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APPLICATION NUMBER:

219972Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

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

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Health Canada (HC), Israel’s Ministry of Health and United Kingdom’s Medicines and Healthcare products Regulatory Agency (MHRA). While the conclusions and recommendations expressed herein reflect FDA’s completed review of the application, the applications may still be under review at the other regulatory agency.

Application Type	New Drug Application, 505(b)(1)
Application Number(s)	219972
Priority or Standard	Priority
Submit Date(s)	03/28/2025
Received Date(s)	03/28/2025
PDUFA Goal Date	11/28/2025
Division/Office	CDER/OND/OOD/DO2
Review Completion Date	Refer to electronic stamp date
Established Name	Sevabertinib
(Proposed) Trade Name	HYRNUO
Pharmacologic Class	Kinase inhibitor
Code name	BAY 2927088
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Formulation(s)	Tablets
Dosing Regimen	20 mg orally twice daily with food
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating <i>HER2 (ERBB2)</i> mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) whose tumors have activating <i>HER2 (ERBB2)</i> tyrosine kinase domain activating mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

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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

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Glossary

ADC	antibody-drug conjugate
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
aqua demin.	demineralized water
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical

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AUC	area under the plasma concentration-time curve (without further suffix from time 0 to infinity)
BCRP	breast cancer resistance protein
BDC	bile duct-cannulated
BICR	blinded independent central review
BID	<i>Bis in die</i> , twice daily
BLA	biologics license application
BOR	best overall response
BQL	below quantitation limit
BTB	breakthrough therapy designation
BTR	best tumor response
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance rate
C _{max}	maximum observed drug concentration in measured matrix
CFR	Code of Federal Regulations
CNS	central nervous system
CMC	chemistry, manufacturing, and controls
COVID-19	coronavirus disease 2019
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DE/BF	Dose escalation/Backfill
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFD	embryofetal development
EFS	efficacy analysis set

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EGFR	epidermal growth factor receptor
EoT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
FiH	first-in-human
GCP	good clinical practice
GIT	gastrointestinal tract
GLP	good laboratory practice
HER2	human epidermal growth factor receptor 2
HLT	high-level term
IC50	concentration required for 50% inhibition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committees
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
LLN	lower limit of normal
LLOQ	lower limit of quantification
LPLV	last participant last visit
LSF	liquid service formulation
LSM	least squares mean
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MLG	MedDRA labeling grouping
MTD	maximum tolerated dose
MRI	magnetic resonance imaging
n.a	not applicable
n.c.	not calculated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level

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NOS	not otherwise specified
NSCLC	non-small cell lung cancer
OATP	organic anion transporting polypeptide
OECD	Organisation for Economic Co-operation and Development
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PFS	progression-free survival
PIF	photo-irritation-factor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
po	per os (oral administration)
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PS	performance status
QD	<i>Quaque die</i> , once daily
QT	QT interval in ECG
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
QWBA	quantitative whole-body autoradiography
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SD	stable disease

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SMC	safety monitoring committee
SMQ	standardized MedDRA query
SOC	system organ class
t_{max}	time to reach C_{max}
TDD	total daily dose
TEAE	treatment emergent adverse event
TESAE	treatment-emergent serious adverse event
TKD	tyrosine kinase domain
TKI	tyrosine kinase inhibitor
TTR	time to response
US	United States
USPI	United States Prescribing Information
UVR	ultraviolet radiation
V_{ss}	volume of distribution at steady-state
VPC	visual predictive check
WRO	Written Response Only

Definition of terms:

The following definitions apply to Study 21607:

Dose level	Dose level refers to a certain dose of sevabertinib (BAY 2927088) tested during the Dose Escalation/Backfill parts of the study and can be further investigated during the Dose Expansion part in the different groups.
Cohort	A cohort is defined as participants assigned to the same dose level in the Dose Escalation/Backfill parts of the study.
Group	In Dose Expansion and Dose Extension parts of the study, the term 'group' refers to groups of participants with pre-specified criteria for cancer characteristics and prior therapies.

Efficacy and safety analysis populations for Study 21607 presented in this document:

Group D (primary efficacy and safety)	Participants with advanced NSCLC harboring <i>HER2</i> activating mutations (including ex20ins) who have received prior systemic therapy but were naïve to <i>HER2</i> ex20ins-targeted therapy. Participants who had prior treatment with <i>HER2</i> ex20ins-targeted therapy for ≤ 2 months and stopped treatment due to reasons other than progressive disease were also eligible.
Group E (supportive efficacy)	Participants with advanced NSCLC harboring <i>HER2</i> activating mutations (including ex20ins) who have received prior systemic therapy and had documented progression to <i>HER2</i> -targeted ADCs (e.g. trastuzumab deruxtecan). Prior treatment with <i>HER2</i> ex20ins-TKIs (i.e. poziotinib) was exclusionary unless treatment lasted for ≤ 2 months and was stopped due to reasons other than progressive disease.
Whole Study 20 mg BID (safety)	All participants (across all study parts, i.e. Dose Escalation, Backfill, Expansion and Extension) who received sevabertinib at a dose level of 20 mg BID.
Whole Study SAF (safety)	All participants (across all study parts) who received at least one dose of sevabertinib at any dose level.

