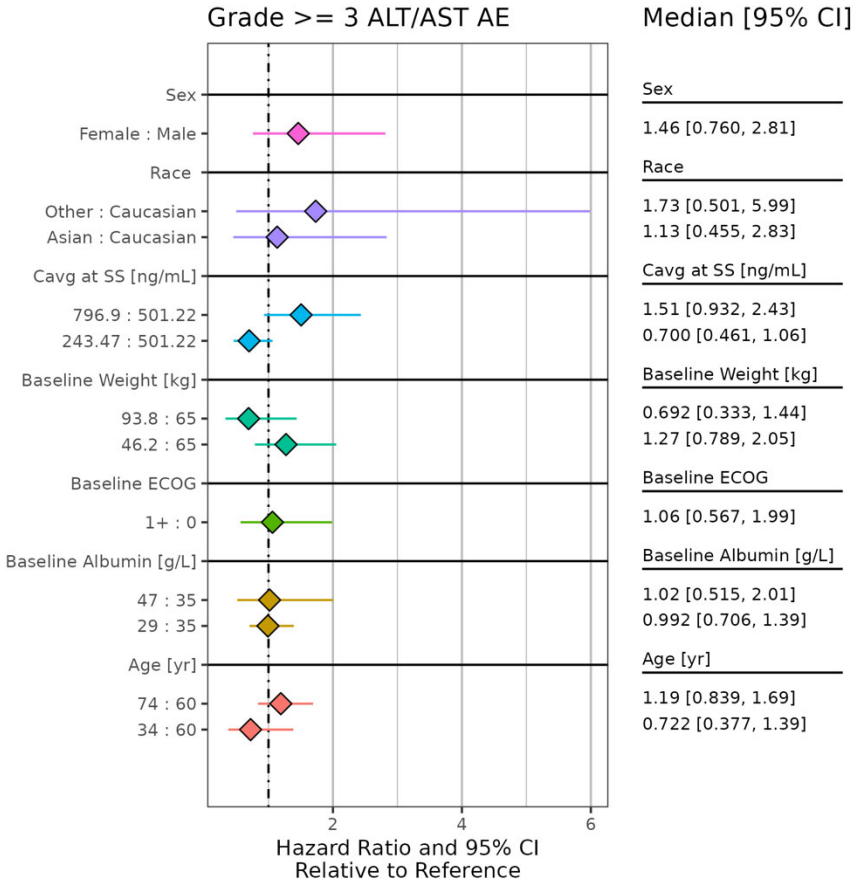
Abbreviations: AE, adverse event; Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SS, steady state.
Source: Report ANTX-Proj1-24-0002 Figure 17

Forest Plot of Grade ≥ 3 TEAE



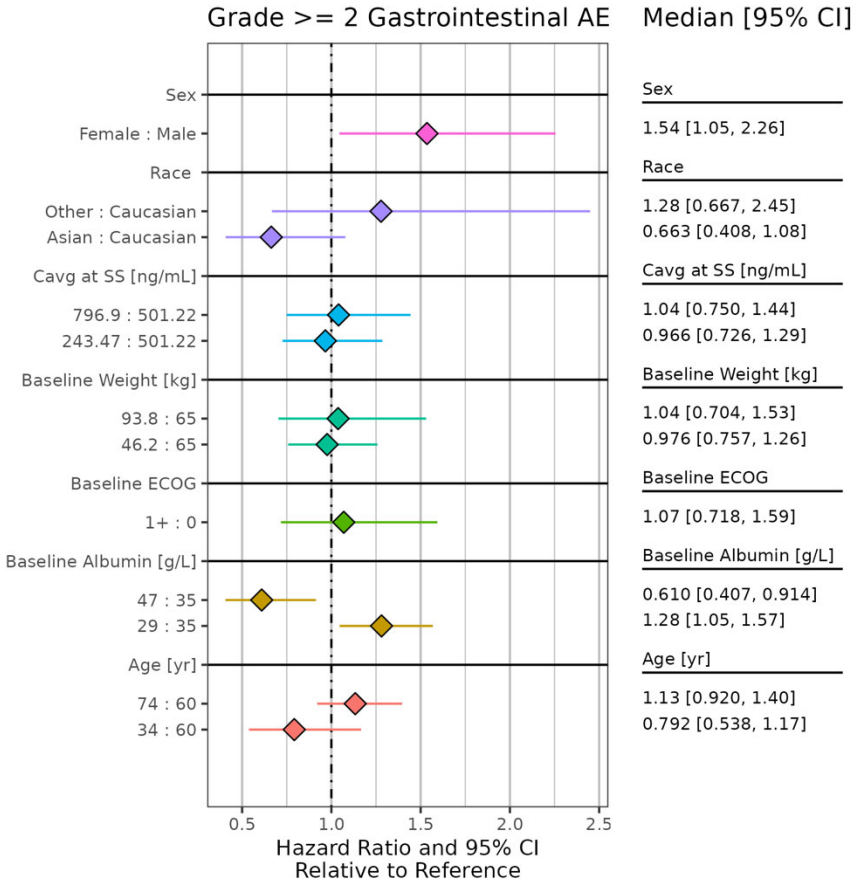
Abbreviations: Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SS, steady state; TEAE, treatment-emergent adverse event.
Source: Report ANTX-Proj1-24-0002 Figure 19.

Forest Plot of Grade ≥ 3 ALT/AST AE



Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; Cavg, timeaveraged concentration in a dosing interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SS, steady state
Source: Report ANTX-Proj1-24-0002 Figure 21.

Forest Plot of Grade ≥ 2 Gastrointestinal AE



Abbreviations: AE, adverse event; Cavg, time-averaged concentration in a dosing interval; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; SS, steady state.
Source: Report ANTX-Proj1-24-0002 Figure 23.

The FDA's Assessment:
Based on the E-R analysis results — a flat E-R relationship for efficacy and a positive E-R relationship for safety — the dosage does not appear to be optimized. With 400 mg QD, an improvement in safety is expected, although the magnitude of risk reduction is predicted to be smaller than the variability with just 600 mg QD which may likely be improved when drug is taken under fed conditions.

19.4.5.1. ER Review Issues

E-R analyses were updated to incorporate data from cohort5 randomized to 400 mg and 600 mg dosage by the Applicant. The analyses results and conclusions were minimally impacted.

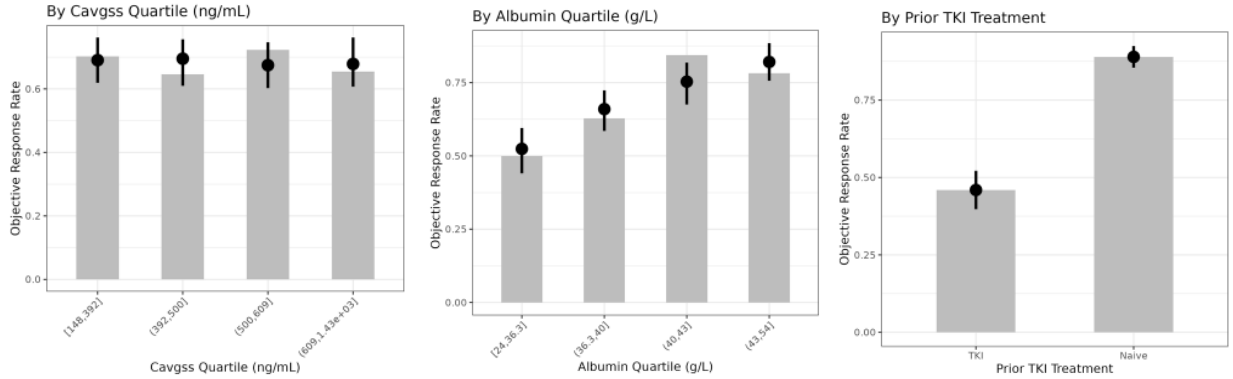
Limited data errors were corrected for E-R analysis for AST/ALT elevation, and the updated parameter estimates provided by the Applicant are attached below (**Table 88**). E-R for efficacy graph was not attached and thereby was supplied by the Reviewer (**Figure 37**); the VPC graphs represent the updated model that includes albumin as an additional significant covariate.