1 Executive Summary

1.1. Product Introduction

Sevabertinib (HYRNUO) is a small molecule kinase inhibitor of human epidermal growth factor receptor 2 (HER2, also known as Erb-B2 receptor tyrosine kinase 2 [ERBB2]), including wild-type HER2 and HER2 activating mutations. Sevabertinib is not currently approved for marketing in any country.

The indication proposed by the Applicant is for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have activating *HER 2 (ERBB2)* mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

The recommended dosage regimen for sevabertinib is 20 mg taken orally twice daily (BID) with food until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

The submitted data provide substantial evidence of effectiveness to support the accelerated approval of sevabertinib for the treatment of adult patients with locally advanced or metastatic non-squamous NSCLC whose tumors have HER2 (ERBB2) tyrosine kinase domain (TKD) activating mutations, as detected by an FDA-approved test, and who have received prior systemic therapy.

The recommendation for accelerated approval is primarily supported by results from Study 21607 (SOHO-01), a non-randomized, open-label, single arm, multi-center, multi-cohort trial. The primary efficacy populations considered by FDA comprise 122 patients with locally advanced or metastatic, non-squamous NSCLC with HER2 (ERBB2) TKD mutations who had received at least one line of prior systemic therapy and received sevabertinib 20 mg orally BID in SOHO-01. This primary efficacy population was comprised of two groups: patients naïve to anti-HER2 therapy (Group D) and patients that had progressed on prior anti-HER2 directed therapy (Group E). Across the two groups, most patients received prior platinum-based chemotherapy (94% and 77% in Groups D and E, respectively), immunotherapy (71% and 56% in Groups D and E, respectively), or platinum-based chemotherapy in combination with immunotherapy (69% and 56% in Groups D and E, respectively). In Group D (n=70), the objective response rate (ORR) per blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was 71% (95% confidence interval [CI]: 59, 82), and the median duration of response (DOR) was 9.2 months (95% CI: 6.3, 15.0), with 54% of responders having an observed DOR $\geq$ 6 months and 18% of responders having an observed DOR $\geq$ 12 months. In

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Group E (n=52), the ORR per BICR per RECIST version 1.1 was 38% (95% CI: 25, 53), and the median DOR was 7.0 months (95% CI: 5.6, not estimable [NE]), with 60% of responders having an observed DOR $\geq$ 6 months.

The demonstrated response rates in the primary efficacy populations are considered clinically meaningful in the context of available therapy for the indicated patient population.

Additional supportive information derives from strong mechanistic evidence of HER2 mutations as molecular drivers of NSCLC.

The submitted evidence meets the statutory evidentiary standard for accelerated approval in accordance with the provisions of 21 CFR 315.510 Subpart H. Given that in the absence of therapy, HER2-mutated NSCLC tumors do not typically regress, ORR can be directly attributed to an effect of the drug; in this disease setting, ORR is considered an intermediate endpoint reasonably likely to predict clinical benefit. There are no therapies with traditional approval specifically for patients with HER2 mutated NSCLC whose disease has progressed after standard first-line therapy, which includes platinum-based chemotherapy and/or an anti-PD-(L)1 antibody. Fam-trastuzumab deruxtecan-nxki (T-DXd), a HER2-directed ADC which demonstrated an ORR of 58% in a population similar to the Group D efficacy analysis population in this application, is currently under accelerated approval. Standard treatment options for the indicated population are otherwise the same as those used for a biomarker unselected population of patients with NSCLC and include single agent chemotherapy (e.g., ORR in the range of 10-15% for docetaxel) or docetaxel plus ramucirumab (ORR of 23% [95% CI: 20, 26]). The effect of sevabertinib based on magnitude and duration of responses observed in the primary efficacy populations in SOHO-01 demonstrates a meaningful advantage over available therapies for this previously treated patient population.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). The trial intended to verify the clinical benefit of sevabertinib is Study 22615 (SOHO-02), an open-label, randomized, controlled, global study of sevabertinib versus standard of care pembrolizumab plus platinum-based doublet chemotherapy in patients with previously untreated, unresectable locally advanced or metastatic non-squamous NSCLC harboring HER2 TKD mutations. The primary efficacy endpoint is progression-free survival (PFS) per RECIST 1.1 by BICR; key secondary endpoints include ORR and overall survival (OS). The Consolidated Appropriations Act (2023) provides FDA with the authority to require that confirmatory studies to verify clinical benefit be underway prior to accelerated approval. SOHO-02 is 60% enrolled as of October 2025, and topline data from the primary PFS analysis are expected Q1 2027. As such, the review division considers the confirmatory trial for this accelerated approval to be underway.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer-related death in the United States (U.S.), with approximately 226,650 new cases of lung cancer expected to be diagnosed in 2025, and approximately 124,730 deaths attributed to lung cancer (Cancer Facts & Figures, 2025). Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers, and 44% to 48% of patients with NSCLC present with stage IV/metastatic disease at the time of diagnosis (Duma 2019; Ganti 2021). *HER2* (*ERBB2*) mutations occur in approximately 2% of all NSCLC and are primarily activating mutations involving Exon 20 of the *HER2* (*ERBB2*) gene. Patients with *HER2*-mutated NSCLC are more likely to be female, non-smokers, and have tumors with adenocarcinoma histology (IASLC, 2023). These patients often develop central nervous system (CNS) disease, with brain metastases reported in up to 47% of patients (Offin, 2019). Median survival in patients with metastatic *HER2*-mutated NSCLC is 17 to 23 months (Pillai, 2017). There are no products targeting *HER2*-mutated NSCLC currently under traditional FDA approval. Initial systemic therapy in the metastatic setting generally consists of platinum-based doublet chemotherapy, with or without anti-PD-(L)1 antibody. Available treatment options for patients who experience disease progression following first-line therapy are the same as those used for a biomarker unselected population of patients with NSCLC and include single agent chemotherapy (e.g., docetaxel with ORR 10-15%), combination chemotherapy (e.g., docetaxel plus ramucirumab with ORR 23%), or anti-PD-(L)1 antibody as a single agent for patients who are anti-PD-(L)1 naïve (ORR 15-20%). Fam-trastuzumab deruxtecan-nxki (T-DXd), a *HER2*-directed antibody and topoisomerase inhibitor conjugate, was granted accelerated approval for NSCLC with activating *HER2* mutations in August 2022 (ORR 58%). Metastatic *HER2*-mutated NSCLC remains a fatal, incurable disease, and an unmet need exists for additional systemic therapies for patients with metastatic NSCLC harboring *HER2* mutations whose disease has progressed after first-line therapy.

Sevabertinib is a small molecule kinase inhibitor of *HER2*, including wild-type *HER2* and *HER2* activating mutations. The recommended dosage regimen for sevabertinib is 20 mg taken orally twice daily with food until disease progression or unacceptable toxicity. Sevabertinib is not currently approved for marketing in any country.

The primary study supporting this application is the SOHO-01 (Study 21607), a non-randomized, open-label, single arm, multi-center, multi-cohort trial of sevabertinib in patients with locally advanced, unresectable or metastatic solid tumors with *HER2* aberrations, with the dose expansion part of the trial (“Phase Ib”) evaluating sevabertinib in patients with locally advanced, unresectable or metastatic *HER2*-mutated

NSCLC. The primary efficacy outcome measure for this marketing application is confirmed ORR according to RECIST v1.1 as assessed by BICR, with DOR by BICR.

The primary efficacy populations considered by FDA comprise 122 patients with locally advanced or metastatic, non-squamous NSCLC with HER2 TKD mutations who had received at least one line of prior systemic therapy and received sevabertinib 20 mg orally BID in two groups of SOHO-01. Among 70 patients who had not received prior HER2-directed therapy (Group D), 94% had received prior platinum-based chemotherapy and 69% had received previous treatment with an anti-PD-1/anti-PD-L1 antibody. The ORR per BICR was 71% (95% CI: 59, 82) and the median duration of response (DOR) was 9.2 months (95% CI: 6.3, 15.0ong), with 54% of responders having an observed DOR $\geq$ 6 months and 18% of responders with an observed DOR $\geq$ 12 months. Responses were generally consistent across subgroups.

Among 52 patients with locally advanced or metastatic, non-squamous NSCLC with HER2 TKD mutations who had received prior systemic treatment with platinum-based chemotherapy and a HER2-targeted ADC (Group E) the ORR was 38% (95% CI: 25, 53), with a median DOR of 7.0 months (95% CI: 5.6, NE) and 60% of responders having a DOR $\geq$ 6 months.

The Applicant submitted data from patients with squamous histology and those with tumors with HER2 non-TKD mutations; however, the sample sizes in these populations were very limited, and response rates were numerically lower (see Section 8.1.1 for further details). FDA considered that there was insufficient evidence of efficacy in this population, and the indication for sevabertinib considered in FDA's review was limited to the treatment of adult patients with locally advanced or metastatic non-squamous NSCLC whose tumors have HER2 TKD activating mutations and who have received prior systemic therapy.

Sevabertinib has an acceptable safety profile when assessed in the context of a life-threatening disease. The assessment of safety at the recommended dosage was based on data from patients with locally advanced or metastatic non-squamous NSCLC who received sevabertinib 20 mg BID in SOHO-01 (n=268; refer to Section 8.2). The safety population used to inform Section 6 of product labeling includes patients in with locally advanced or metastatic non-squamous NSCLC with HER2 mutations enrolled in Groups D and E (n=136). In the pooled safety population, the most common ($\geq$ 20%) adverse reactions were diarrhea, rash, stomatitis, and paronychia. The most common ($\geq$ 2%) Grade 3 or 4 laboratory abnormalities were decreased potassium, increased lipase, decreased lymphocyte, decreased sodium, increased amylase, increased ALT, and increased AST. In the safety population for Groups D and E, the most common adverse reactions ($>$ 20%) in patients who received HYRNUO were diarrhea, rash, paronychia, stomatitis, and nausea. The most common Grade 3 or 4 laboratory abnormalities ($\geq$ 2%) were potassium decreased, lipase increased, lymphocyte count decreased, sodium decreased, amylase increased, aspartate aminotransferase (AST)

increased, and alanine aminotransferase (ALT) increased. Serious adverse reactions occurred in 31% of patients; those occurring in $\geq 2\%$ of patients included diarrhea (6%), pneumonia (3.7%), dyspnea (2.2%), and pleural effusion (2.2%). Permanent discontinuation of sevabertinib due to adverse reactions occurred in 3.7% of patients; adverse reactions which resulted in permanent discontinuation included corneal epithelial microcysts, hepatic function abnormal, electrocardiogram QT prolonged, pain in extremity and dyspnea (0.7%, 1 patient each). Permanent discontinuation of sevabertinib due to an adverse reaction occurred in 3.7% of patients. Adverse reactions which resulted in permanent discontinuation were corneal epithelial microcysts, hepatic function abnormal, electrocardiogram QT prolonged, pain in extremity and dyspnea (0.7%, 1 patient each). Dose reductions due to adverse reactions occurred in 28% of patients; adverse reactions which resulted in dose reductions in $>2\%$ of patients were diarrhea, rash, and hypokalemia.