Table 88. Applicant - Parameter Estimates: E-R of Grade ≥ 3 ALT/AST AE (Updated)

Predictor	Hazard Ratio[a]	95% CI[c]	p value
Sex (Female:Male)	1.5369	0.85253–2.7707	0.1529
Age [yr]	1.0000	0.97922–1.0213	0.9977
Race (Asian:Caucasian)	0.60743	0.30216–1.2211	0.1617
Race (Other:Caucasian)	2.3820	1.0691–5.3070	0.03371
Baseline Weight [kg]	0.98154	0.96078–1.0028	0.08776
Baseline Albumin [g/L]	1.0087	0.96063–1.0593	0.7271
Baseline ECOG (1+:0)	0.97921	0.58100–1.6503	0.9371
Cavgss [ng/mL]	1.0018	1.0005–1.0032	0.006487

Source: Report NUV-Proj1-24-0005 Table 15

Figure 37. Applicant - VPC Plots of the Updated E-R Model of ORR



Source: Report NUV-Proj1-24-0005 Figure 25. The bar represents the observed data. The dot represents the predicted median and the error bar represents the 90% prediction interval.

19.4.5.2. Reviewer's Independent Analysis

A 30% increase in exposure was observed in Asian patients, which aligned with a lower MTD compared to White patients. To evaluate the impact of race on safety, further analyses were conducted by the Reviewer. Overall, the increase in AST/ALT risk and dose reductions related to hepatobiliary toxicity aligns with exposure increase in Asian patients.

Race effect on AST/ALT elevation

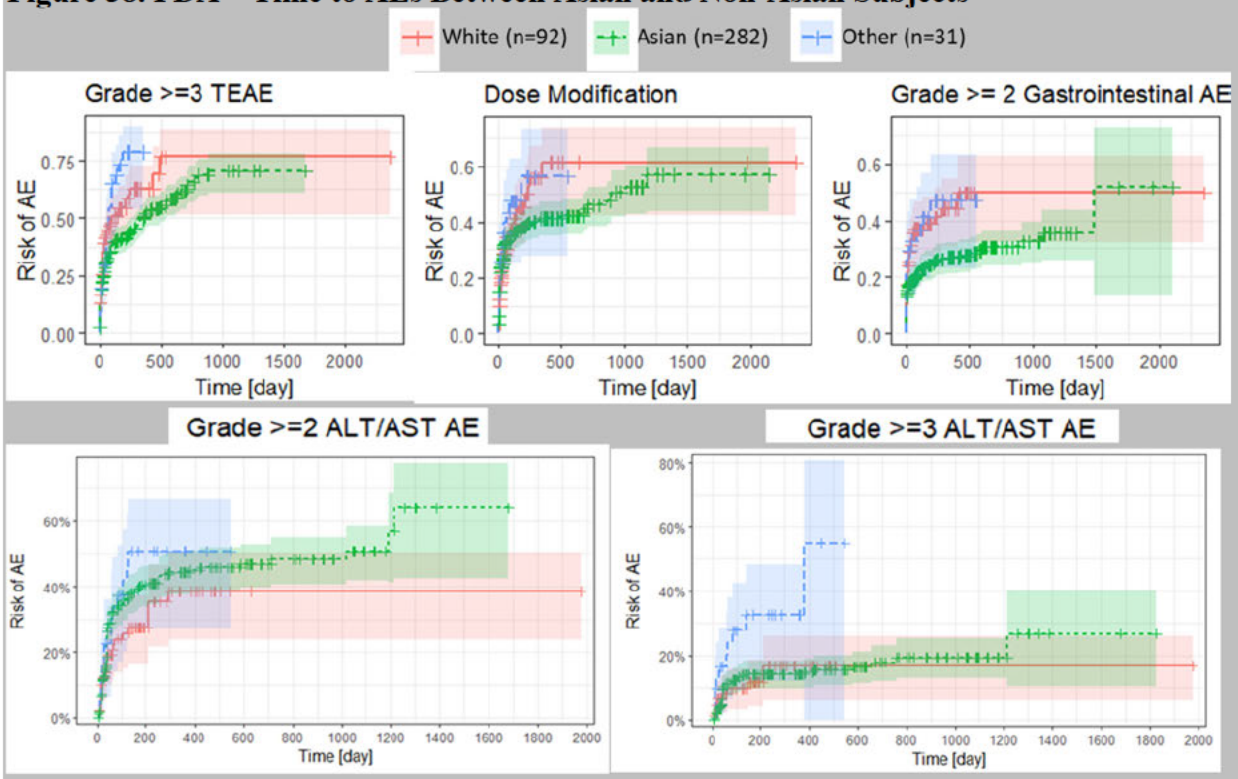
In Asian patients with elevated exposure, an increase in AE risk is expected based on E-R relationships. As shown in **Figure 38**, a higher rate of Gr≥2 AST/ALT elevation was observed in Asian patients compared to White patients, while the rate of Gr≥3 AST/ALT elevation was not apparently different likely due to fewer events and a substantial censoring in White patients. In contrast, the rates of Gr≥3 TEAEs, dose modification, and Gr≥2 GI AEs were lower in Asian patients, indicating that the differences in these AEs were determined by other factors than exposure. Concordantly, in multivariate E-R analysis conducted by the Applicant for Gr≥3 TEAEs and dose modifications, Asian race was identified as a significant covariate with a prominent risk reduction. For Gr≥2 AST/ALT elevation, Asian race nor other patient factors was identified as significant covariates, suggesting that the elevation of AST/ALT risk was determined by exposure increase.

Dose reduction due to AE by race

Dose modifications including interruptions and reductions could be attributed to different toxicities and thus were further evaluated. It was noted that in the global study G208, the proportion of patients with dose reductions was higher in Asian patients than White patients, indicating a greater need for dose reduction likely due to elevated exposure. When incorporating study C203, the trend reversed, indicating a lower proportion of dose reductions in the China only study (**Figure 39**).

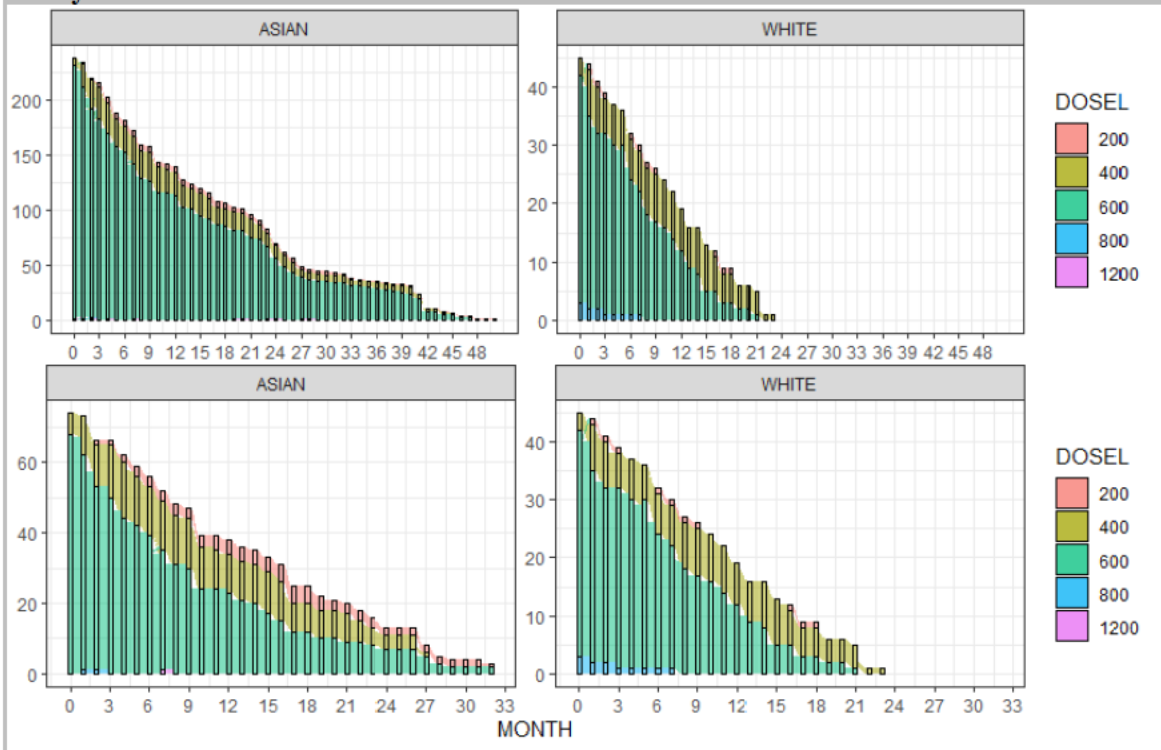
In study C203, the main reason for dose reductions in Asian patients was hepatobiliary AEs. In study G208, the main reason for dose reduction was also hepatobiliary AEs, which accounted for similar proportion between Asian and White patients. Notably, dose reductions due to GI AEs were higher in White patients than Asian patients, which was not likely related to elevated exposure (**Figure 40**). Given that hepatobiliary AEs (main clinically relevant adverse event for dose reductions) was not disproportionally exacerbated in Asian patients, specific instructions or further assessment are not required for Asian race, especially under frequent AST/ALT monitoring as proposed in the labeling.

Figure 38. FDA – Time to AEs Between Asian and Non-Asian Subjects



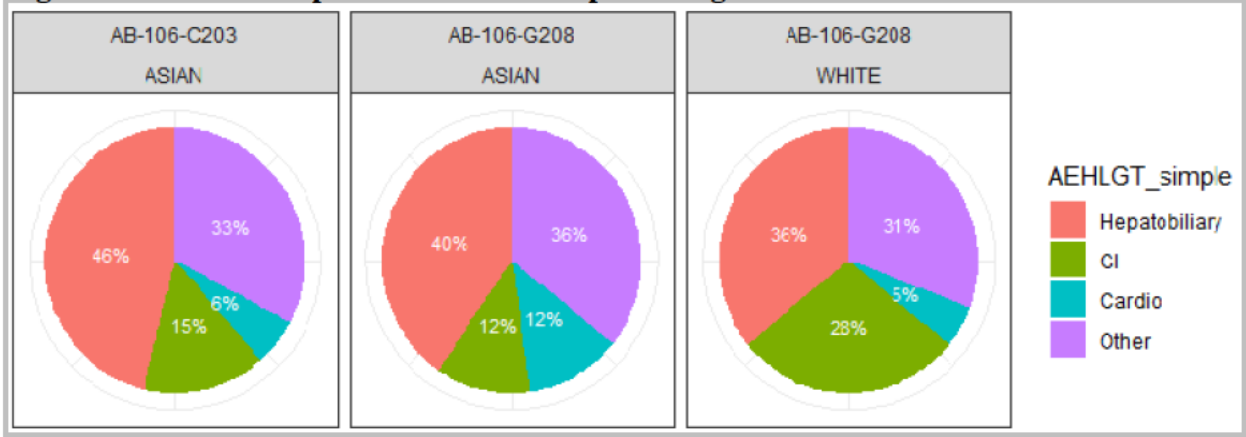
Source: Reviewer's analysis. E-R for safety dataset was used in the analysis. ALT/AST AEs events based on lab were corrected for limited data errors.

Figure 39. FDA - Dose Survey Every Month for the Pooled Data (G208 and C203) and Study G208 Alone



Source: Reviewer's analysis. Top: pooled data of study G208 and C203. Bottom: study G208.

Figure 40. FDA - Composition of AE Group Leading to Dose Reduction



Source: Reviewer's analysis. High level group term was used to summarize AE category.

19.4.5.3. Overall Benefit-Risk Evaluation Based on E-R Analyses

The Applicant's Position:

The ER analyses indicate that the 600 mg QD dose provides exposures within the efficacious range. The exposure range achieved with the 600 mg QD dosing regimen appears to be appropriate across diverse participant populations. There is no apparent benefit to higher exposures from an efficacy standpoint or a need to reduce the dose for safety reasons. Taking into the consideration the overall benefit/risk, the 600 mg QD dose appears to provide acceptable safety and efficacy.

The FDA's Assessment:

The dosage does not appear to be optimized given a flat E-R relationship for efficacy and positive E-R relationship for safety. With 400 mg QD, an improvement in safety is expected. In alignment with the model prediction, safety was improved comparing 400 mg to 600 mg based on G208 cohort 5 data. The ORR in TKI naïve patients appears comparable between the two dosages; however, a numerical ORR reduction in patients previously treated with TKI was observed with the 400 mg dosage. This observation is limited by the small sample size (n=~15) and could be potentially confounded by baseline imbalance where the 400 mg arm had a larger proportion of patients who had received 2 or more lines of prior ROS1 TKI.

Taken together, 400 mg QD is a promising dosage that may improve benefit risk ratio. Due to the small sample size, further evaluation is warranted. As discussed in the popPK section (**19.4.3**), the PK variability and GI toxicity for taking taletrectinib under 2-hour fast could be lowered by taking the drug with standard meals, although the current assessment was unable to propose a dosage from an exposure matching perspective. Therefore, the FDA recommends 400 mg QD with standard meals to be evaluated in a PMR study for the purpose of dosage optimization.

19.4.6. FDA Physiologically Based Pharmacokinetic Modeling Review

19.4.6.1. Executive Summary

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

- evaluate the drug-drug interaction (DDI) potential of taletrectinib as a substrate of strong, moderate and weak CYP3A inhibitors at the therapeutic dose (600 mg) in Western healthy subjects
- evaluate the DDI potential of taletrectinib as a substrate of strong, moderate and weak CYP3A inducers in Western healthy subjects

- evaluate the DDI potential of taletrectinib as a precipitant of CYP3A, CYP2D6, P-gp, OATP1Bs and BCRP, and an inducer of CYP3A and CYP1A2 at the therapeutic dosing regimen (600 mg once daily) in Western healthy subjects

The Division of Pharmacometrics has reviewed the PBPK reports (ANHE/1/F) and related model summary reports, responses to FDA Clinical Pharmacology PBPK information requests dated January 8, 2025 (seq0015), February 21, 2025 (seq0030) and March 14, 2025 (seq0037), and the modeling supporting files, and concluded that:

- The taletrectinib PBPK model could be used to predict the effects of inhibitors or inducers on taletrectinib exposure in Western subjects:
    - The moderate CYP3A inhibitors fluconazole, erythromycin and verapamil were predicted to increase taletrectinib AUC up to 2.6-fold following administration of a single 600 mg taletrectinib.
    - The weak CYP3A inhibitor cimetidine was predicted to have a minimal effect on taletrectinib exposure.
    - The strong CYP3A inducer rifampin was predicted to reduce taletrectinib AUC by approximately 88%.
    - The moderate CYP3A inducer efavirenz was predicted to reduce taletrectinib AUC by approximately 66%.
    - The weak CYP3A inducer modafinil was predicted to have a minimal effect on taletrectinib exposure.
- Taletrectinib was predicted to increase AUC of desipramine and dextromethorphan up to 2-, and 5-fold, respectively, when taletrectinib 600 mg once daily was co-administered with desipramine or dextromethorphan in general cancer patients.
- The potential interaction of taletrectinib with substrates of OATP1B and/or BCRP cannot be ruled out.
- The potential interaction of taletrectinib on substrates of CYP3A and CYP1A2 cannot be confidently predicted due to the uncertainties about extrapolating in vitro induction parameters to in vivo.
- The potential interaction of taletrectinib with MATE1 substrates cannot be confidently predicted. The ability of metformin model to predict MATE1 inhibition has not been well verified because the in vitro to in vivo extrapolation of MATEs/OCTs inhibition parameter K_i value has not been established.