Safety issues identified as significant and serious enough to warrant inclusion in the Warnings and Precautions section of labeling for sevabertinib, based on data from the pooled safety population, are diarrhea, hepatotoxicity, interstitial disease (ILD)/pneumonitis, ocular toxicity, and pancreatic enzyme elevation. 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). Sevabertinib will be prescribed by oncologists who are familiar with monitoring, identifying, and managing the toxicities described in the USPI.

A supplementary PMA (sPMA) application for the Life Technologies Corporation (subsidiary of Thermo Fisher Scientific) Oncomine™ Dx Target Test (ODxTT) was submitted to the Center for Devices and Radiological Health (CDRH) as a companion diagnostic. CDRH determined that the data submitted in the sPMA are supportive of approval of the ODxTT as a companion diagnostic device to identify patients with locally advanced or metastatic non-squamous NSCLC harboring HER2 (ERBB2) TKD activating mutations who may be eligible for treatment with sevabertinib, and the sPMA will be approved contemporaneously with this NDA.

The submitted evidence meets the statutory evidentiary standard for accelerated approval of sevabertinib for the treatment of adult patients with locally advanced or metastatic non-squamous NSCLC whose tumors have HER2 TKD activating mutations and who have received prior systemic therapy. The benefit-risk profile in the indicated population is considered favorable based on the magnitude and durability of the observed responses with sevabertinib, which are consistent with a clinically meaningful advantage over available therapies for an indicated patient population that has a life-threatening disease and an unmet medical need. Sevabertinib has an acceptable safety profile when assessed in the context of a life-threatening disease and considering the observed efficacy results in patients with non-squamous NSCLC whose tumors have HER2 TKD activating mutations.

Based on this assessment, sevabertinib will be granted accelerated approval for the following indication: “For the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have *HER2 (ERBB2)* tyrosine kinase domain activating mutations, as detected by an FDA approved test, and who have received prior systemic therapy.”

Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial, conducted as a postmarketing requirement. The trial intended to verify the clinical benefit of sevabertinib is Study 22615 (SOHO-02), an open-label, randomized, controlled, global study of sevabertinib versus standard of care pembrolizumab plus platinum-based doublet chemotherapy in patients with previously untreated locally advanced, or metastatic non-squamous NSCLC harboring HER2 TKD mutations. The primary efficacy endpoint is progression-free survival (PFS) per RECIST 1.1 by BICR; key secondary endpoints include ORR and overall survival (OS). The Consolidated Appropriations Act (2023) provides FDA with the authority to require that confirmatory studies to verify clinical benefit be underway prior to accelerated approval. SOHO-02 is 60% enrolled as of October 2025, and topline data from the primary PFS analysis are expected Q1 2027. As such, the review division considers the confirmatory trial for this accelerated approval to be underway.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	• Lung cancer is the leading cause of cancer-related death in the United States with non-small cell lung cancer (NSCLC) representing 85% of cases. Nearly half of patients with NSCLC present with metastatic disease. • HER2 (ERBB2) mutations occur in approximately 2% of all NSCLC. Patients with HER2-mutated NSCLC are more likely to be female, non-smokers, and have tumors with adenocarcinoma histology. Brain metastasis is reported in up to 47% of these patients. • Median survival in patients with metastatic HER2-mutated NSCLC is 17 to 23 months.	Locally advanced or metastatic NSCLC with a HER2 (ERBB2) mutation is a serious and life-threatening condition with poor survival. Tumors with a HER2 (ERBB2) mutation represent a rare subset of NSCLC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are no products specifically targeting HER2-mutated NSCLC currently under traditional approval in the U.S. Treatments used for patients with HER2-mutated NSCLC are the same as those used for patients with NSCLC without a specific driver mutation. • Initial systemic therapy in the metastatic setting generally consists of platinum-based doublet chemotherapy, with or without anti-PD-(L)1 antibody. • For patients with disease progression following initial systemic therapy, available treatment options include chemotherapy (single agent or docetaxel with ramucirumab), associated with ORRs of 10-23% with median DORs of 4-9 months, or anti-PD-(L)1 antibody as a single agent for patients who are anti-PD-(L)1 naïve, associated with ORRs of 15-20% and median DORs of 16-17 months. • Fam-trastuzumab deruxtecan-nxki (T-DXd), a HER2-directed antibody and topoisomerase inhibitor conjugate, which demonstrated an ORR of 58% (95% CI: 43-71) and median DOR of 8.7 months (95% CI: 7.1, NE), was granted accelerated approval for NSCLC with activating HER2 mutations in August 2022.	Treatment options are limited for patients with previously treated NSCLC harboring HER2 (ERBB2) mutations whose disease has progressed after prior systemic therapy and an unmet medical need exists for more effective therapies.
Benefit	• SOHO-01 (Study 21607), the primary study supporting this NDA, is a non-randomized, open-label, single arm, multi-center, multi-cohort trial of sevabertinib in patients with locally advanced or metastatic solid tumors with HER2 aberrations, with the dose expansion part of the trial evaluating sevabertinib in patients with locally advanced or metastatic HER2-mutated NSCLC. The primary efficacy population considered by FDA comprises 122 patients with locally advanced or metastatic, non-squamous NSCLC with HER2 TKD mutations who had received at least one line of prior	The submitted evidence meets the statutory evidentiary standard for accelerated approval for the treatment of adult patients with locally advanced or metastatic non-squamous NSCLC whose tumors have HER2 TKD activating mutations and who have received prior systemic therapy. The magnitude of the ORR and durable responses observed with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	systemic therapy and received sevabertinib 20 mg orally BID in two cohorts (Groups D and E) of SOHO-01. - Among 70 patients who had not received prior HER2-directed therapy (Group D), 94% had received prior platinum-based chemotherapy and 69% had received previous treatment with an anti-PD-1/anti-PD-L1 antibody. The ORR per BICR was 71% (95% CI: 59, 82) and the median duration of response (DOR) was 9.2 months (95% CI: 6.3, 15), with 54% of responders having an observed DOR $\geq$ 6 months and 18% of responders with an observed DOR $\geq$ 12 months. Responses were generally consistent across subgroups. - Among 52 patients with locally advanced or metastatic, non-squamous NSCLC with HER2 TKD mutations who had received prior systemic treatment with platinum-based chemotherapy and a HER2-targeted ADC (Group E) the ORR was 38% (95% CI: 25, 53), with a median DOR of 7.0 months (95% CI: 5.6, NE) and 60% of responders having a DOR $\geq$ 6 months.	sevabertinib represent a clinically meaningful advantage over currently available therapy. ORR and DOR are reasonably likely to predict clinical benefit in this disease setting. A PMR will be issued under the provisions of accelerated approval for verification and further description of the clinical benefit of sevabertinib in the confirmatory trial, Study 22615 (SOHO-02), an open-label, randomized, controlled, global study of sevabertinib versus standard of care pembrolizumab plus platinum-based doublet chemotherapy in patients with previously untreated, locally advanced, or metastatic non-squamous NSCLC harboring HER2 TKD mutations. SOHO-02 is 60% enrolled as of October 2025, and topline data from the primary PFS analysis are expected Q1 2027.
Risk and Risk Management	- The assessment of safety at the recommended dosage was based on data from patients with unresectable or metastatic non-squamous NSCLC with HER2 mutations who received sevabertinib 20 mg BID in SOHO-01 (pooled safety population, n=268). - The safety population used to inform Section 6 of product labeling includes patients in with locally advanced or metastatic non-squamous NSCLC with	Although sevabertinib can cause serious toxicities, information in the Warnings and Precautions and Dosage and Administration sections of product labeling addresses these safety issues adequately. The observed safety profile is considered acceptable when assessed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	HER2 mutations enrolled in Groups D and E (n=136). Among these 136 patients, serious adverse reactions occurred in 31% of patients, permanent discontinuation due to adverse reactions occurred 3.7% of patients, dosage interruptions due to adverse reactions occurred in 46% of patients, and dose reductions due to adverse reactions occurred in 28% of patients. The most common adverse reactions (>20%) in patients who received sevabertinib were diarrhea, rash, paronychia, stomatitis, and nausea. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were potassium decreased, lipase increased, lymphocyte count decreased, sodium decreased, amylase increased, aspartate aminotransferase (AST) increased, and alanine aminotransferase (ALT) increased.	in the context of a serious and life-threatening illness. There were no significant safety concerns during the NDA review requiring risk management beyond labeling and no safety concerns identified warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS).

1.4. Patient Experience Data

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

- The patient experience data that was submitted as part of the application, include:
 - Clinical outcome assessment (COA) data, such as
 - Patient reported outcome (PRO)
 - Observer reported outcome (ObsRO)

Section where discussed, if applicable
[e.g., Section 6.1 Study endpoints]

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- 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 most common cancer and the leading cause of cancer deaths, with an estimated 2.5 million new cases (12.4% of all cancer diagnoses) and 1.8 million deaths (18.7%) worldwide in 2022 (1). In the US, an estimated 234,580 new cases of lung cancer were diagnosed in 2024, with 125,070 deaths from lung cancer (2).

NSCLC

NSCLC is the most common type of lung cancer (3), accounting for $\geq 85\%$ of lung cancer cases (4-6). NSCLC is a heterogeneous disease where malignant cells are formed primarily in the lung parenchyma. It is a general term for several different types of cancer in the lungs, including adenocarcinoma, squamous cell carcinoma, large cell (undifferentiated) carcinoma, and other rare forms. NSCLC primarily originates in the epithelial cells of the lungs where adenocarcinoma develops in the peripheral lung tissue while squamous cell carcinoma develops near the central bronchus. The histologic type of NSCLC correlates with the site of origin, reflecting the variation in respiratory tract epithelium of the bronchi to alveoli (7). The overall 5-year survival rate of NSCLC patients is approximately 16% (8, 9), while it is much lower in patients with advanced NSCLC, ranging from 2.8% to 14.6% (8, 9). Nearly 75% of patients with NSCLC are diagnosed at an advanced stage.