19.4.6.2. Method

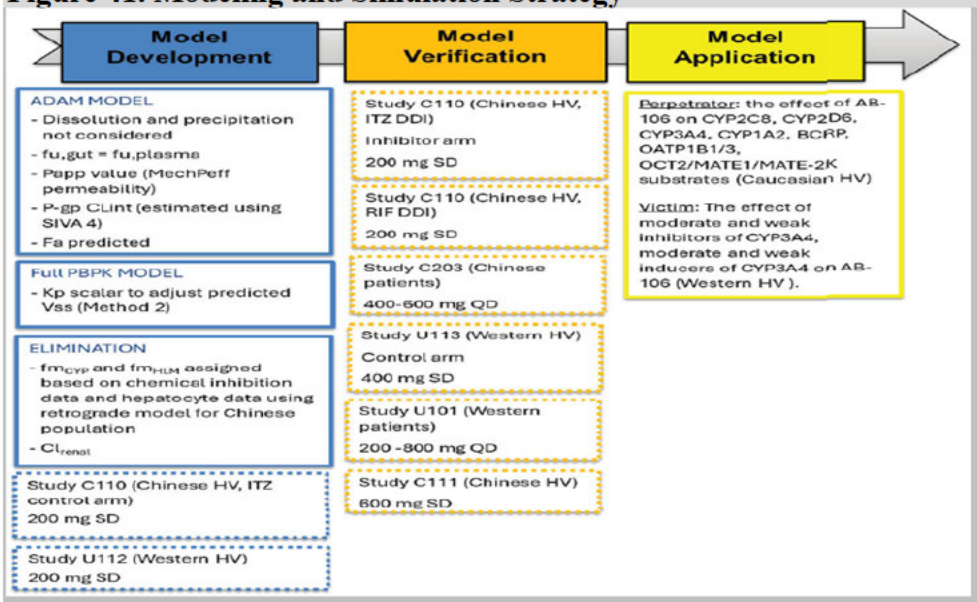
All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (versions 21 and version 23, Certara, Sheffield, UK). Simulations were performed using sim-NEurCaucasian and sim-Chinese models, assuming that disease state has no effects on taletrectinib PK. This assumption is supported by the population PK analysis (Report ANTX-Proj1-24-0002). Schemes of the PBPK modeling and simulation strategy are shown in **Figure 41**, which summarizes the studies used for taletrectinib model development and verification, and model applications in predicting DDI of taletrectinib as a victim of CYP3A4 induction or inhibition and as a perpetrator of various transports and CYP enzymes. The final model input parameters were summarized in **Table 89**. The taletrectinib PBPK model consists of an Advanced Dissolution, Absorption and Metabolism (ADAM) model for describing drug absorption in each gut segment, a full PBPK model (method 2) for distribution, and an enzyme kinetics model and renal clearance for elimination. The Simcyp Version 21 library files itraconazole soln_fasted, erythromycin, verapamil, fluconazole, cimetidine, efavirenz, dexamethasone, midazolam, repaglinide, caffeine, desipramine, dextromethorphan, metformin, and pravastatin except for rifampin and rosuvastatin were used without any modification unless otherwise noted. A rifampin file (SV-Rifampicin-MD) from version 23 and the rosuvastatin model published by Costales et al (PMID: 34164937) were also used in the simulations.

The Applicant provided the following verification documents at the FDA's request.

- The Applicant provided the data used for development and validation of the Sim-Chinese population model. The model could reasonably reproduce the alprazolam concentration-time profiles and PK parameters following a single 0.5 mg dose given intravenously or orally to Chinese healthy subjects. This population model could also describe the PK of midazolam in Chinese subjects with different CYP3A5 genotype following intravenous or oral administration of various single doses of midazolam (NDA 219713 - RFI6 dated 08Jan2025_Q34_FINAL).

- The Applicant simulated the rosuvastatin interaction studies using the rosuvastatin model published by Costales et al (PMID: 34164937) and submitted the verification files as requested by the FDA. With the exception of the 0.25 mg dose, the model could reasonably simulate the rosuvastatin plasma concentration time profiles and AUCs following oral administration of single doses of rosuvastatin ranging from 0.05 mg to 80 mg. However, the model tended to underpredict the C_{max} of rosuvastatin. Additionally, the model reasonably predicted the impact of SLCO1B1 or ABCG2 genotype on rosuvastatin PK (1.11.3 NDA 219713 IR20 ClinPharm - Resp to FDA IR dated 21Feb2025_FINAL). Therefore, the rosuvastatin model is considered adequate for predicting taletrectinib on OATP1B and BCRP.

Figure 41. Modeling and Simulation Strategy



ADAM: Advanced Dissolution, Absorption and Metabolism; CLint: intrinsic clearance; fm: fraction metabolised; fugut: fraction unbound in the gut, i.e., within the enterocyte; HV: healthy volunteer; ITZ: itraconazole; Kp: tissue-plasma partition coefficient; Papp: apparent permeability; RIF: rifampicin; SD: single dose; SIVA: Simcyp In Vitro Data Analysis toolkit; VSS: volume of distribution at steady state.
Source: Figure 1 in the PBPK report ANHE/1/F

Table 89. Final Input Parameters in the Taletrectinib Model

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	405.47	Investigator's Brochure, Version 7 (Nov 2022)
Log P	3.56	Reported as > 3.56; Report PF124073-02
Compound type	Diprotic base	Assigned based on chemical structure
pKa	5.39 (b), 8.65 (b)	Report PF124073-02
B:P	1.34	Average from B:P measured at 3 concentrations; Report 423090-20221012-BPR
fu	0.049	Average from fu measured at 2 *in vivo* relevant concentrations (100 ng/mL and 1000 ng/mL); Report VPT1218/2013
Main binding protein	HSA	Assumed
Absorption Model – ADAM Model		
fu_{gut}	0.049	Defined same as fu
$P_{eff,man}$ (pred) ($x10^{-4}$ cm/s)	1.097	Predicted from $P_{trans,0}$ (MechPeff model)
$P_{trans,0}$ ($x10^{-6}$ cm/s)	1345	Adjusted to match predicted $P_{eff,man}$ from Caco-2 permeability data (fitted Caco-2 P_{app} in SIVA: 4.91 ($x10^{-6}$ cm/s))
P-gp $CL_{int,T}$ (µL/min)	23.0	Estimated in SIVA 4 from Caco-2 permeability data (DMPK Study 423090-20210624)
RAF (Relative activity factor)	1	Assumed
fu_{inc}	1	Assumed
Formulation type	Solution	Assumed based on excellent solubility in the low pH environment (stomach)
Distribution Model – Full PBPK Model		
V_{SS} (L/kg)	49.4	PE using Wt=1/(yhat*yhat) error model with clinical data from Clinical Study C110 (200 mg single dose, itraconazole control arm)
K_p scalar	5.41	Used to adjust predicted V_{SS} (Method 2) to the estimated V_{SS} from PE
Elimination Parameters		
CL/F (L/h)	83.35	Clinical Study C110 (Itraconazole control arm); geomean value
CYP3A4 CL_{int} (µL/min/pmol)	2.77	Retrograde model. CL/F obtained from Clinical Study C110 (83.35 L/h); CYP3A4, CYP2C8, CYP2C9 and acetylation contribute 78.4, 2.85, 1.54 and 17.2% to total systemic metabolic clearance respectively.
CYP2C8 CL_{int} (µL/min/pmol)	1.948	
CYP2C9 CL_{int} (µL/min/pmol)	0.084	
Additional HLM CL_{int} (µL/min/mg)	69.824	
CL_R (L/h)	3.59	Estimated from Clinical Study U112 data (geomean value)

PARAMETER	Value	Reference
Interaction Parameters		
CYP3A4 K_i (µM)	2.3	Report VPT1184/2013
CYP2C8 K_i (µM)	0.98	Report VPT1184/2013
CYP2D6 K_i (µM)	0.52	Report VPT1184/2013
CYP2C9 K_i (µM)	21	Report VPT1184/2013
fu_{mic} of CYP K_i	0.895	Predicted
OATP1B1 K_i (µM)	4.71	DMPK Study 423090-20210624 (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
OATP1B3 K_i (µM)	17.6	DMPK Study 423090-20210624 (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
OCT2 K_i (µM)	18.0	DMPK Study 423090-20210624 (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
OAT1 K_i (µM)	15.4	DMPK Study 423090-20210624 (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
OAT3 K_i (µM)	61.1	DMPK Study 423090-20210624 (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
MATE1 K_i (µM)	0.162	Liver and kidney; DMPK Study 423090-20210624 (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
MATE2-K K_i (µM)	0.154	Kidney; DMPK Study 423090-20210624 (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
P-gp K_i (µM)	2.29	Gut, liver and kidney; Report 423090-20210624-MDPGPI (assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
BCRP K_i (µM)	4.34	Gut and liver; Report 423090-20210624-BCRP (Assumption: K_M is high and [S] is low, so $IC_{50}=K_i$)
fu_{inc} of transporter K_i	1	Assumed
CYP3A4 Ind_{max}	3.71	Estimated from *in vitro* data (Simple 3-Parameter E_{max} model); Report 423090-20210624-HI
CYP3A4 $IndC_{50}$ (µM)	6.52	Estimated from *in vitro* data (Simple 3-Parameter E_{max} model); Report 423090-20210624-HI
CYP1A2 Ind_{max}	2.98	Estimated from *in vitro* data (Simple 3-Parameter E_{max} model); Report 423090-20210624-HI
CYP1A2 $IndC_{50}$ (µM)	0.456	Estimated from *in vitro* data (Simple 3-Parameter E_{max} model); Report 423090-20210624-HI
fu_{inc} of CYP $IndC_{50}$	0.623	Predicted

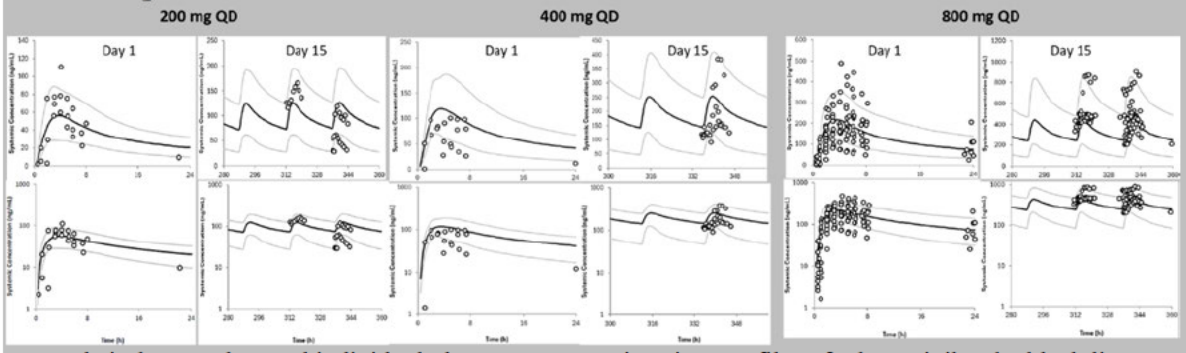
Source: Table 7 in the PBPK report ANHE/1/F

19.4.6.3. Review Questions

1. Can the PBPK model adequately describe the PK profiles of taletrectinib?

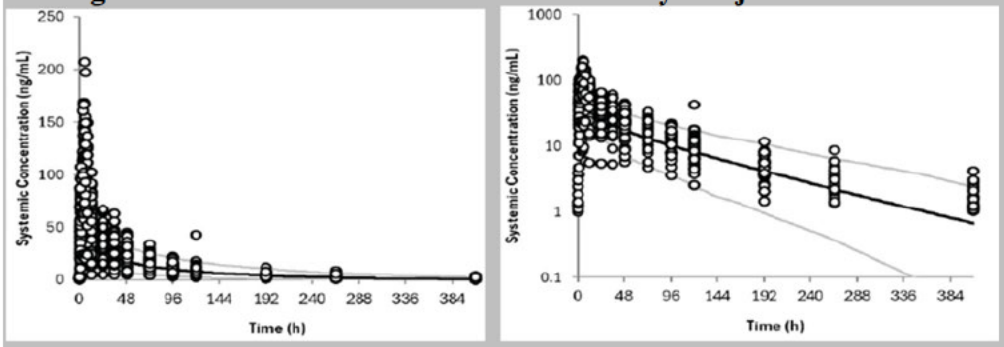
Yes. Clinical PK data that had not been used in model development was used to verify the taletrectinib PBPK model. The model could reasonably describe the plasma concentration-time profiles of taletrectinib following single and multiple oral doses of taletrectinib in Western patients and healthy subjects (**Figure 42** and **Figure 43**). The model-estimated AUC were mostly within 0.8- and 1.25-fold of the observed values, but the C_{max} values were mostly underpredicted (**Table 90** and **Table 91**).

Figure 42. Simulated and Observed Plasma Concentrations of Taletrectinib After Single and Multiple Doses of Taletrectinib in Western Patients With Cancer



Opened circles are observed individual plasma concentration-time profiles of taletrectinib. The black line represents the simulated mean plasma concentration-time profiles of taletrectinib; gray lines represent the simulated 5th and 95th geometric percentiles of the simulations.
Source: Figures 17 - 22 in the PBPK report ANHE1F

Figure 43. Simulated and Observed Plasma Concentrations of Taletrectinib After Single 400 mg Dose of Taletrectinib in Western Healthy Subjects



Opened circles are observed individual plasma concentration-time profiles of taletrectinib. The black line represents the simulated mean plasma concentration-time profiles of taletrectinib; gray lines represent the simulated 5th and 95th geometric percentiles of the simulations.
Source: Figure 23 in the PBPK report ANHE1F

Table 90. Simulated and Observed Geometric Mean for C_{max} and AUC of Taletrectinib After Single and Multiple Doses of Taletrectinib in Western Patients With Cancer

Dosing regimen		Cycle 1, Day 1				Cycle 1, Day 15		
		AUC_{0-24} (ng.h/mL)	C_{max} (ng/mL)	t_{max}* (h)	AUC_{0-8} (ng.h/mL)	AUC_{0-8} (ng.h/mL)	C_{max} (ng/mL)	t_{max}* (h)
200 mg QD	Simulated	797	57.6	3.70	345	904	128	3.50
	Observed	738	89.1	4.02	337	695	116	2.02
	Sim./Obs.	1.08	0.65	0.92	1.02	1.30	1.10	1.73
400 mg QD	Simulated	1665	123	3.35	732	1804	257	3.22
	Observed	1230	98.8	5.02	370	1390	279	5.00
	Sim./Obs.	1.35	1.24	0.67	1.98	1.30	0.92	0.64
800 mg QD	Simulated	2957	221	3.50	1318	3141	450	3.30
	Observed	3160	228	4.02	1100	3420	526	4.01
	Sim./Obs.	0.94	0.97	0.87	1.20	0.92	0.86	0.82

Source observed data: Clinical Study U101
Source: Tables 14 -16 in the PBPK report ANHE1F

Table 91. Simulated and Observed Geometric Mean for C_{max} and AUC of Taletrectinib After Single 400 mg Dose of Taletrectinib in Western Healthy Subjects

	AUC_{0-408} (ng.h/mL)	C_{max} (ng/mL)	t_{max}* (h)
Simulated	3129	89.4	3.50
Observed	3733	84.8	5.00
S/O	0.84	1.05	0.70

Source observed data: Clinical Study U113.
Source: Tables 17 in the PBPK report ANHE1F

2. **Can PBPK analyses predict the effects of CYP3A perpetrators on the PK of taletrectinib?**

Yes. The taletrectinib PBPK model could be used to predict the effects of CYP3A inhibitors or inducers. The moderate CYP3A inhibitors were predicted to increase taletrectinib AUC 2- to 3-fold. The moderate CYP3A inducer efavirenz were predicted to decrease taletrectinib AUC by 66%. The weak CYP3A inhibitor cimetidine and the weak CYP3A inducer modafinil were predicted to have a minimal effect on taletrectinib exposure (**Table 92**). See detailed discussion in the comments below.