HER2 activating mutations in NSCLC

Receptor tyrosine kinases (RTKs) regulate important biological processes, including cell proliferation, differentiation, metabolism, and survival, by activating an array of downstream signaling pathways. The ERBB family of RTKs consists of 4 members: EGFR (also known as ERBB1/HER1), ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (HER4) (10). Mutations within the kinase domain of *HER2* and *EGFR* are common oncogenic driver events in NSCLC (11).

Activating driver mutations in *HER2* have emerged as novel targets for treating NSCLC. These mutations are found in 2% to 4% of advanced NSCLC in Caucasian and Asian populations, with the vast majority being *HER2* ex20ins (96%) and a minority consisting of point mutations (11, 12). *HER2* activating mutations have been associated with female sex, Asian ethnicity, non-smoking status, adenocarcinoma histology, and younger patients, with a median age of approximately 60 years (13). In other tumor types (e.g. breast, ovarian, and bladder cancer) *HER2* ex20ins mutations are less frequent (majority < 1%) (14). Other activating point mutations in *HER2* can be detected as well, and in some tumor types those are more frequent than *HER2* ex20ins (15). Overall, patients with *HER2*-mutant NSCLC have a worse prognosis (median OS

of 1.6 to 1.9 years from time of diagnosis) than NSCLC with *EGFR* or *ALK* mutations partially due to the lack of effective targeted therapies (16).

The FDA’s Assessment:

FDA agrees with the Applicant’s analysis of the condition. *HER2 (ERBB2)* mutations occur in approximately 2% of all NSCLC and are primarily activating mutations involving Exon 20 of the *HER2 (ERBB2)* gene. Patients with *HER2*-mutated NSCLC are more likely to be female, non-smokers, and have tumors with adenocarcinoma histology (IASLC, 2023). These patients often develop central nervous system (CNS) disease, with brain metastases reported in up to 47% of patients (Offin, 2019). Median survival in patients with metastatic *HER2*-mutated NSCLC is 17 to 23 months (Pillai, 2017).

2.2. Analysis of Current Treatment Options

The Applicant’s Position:

Currently, targeted therapies are the standard treatment for most oncogene-driven NSCLC patients. The international guidelines for metastatic NSCLC indicate that subtyping of NSCLC, as well as testing for mutations, is necessary for effective treatment decision-making (17, 18). However, no targeted therapy has received full approval specifically for the treatment of patients with NSCLC, whose tumors harbor *HER2* mutations. Therefore, the standard treatment options for these patients are the same as those used for patients with NSCLC without a specific mutation.

In the absence of approved targeted therapies, platinum-based chemotherapy, with or without immunotherapy, is the recommended first-line treatment option for patients with *HER2*-mutant metastatic NSCLC. However, the outcome of patients treated with upfront chemotherapy (ORR of 36% and median PFS of 5.1 months; (18) or immuno-chemotherapy (ORR of 37% and median PFS of 7.1 months; 19) is still unsatisfactory and may be further improved. For patients with progression of disease following platinum-based chemotherapy, standard treatment options include either single agent docetaxel or docetaxel in combination with ramucirumab, which have been associated with ORRs of 6% to 23%, or single agent anti-PD-L1 therapy if not received in the first-line setting, with ORRs of 14% to 20% (see **Table 1**).

HER2-targeted therapies have demonstrated inconsistent results in the second-line setting (19-22). The results from irreversible pan-HER TKIs (afatinib, dacomitinib, neratinib, and poziotinib) have been disappointing (23). The ORR was 28% and the median PFS was 5.5 months for poziotinib.

To date, ADC trastuzumab deruxtecan (Enhertu) is the only *HER2*-targeted treatment for NSCLC patients (**Table 1**). On 11 AUG 2022, the FDA granted accelerated approval to trastuzumab deruxtecan for the treatment of adult patients with unresectable or metastatic

NSCLC whose tumors have activating *HER2* mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

The efficacy results from the interim analysis (N=52) of the Phase 2 DESTINY-Lung02 study provided the first clinical data of 5.4 mg/kg trastuzumab deruxtecan in patients with previously treated *HER2*-mutated NSCLC and served as the basis for accelerated approval by the FDA. The confirmed ORR was 57.7% and the median DOR was 8.7 months (Table 1). At the primary analysis (N=102), the ORR was 49.0% and the median DOR was 16.8 months (24). Safety was a concern, since adjudicated drug-related ILD occurred in 12.9% of patients and resulted in the death of one patient. Drug-related TEAEs of Grade ≥ 3 were reported in 38.6% of patients. Dose interruption, reduction, and treatment discontinuation were reported in 44.6%, 17.8%, and 14.9% of patients, respectively (24).

Therefore, despite these recent advances, there is an urgent need for more effective and better tolerated agents that can improve response rates and response durability, eventually delaying progression and improving survival, in NSCLC patients with *HER2* activating mutations.