Table 92. Predicted C_{max} and AUC Ratio of Drug-Drug Interactions With a Single Dose of Taletrectinib 600 mg as a Victim in Western Healthy Subjects

Categories	Perpetrator	C_{max} Ratio	AUC† Ratio	Study Type
Strong CYP3A inhibitor	Itraconazole 200 mg QD	1.76	3.28	Observed*
		1.45	2.65	Simulated*
		0.83	0.81	Sim/Obs
		1.55	3.44	Simulated
Moderate CYP3A inhibitor	Fluconazole 200 mg QD	1.24	1.91	Simulated
	Erythromycin 500 mg TID	1.25	2.10	
	Verapamil 80 mg TID	1.51	2.64	
Weak CYP3A inhibitor	Cimetidine 400 mg TID	1.11	1.22	
Strong CYP3A inducer	Rifampicin 600 mg QD	0.58	0.14	Observed*
		0.37	0.15	Simulated*
		0.63	1.13	Sim/Obs
		0.29	0.12	Simulated
Moderate CYP3A inducer	Efavirenz 600 mg QD	0.60	0.34	Simulated
Weak CYP3A inducer	Modafinil 200 mg QD	0.94	0.82	

*.Studies were conducted in Chinese healthy subjects.
Source: PBPK report ANHE1F

- To predict the effects of CYP3A inhibitors and inducers on taletrectinib PK, the fraction metabolized by CYP3A ($f_{m,CYP3A}$) is one of the key parameters that need to be verified in the taletrectinib PBPK model. The f_m values of taletrectinib were determined using *in vitro* hepatocyte and chemical inhibition data. A hepatocyte metabolism study (VPT1406/2013) showed that the primary metabolic pathway for taletrectinib was oxidation, comprising approximately 52.4% of the total metabolism in human hepatocytes. This was followed by acetylation and N-dealkylation, accounting for approximately 17.2% and 9.2% of, the total metabolism, respectively. Separately, a chemical inhibition study using human liver microsomes (BWU202308) indicated that CYP3A4 was responsible for approximately 94.7% of taletrectinib metabolism. Contributions from CYP2C8 and CYP2C9 were minimal, at 3.4% and 1.9%, respectively. These results assume that inhibition values of less than 20% are insignificant and considered assay noise.

  Given that oxidation represents approximately 82.8% of the total metabolism (100% - 17.2% acetylation), the $f_{m,CYP3A}$ value for taletrectinib was calculated to be 78.4%. The taletrectinib PBPK model, incorporating this $f_{m,CYP3A}$ value, reproduced the observed effects of itraconazole on taletrectinib exposure (**Table 92**), thereby confirming the adequacy of the $f_{m,CYP3A}$ value.

- Itraconazole is an inhibitor of CYP3A and P-gp. Taletrectinib, on the other hand, is a substrate of CYP3A and P-gp. Taletrectinib exhibits low to moderate permeability (423090-20210624-caco2). The human ADME study showed that at least 82% of taletrectinib is

absorbed, assuming 100% recovery of radioactivity. These findings indicate that P-gp may influence taletrectinib absorption, and the observed PK interaction with itraconazole could be attributable to inhibition of both CYP3A and P-gp. The intrinsic clearance of P-gp efflux was incorporated in the model. Verifying the adequacy of this parameter is challenging; however, simulations using the taletrectinib model without incorporating the P-gp parameter predicted that itraconazole would increase taletrectinib AUC and C_{max} by 2.75- and 1.35-fold, respectively. These predictions aligned closely with those predicted from the model incorporating the P-gp parameter.

Rifampin, a P-gp inducer, is known to reduce the exposure of P-gp substrates through increased efflux. Although P-gp may not significantly affect taletrectinib absorption, the induction of P-gp expression by rifampin could alter the kinetics of taletrectinib absorption, particularly given its low to moderate permeability. Simulations using a rifampin model that did not account for P-gp induction underestimated the effects of rifampin on taletrectinib C_{max} and AUC by more than 2-fold. Conversely, a rifampin model incorporating P-gp induction adequately predicted the induction effects of rifampin on taletrectinib AUC but overpredicted C_{max} by less than 50% (**Table 92**). These data confirm the appropriateness of the P-gp kinetic parameter in the model.

Taken together with the simulated results of the itraconazole interaction, the taletrectinib model incorporating P-gp efflux clearance is suitable to predict the effects of CYP3A inhibitors that are also inhibitors of P-gp such as erythromycin and verapamil. This model is also applicable to predict the effects of the moderate CYP3A inducer efavirenz, which has minimal effect on P-gp (PMID: 20660679).

- For the weak CYP3A inhibitor cimetidine, its PBPK model to predict inhibitory effects of cimetidine on CYP3A substrates was inadequately verified. As shown in **Table 93**, the observed inhibitory effects of cimetidine on the exposure of CYP3A substrates were not predicted in >50-60% of the studies, even though predicted ratios of C_{max} and AUC were within 0.8- 1.25-fold of the observed values. For those that cimetidine was predicted to have inhibitory effects (>1.25 fold), its effects were generally underpredicted. The Applicant was requested to improve the prediction results by optimizing the CYP3A K_i parameter in the cimetidine model (FDA information request_10Jan2025). The Applicant reduced CYP3A K_i value from 25 μM to 11 μM, which improved the predictions except for two studies (**Table 93**). This improved cimetidine model was used to predict the interaction of cimetidine with taletrectinib (**Table 92**).

Table 93. Verification of the Cimetidine PBPK Model To Predict Its Interactions With CYP3A Substrates

Cimetidine Dosing Regimens	Dosing Regimens of CYP3A Substrates	Observed		Predicted (K_I = 25 µM)		Predicted (K_I = 11 µM)	
		$C_{max}R$	AUCR	$C_{max}R$	AUCR	$C_{max}R$	AUCR
400 mg cimetidine BID (3 doses)	Midazolam 15 mg SD (D2) (30 min	NA	1.35	1.33	1.4	1.63	1.82
400mg cimetidine SD	Midazolam 15mg SD (2 hrs after	1.37	1.37	1.23	1.26	1.46	1.55
Cimetidine 200 mg TID with 400 mg pm on D1. 200 mg on D2	Midazolam 15 mg SD (D2) 2.5h after	2.38	2.02	1.1	1.11	1.21	1.24
Cimetidine 300 mg QID for 2 days	Triazolam 0.5 mg SD (D2)	1.39	1.32	1.18	1.21	1.34	1.43
Cimetidine 200 mg TID with 400 mg pm for 9 days	Triazolam 0.5 mg QD at night for 7 days	1.51	2.2	1.25	1.3	1.45	1.6
Cimetidine 300 mg QID (4 doses)	Triazolam 0.5mg SD (1 hr after 3rd cimetidine dose)	1.35	1.55	1.18	1.22	1.35	1.46
Cimetidine 200 mg TID with 400 mg pm for 9 days	Alprazolam 0.5mg TID for 7 days and morning dose on D8	1.82	1.64	1.06	1.08	1.13	1.17
Cimetidine 800 mg QD for 5 days	Nifedipine 10 mg TID for 4 Ds, 1 dose D5	2.3	2	1.41	1.64	1.55	2.04
Cimetidine 200 mg TID with 400 mg pm for 7 days	Nifedipine 10 mg QID for 6 Ds, 1 dose D7	2.02	1.6	1.13	1.23	1.28	1.53
Cimetidine 200 mg TID with 400mg pm for 3 days	Nifedipine 20 mg SD D2 (1 hr after first cimetidine dose)	NA	1.31	1.17	1.23	1.35	1.51
Cimetidine 300 mg QID for 7 days	Nifedipine 20 mg SD D7	1.4	1.52	1.21	1.33	1.43	1.72
Cimetidine 800 mg QD for 5 days	Nifedipine 20 mg SD D5 (1hr after cimetidine)	1.65	1.77	1.56	1.74	1.96	2.42
Cimetidine 300 mg QID for 7 days	Quinidine 330 mg (free base) SD on D6	1.2	1.57	1.07	1.16	1.13	1.32
Cimetidine 300mg QID for 3 days, a.m. dose day 4	Quinidine 330 mg (free base) SD on D4	1	1.27	1.07	1.1	1.13	1.2
Cimetidine 800 mg QD for 4 days	Sildenafil 50 mg SD D3 (2 hrs after)	1.54	1.56	1.36	1.41	1.65	1.78

SD, singlde dose; BID, twice daily; QD, once daily; TID, 3 times a day; D, day; am, in the morning; pm, at the night
Source: sv-cimetidinesummary-V21-kiupdated (NDA219685 seq0023)

- For the weak CYP3A inducer dexamethasone, its PBPK model has not been adequately verified to be used to simulate the effect of a weak CYP3A inducer on taletrectinib. The effects of dexamethasone on triazolam and aprepitant were too weak (AUCR>0.8) to be used to verify its induction effect on CYP3A (Table 4 in Simcyp V21 Dexamethasone summary report). The Applicant was requested to choose an alternative inducer whose induction effects result in AUC ratios of sensitive CYP3A substrates (e.g. midazolam, triazolam, etc.) < 0.7 (FDA information request_10Jan2025). The applicant selected modafinil as a weak CYP3A inducer. The modafinil PBPK model could adequately simulated its effects on CYP3A substrates (**Table 94**). This modafinil model was used to predict the interaction of a weak CYP3A inducer with taletrectinib (**Table 92**).

Table 94. Verification of the Modafinil PBPK Model To Predict Its Interactions With CYP3A Substrates

CYP3A substrate drugs	Observed		Predicted		Observed/predicted		PMID References
	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	C_{max} Ratio	AUC Ratio	
Midazolam	0.73	0.65	0.68(0.58 to 0.76)	0.63(0.53 to 0.72)	0.93	0.97	28082902
Ethinylestradiol	0.89	0.82	0.86(0.83 to 0.89)	0.82(0.78 to 0.85)	0.97	1.00	11823757
Triazolam	0.56	0.41	0.69(0.65 to 0.74)	0.56(0.52 to 0.63)	1.24	1.37	11823757
Omeprazole	1.22	1.36	1.37(1.23 to 1.53)	1.55(1.36 to 1.81)	1.12	1.14	28082902
Omeprazole	1.54	1.85	1.40(1.20 to 1.58)	1.58(1.29 to 1.88)	0.91	0.85	28082902

Source: Simcyp V20 modafinil summary report.

3. Can PBPK analyses be used to estimate the effects of taletrectinib on substrates of CYP3A, CYP1A2, CYP2D6, OATP1B, BCRP and MATE1?

Effects of taletrectinib on the CYP3A substrate midazolam

The effect of taletrectinib on CYP3A substrates cannot be confidently predicted without additional clinical data for the reasons discussed below.

1) In vitro, taletrectinib is a reversible inhibitor and inducer of CYP3A. Following oral administration of multiple doses of taletrectinib, taletrectinib exposure increased approximately proportional to the dose. A dedicated clinical DDI study of taletrectinib with midazolam in cancer patients has not been conducted. The available clinical data are insufficient to differentiate the CYP3A inhibition or induction of taletrectinib thus the CYP3A inhibition and induction parameters of taletrectinib cannot be independently verified.

2) Following taletrectinib 600 mg QD, taletrectinib was predicted to have minimal effects on midazolam AUC_{inf} and C_{max} if both CYP3A inhibition and induction effect of taletrectinib were considered. These results were obtained by calibrating the maximum fold induction Ind_{max} of taletrectinib to the fold increase in CYP3A4 mRNA by the positive control rifampin observed at 10 μM in the hepatocyte induction study. This approach, assuming the in vitro rifampin $IndC_{50}$ value equals to 1, overlooks the variability in rifampin Ind_{max} and $IndC_{50}$ (the concentration that gives half maximal fold induction) between donors and laboratories. Specifically, rifampin's $IndC_{50}$ values vary widely, ranging from 0.09 to 40 μM across different studies (FDA internal database). Moreover, the highest concentration of taletrectinib tested in the hepatocyte induction study did not elicit the maximal response (423090-20210624-hi), suggesting that the Ind_{max} of taletrectinib may be underestimated.

Taken together, the effect of taletrectinib on CYP3A substrates cannot be confidently predicted without additional clinical data.

Induction effects of taletrectinib on CYP1A2

The PBPK analysis cannot rule out a potential induction effect of taletrectinib on CYP1A2 substrates, for reasons detailed below:

The applicant assessed the induction effect of taletrectinib's potential to induce CYP1A2 using caffeine as a probe substrate. However, the predictive reliability of PBPK analysis for CYP1A2 induction, particularly when using induction parameters derived from in vitro hepatocyte induction studies, is not well-established. In the qualification document (v20-cyp1a2-induction-qualification-nov2023) provided by the software developer, Simcyp was used to predict drug interactions of various CYP1A2 inducers with drugs predominantly metabolized by CYP1A2. The predicted and observed C_{max} and AUC ratios were compared in the CYP1A2-mediated DDI studies involving caffeine, theophylline and tizanidine with rifampin, as well as caffeine with omeprazole. The extent of induction was predicted within the range of 0.8 -1.25-fold of observed values in 5 out of 7 studies. Nevertheless, it is important to note that the induction parameters in the PBPK models for both rifampin and omeprazole were optimized using clinical DDI data. As shown in **Table 95**, induction parameters used in these models were markedly different from those generated from the mRNA of hepatocyte induction studies,

indicating significant discrepancies between in vitro and in vivo CYP1A2 induction parameters. Consequently, the potential induction effects of taletrectinib on CYP1A2 substrates cannot be reliably predicted without clinical data.

Table 95. Comparison of Model Inputted and Experimentally Measured Induction Parameters of Competitive CYP1A2 Inducers

CYP1A2 inducers	Model parameters		In vitro parameters based on mRNA		In vitro/model parameters		In vitro data source	Number of in vitro observations
	EC_{50} (μM)	E_{max} (fold)	EC_{50} (μM)	E_{max} (fold)	EC_{50}	E_{max}		
rifampin	0.1	2.7	>25*	0.16†	>250	0.1	PMID: 17639026 and 21930825	1
omeprazole	0.15	2.4	10 - 35	38 - 102	67 - 233	16 -43	PMID: 29802934; FDA Database	4

*Estimates of EC50 were above the highest tested concentration (25 μM) (PMID: 21930825);
†mean slope of the line with intercept (PMID: 21930825)
Source: response to FDA IR Clinical Pharmacology submitted 19 December 2023 (NDA217700 seq0021) and references within the table

Effects of taletrectinib on CYP2D6 substrates desipramine and dextromethorphan

Taletrectinib is expected to have weak to moderate inhibitory effects on CYP2D6 substrates in general cancer patients for reasons discussed below.

The Applicant assessed the inhibition potential of taletrectinib on CYP2D6 by applying the in vitro IC50 value generated using bufuralol as a CYP2D6 substrate (VPT1184/2013). Because substrate-dependent inhibition with CYP2D6 was observed in vitro (PMID21976621), the predicted drug interactions with desipramine or dextromethorphan need to be interpretated with caution.

The verification of the desipramine model has been discussed in the PBPK review of capivasertib (NDA218197 PBPK review). Although there is a trend towards underprediction, the overall performance of the desipramine model seems reasonable. Similarly, the dextromethorphan model can reasonably predict its interaction with quinidine, fluoxetine and cinacalcet (CYP2D6 V21 Qualification). During the capivasertib PBPK review, the reviewer found that the in vitro $K_{i,u}$ values were approximately 2- to 40-fold greater than those used in the PBPK models of CYP2D6 inhibitors. In other words, the in vitro $K_{i,u}$ value of an inhibitor needs to be reduced by 2- to 40-fold to reproduce the observed effects of this inhibitor on the exposure of CYP2D6 substrates (NDA218197 PBPK review).