Table 1. Approved Therapies for NSCLC Patients (Unselected and HER2 Activating Mutations) Who Have Received Prior Systemic Therapy

Product(s) name	Relevant indication	FDA approval year and type	Dosing	Efficacy information	Important safety and tolerability issues (warnings and precautions)
Single agent ADC					
Fam-trastuzumab deruxtecan-nxki (Enhertu)	Unresectable or metastatic NSCLC whose tumors have activating HER2 mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy	2022 Accelerated	5.4 mg/kg every 3 weeks IV	DESTINY-Lung02 (N=52) • ORR: 57.7% • mDOR: 8.7 months	ILD/pneumonitis, neutropenia (including febrile neutropenia), left ventricular dysfunction, embryo-fetal toxicity
Anti-PD(L)1 therapies					
Nivolumab (Opdivo)	Metastatic NSCLC with progression on or after platinum-based chemotherapy	2015	240 mg every 2 weeks or 480 mg every 4 weeks IV	CHECKMATE-017 (N=135, squamous) • ORR: 20% • mPFS: 3.5 months • mOS: 9.2 months CHECKMATE-057 (N=292, non-squamous) • ORR: 19% • mPFS: 2.3 months • mOS: 12.2 months	Severe and fatal immune-mediated adverse reactions ^a , infusion-related reactions, complications of allogeneic HSCT, increased mortality in patients with multiple myeloma when Opdivo is added to a thalidomide analogue and dexamethasone, embryo-fetal toxicity
Pembrolizumab (Keytruda)	Metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%), as determined by an FDA-approved test, with	2016	200 mg every 3 weeks or 400 mg every	KEYNOTE-010 (N=344; 2 mg/kg) • ORR: 18% • mPFS: 3.9 months • mOS: 10.4 months	Severe and fatal immune-mediated adverse reactions ^a , infusion-related reactions, complications of allogeneic HSCT, increased mortality in patients

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	disease progression on or after platinum-based chemotherapy		6 weeks IV	KEYNOTE-010 (N=346; 10 mg/kg) • ORR: 19% • mPFS: 4.0 months • mOS: 12.7 months	with multiple myeloma when Keytruda is added to a thalidomide analogue and dexamethasone, embryo-fetal toxicity
Atezolizumab (Tecentriq)	Metastatic NSCLC with disease progression during or following platinum-containing chemotherapy	2016	840 mg every 2 weeks or 1200 mg every 3 weeks or 1680 mg every 4 weeks IV	OAK (N=425) • ORR: 14% • mDOR: 16.3 months • mPFS: 2.8 months • mOS: 13.8 months	Severe and fatal immune-mediated adverse reactions ^a , infusion-related reactions, complications of allogeneic HSCT after PD-1/PD-L1 inhibitors, embryo-fetal toxicity
Combination chemotherapy					
Docetaxel+ Ramucirumab (Cyramza)	Metastatic NSCLC with disease progression on or after platinum-based chemotherapy	2014	As below + 10 mg/kg on Day 1 of a 21-day cycle prior to docetaxel IV	REVEL (N=628) • ORR: 23% • mPFS: 4.5 months • mOS: 10.5 months	Hemorrhage, gastrointestinal perforations, impaired wound healing, arterial thromboembolic events, hypertension, infusion-related reactions, worsening of pre-existing hepatic impairment, posterior reversible encephalopathy syndrome, proteinuria, including nephrotic syndrome, thyroid dysfunction, embryo-fetal toxicity
Single agent chemotherapy					
Docetaxel (Taxotere)	Locally advanced or metastatic NSCLC after platinum therapy failure	1999	75 mg/m ² every 3 weeks IV	TAX 317 (N=55) • ORR: 5.5% • mOS: 7.5 months	

TAX 320 (N=125)

- ORR: 5.7%
- mOS: 5.7 months

Toxic deaths (treatment-related mortality), hepatic impairment^b, hematologic effects (neutropenia, febrile neutropenia), enterocolitis and neutropenic colitis, hypersensitivity reactions, fluid retention, second primary malignancies, cutaneous reactions, neurologic reactions, eye disorders (cystoid macular edema), asthenia, embryo-fetal toxicity, intoxication due to alcohol content, tumor lysis syndrome

ADC=Antibody-drug conjugate; FDA=Food and Drug Administration; HER2=Human epidermal growth factor receptor 2; HSCT=Hematopoietic stem cell transplantation; ILD = Interstitial lung disease; IV=Intravenous; mDOR=Median duration of response; mOS=Median overall survival; mPFS=Median progression-free survival; N=Total number of participants; NSCLC=Non-small cell lung cancer; ORR=Objective response rate; PD-L1=Programmed Death Ligand 1; TPS=Tumor proportion score; USPI=United States Prescribing Information

a: Immune-mediated adverse reactions, e.g. pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions.

b: Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of severe neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death.

Source: Latest available USPI for Enhertu, Opdivo, Keytruda, Tecentriq, Cyramza, and Taxotere.

The FDA's Assessment:

FDA agrees with the Applicant's description of the available therapies for patients with metastatic NSCLC with HER2 (ERBB2) mutations. There are no products targeting *HER2*-mutated NSCLC currently under traditional approval in the U.S. Initial systemic therapy in the metastatic setting generally consists of platinum-based doublet chemotherapy, with or without anti-PD-(L)1 antibody. Available treatment options for patients who experience disease progression following first-line therapy include single agent chemotherapy (e.g., docetaxel), combination chemotherapy (e.g., docetaxel plus ramucirumab), or anti-PD-(L)1 antibody as a single agent for patients who are anti-PD-(L)1 naïve. As noted by the Applicant, Fam-trastuzumab deruxtecan-nxki (T-DXd), a HER2-directed ADC, was granted accelerated approval for the treatment of patients with NSCLC whose tumors have activating HER2 mutations and who have received prior systemic therapy in August 2022. Zongertinib, a tyrosine kinase inhibitor, was granted accelerated approval on August 8, 2025, for the treatment of adult patients with unresectable or metastatic non-squamous non-small

cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase activating mutations, as detected by an FDA-approved test, and who have received prior systemic therapy.