The $f_{u,mic}$ value of taletrectinib was predicted to be 0.895 at the protein concentration used for the in vitro reversible inhibition assay (report VPT1184/2013). Taking this nonspecific binding into account, taletrectinib is predicted to have minimal effect on the exposure of desipramine and dextromethorphan. Reducing the in vitro CYP2D6 $K_{i,u}$ of taletrectinib by 10- to 40-fold, taletrectinib was predicted to increase AUC of desipramine and dextromethorphan by

up to 2-, and 5-fold, respectively, when taletrectinib 600 mg once daily was co-administered with desipramine or dextromethorphan in general cancer patients (**Table 96**).

Table 96. Predicted Effects of Taletrectinib on the Exposure of CYP2D6 Substrates Following Administration of Multiple Doses of Taletrectinib in Western Healthy Subjects

Taletrectinib Dosing regimen	CYP2D6 $IC_{50,u}$ = 0.465	Desipramine		Dextromethorphan	
		$C_{max}R$	AUCR	$C_{max}R$	AUCR
600 mg QD	$K_{i,u} = IC_{50,u}$	1.05	1.08	1.21	1.20
	$K_{i,u}$ /10	1.26	1.57	2.44	2.48
	$K_{i,u}$ /20	1.33	1.86	2.90	3.38
	$K_{i,u}$ /40	1.42	2.22	3.90	4.99
400 mg QD	$K_{i,u} = IC_{50,u}$	1.03	1.06	1.15	1.14
	$K_{i,u}$ /10	1.21	1.42	2.05	2.06
	$K_{i,u}$ /40	1.37	2.04		
200 mg QD	$K_{i,u} = IC_{50,u}$	1.02	1.03	1.08	1.07
	$K_{i,u}$ /10	1.13	1.24	1.60	1.58
	$K_{i,u}$ /40	1.28	1.64		

Source: Tables 25 and 26 in the PBPK report ANHE/1/B and reviewer's analysis

Effects of taletrectinib on OATP1B substrate pravastatin

The PBPK analysis cannot rule out a potential inhibition effect of taletrectinib on OATP1B substrates for reasons discussed below:

Drug interactions of pravastatin with OATP1B1/3 inhibitors were frequently not predicted using the pravastatin model in the Simcyp library, even when the lowest in vitro transporter inhibition parameters of the inhibitors in the Certara DDI Database were applied in the simulations. The observed interactions with pravastatin could only be reproduced, within 0.8 -1.25 of clinical observations, when the lowest experimentally generated unbound K_i or IC_{50} values of OATP1B1/3 inhibitors were reduced approximately 10- to 100-fold (2024 ISSX webinar on Challenges in Predicting PK for Transporter Substrates). These lowest K_i or IC_{50} parameters were mostly generated using estradiol-17β-glucuronide as an OATP1B1 probe substrate in HEK293-OATP1B1 cells with a 15- to 60-minute preincubation (data not shown).

Taletrectinib 600 QD was predicted to increase pravastatin AUC and C_{max} up to 1.7-fold when K_i values for both OATP1B1 and OATP1B3 were reduced up to 200-fold (**Table 97**). Notably, taletrectinib OATP1B1 inhibition study for taletrectinib utilized estrone-3-sulfate as a probe substrate, which is known to be 6- to 15-fold less sensitive to OATP1B inhibition compared to using estradiol-17β-glucuronide (PMID: 23920221). Additionally, the use of a predicted rather than measured nonspecific binding value in the PBPK model introduces another layer of uncertainty to the predicted results.

Table 97. Predicted Effects of Taletrectinib on Statin Exposure Following Administration of 600 mg Taletrectinib Once Daily in Western Healthy Subjects

OATP1B substrates	OATP1B1/3 IC_{50} (μM)	BCRP IC_{50} (μM)	AUC ratios	C_{max} ratios	Source
Pravastatin	4.71/17.6		1.01	1.01	PBPK report ANHE/1/F
	Ki/10		1.06	1.05	
	Ki/100		1.42	1.42	
	Ki/200		1.69	1.67	
Rosuvastatin	4.71/17.6	4.34	1.05	1.08	PBPK report ANHE/1/F
	Ki/10	Ki/15	1.66	2.12	
	Ki/100	Ki/15	2.20	3.11	
	Ki/200	Ki/15	2.61	3.81	
	Ki/50	Ki/50	3.35	8.37	Reviewer's analyses
	Ki/100	Ki/50	3.96	10.23	

Simulations conducted by the reviewer were performed using Simcyp version 23.
Source: Tables 25 and 26 in the PBPK report ANHE/1/F and reviewer's analyses

Effects of taletrectinib on OATP1B and BCRP substrate rosuvastatin

The PBPK analysis cannot rule out a potential inhibition effect of taletrectinib on BCRP substrates for reasons discussed below:

As for the OATP1B inhibition parameters, the in vitro to in vivo extrapolation of BCRP inhibition parameter (K_i or IC50) has not been established. Based on the data from BCRP inhibitors that have observed interaction data with both OATP1B1 endogenous substrates and rosuvastatin, the reviewer's independent analysis indicated that the estimated in vivo K_i values for BCRP, using the Costales' rosuvastatin model, were approximately 3- to 50-fold lower compared to the corresponding lowest IC50 values of these inhibitors in the Certara DDI and FDA Databases (data not shown). Taletrectinib was predicted to increase rosuvastatin AUC and C_{max} significantly when simulations were carried out with in vitro IC50 values of OATP1B and BCRP reduced simultaneously (**Table 97**). It should also be noted that the lowest IC50 values of BCRP inhibitors in the DDI Database were mostly generated from the membrane vesicle system, not the Caco-2 monolayer system used for taletrectinib. The BCRP IC50 generated using the Caco-2 monolayer system was on average 11-fold less potent, ranging from 0.3 to 53-fold less potent, compared to the HEK293 membrane vesicle system. Furthermore, taletrectinib had low to moderate permeability across the Caco-2 cell monolayer (Report No. 423090-20210624-Caco2). Given inhibition occurs at the intracellular domain of BCRP molecules, the actual IC50 value may be lower than that estimated based on the nominal concentrations in the BCRP inhibition study. Taken together, these findings suggest that a significant interaction between taletrectinib and rosuvastatin cannot be ruled out.

Effects of taletrectinib on MATE1 substrate Metformin

The ability of metformin model to predict MATE1 inhibition has not been well verified because the in vitro to in vivo extrapolation of MATEs/OCTs inhibition parameter K_i value has not been established. Three inhibitors of MATEs cimetidine, pyrimethamine and trimethoprim were reported to increase metformin exposure, and data from clinical DDI studies of metformin with these inhibitors were used to verify the metformin model (Simcyp metformin summary report). Although the simulated effects of these inhibitors on metformin exposure were within 0.78 to 1.41-fold of the observed effects, the K_i value of MATEs in the cimetidine model was 3- to 15-fold lower than its IC50 values of MATE1 in the Certara DDI database and 8- to 33-fold lower than its IC50 values of MATE-2K published in the database. For OCT2, the in vitro K_i values reported in the database were equal to or 12-fold lower than that in the cimetidine model, approximately 4-fold lower than that in the pyrimethamine model, and 2-fold higher than that in the trimethoprim model. These differences between in vitro K_i and model used K_i suggest that, without the results from the clinical DDI studies, the effects of these inhibitors on metformin exposure cannot be confidently predicted. It should be noted that, if metformin efficacy is of concern, evaluating metformin plasma exposure alone may be insufficient to inform the metformin dosing (PMID: 29761830). Overall, the PBPK analysis of the interaction of taletrectinib with metformin is considered inadequate.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Refer to **Section 8.2** for FDA's safety analyses.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED / APPROVED	AUTHORED / APPROVED
Nonclinical Reviewer	Stephanie Aungst, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	**Select one:** _X_ Authored _X_ Approved
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Division Director (acting)	Erin Larkins, M.D.	CDER/OOD/DO2	Sections: All	**Select one:** _X_ Authored _X_ Approved
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