3 Regulatory Background

3.1. US Regulatory Actions and Marketing History

The Applicant’s Position:

Sevabertinib (BAY 2927088) has had an active IND Application (155685) in the US since AUG 2021 and is not currently registered (or approved) in any region. An overview of the key regulatory milestones during the clinical development of sevabertinib is provided in Section 3.2.

The FDA’s Assessment:

FDA agrees with the Applicant’s position. Sevabertinib is not currently approved in the United States or other regions for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant’s Position:

The key regulatory interactions with the FDA are summarized in **Table 2**.

Table 2. Key Regulatory Interactions for Sevabertinib

Date	Milestone
20 JUL 2021	The initial IND 155685 for the FiH Phase 1/2 Study 21607 was submitted. Study may proceed granted on 19 AUG 2021.
20 MAR 2023	Type C WRO. The Agency provided feedback on sample-type parameters for a companion diagnostic to support the registration of a potential NDA submission based on the Expansion and potential Extension parts of Study 21607 (Reference ID: 5144246).
28 JUL 2023	Type D WRO. The Agency provided feedback on the integrative approach that the Sponsor plans to apply to select the optimal dosing regimen of sevabertinib alone and in combination with amivantamab for further clinical development (Reference ID: 5217158).
30 NOV 2023	The Sponsor and the Division of Oncology 2 held a teleconference to discuss the data from Study 21607 in NSCLC patients and the opportunity to pursue BTM. The Division invited the Sponsor to submit a full application for BTM for the target indication.
30 JAN 2024	Type B (End-of-Phase 1) meeting to discuss the clinical benefit of sevabertinib observed in pre-treated NSCLC patients with <i>HER2</i> activating mutations from emerging data of the Phase 1/2 Study 21607, and on the proposed clinical development plan for sevabertinib intended for the accelerated approval (Reference ID: 5320661). The Agency agreed that the proposed randomized study may be adequate to verify a clinical benefit. The Agency advised that the Sponsor may consider a marketing application once enrollment in Cohort D is complete with adequate follow-up to characterize duration of response and if there is a positive benefit-risk profile.

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22 FEB 2024	BTD was granted for the proposed indication of “the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy”.
14 MAR 2024	The IND 170680 for Phase 3 confirmatory Study 22615 was submitted. Study may proceed was granted on 12 APR 2024.
31 MAY 2024	Type B meeting to discuss how to expedite the development of sevabertinib in the target indication (Reference ID: 5395385). The Sponsor agreed to the Agency’s proposal to provide an efficacy update for Group D (naïve to HER2-targeted treatment) during the NDA review; the Sponsor and the Agency agreed that the update would include the duration of response follow-up data of ≥6 months for approximately 100% of responders. The Agency also acknowledged the Sponsor’s proposal to revise the interim analysis for PFS to 80% from 70% of events in the Phase 3 confirmatory study. The Agency noted this may be acceptable depending on the results observed at this timepoint and the risk, even though still present, would be reduced with greater maturity of the data. The Agency also provided additional feedback on CMC, regulatory and toxicology topics.
10 JUN 2024	Thermo Fisher Scientific in partnership with Bayer Healthcare Pharmaceuticals, Inc., submitted a Pre-Submission (Q241442) to obtain feedback from the Agency regarding the proposed clinical validation strategy for the ODxTT for use as a CDx for patients with NSCLC harboring activating mutations in HER2 (ERBB2) for selection of treatment with sevabertinib.
23 SEP 2024	Thermo Fisher Scientific in partnership with Bayer Healthcare Pharmaceuticals, Inc., submitted a Pre-Submission (Q242491) to obtain feedback from the Agency regarding the proposed clinical validation strategy for the ODxET for use as a CDx for testing tumor and plasma specimens from patients with NSCLC to determine whether they harbor activating mutations in HER2 (ERBB2) for selection of treatment with sevabertinib.
23 OCT 2024	The IND (b) (4) for Phase 2 pan tumor Study 22752 was submitted. Study may proceed was granted on 22 NOV 2024.
06 JAN 2025	Type B meeting to discuss the topline results of the Phase 1/2 Study 21607, and obtain the Agency’s feedback on Sponsor’s plan of submitting an NDA to pursue accelerated approval in the second-line indication (Reference ID: 5505812). The Agency found the clinical efficacy and safety data reasonable to support an NDA filing and final wording of the proposed indication will be decided during review of the NDA. The Agency agreed to the proposed safety information to be provided in the 120-Day (90-Day if granted Priority Review) safety update report and accepted to use the additional follow-up efficacy data (which will be provided together with the safety update report) as the basis for approval and to be included into the USPI. The Agency also provided feedback on the clinical pharmacology and nonclinical programs, CMC, content and organization of the NDA, and Project Orbis.
10 MAR 2025	Type D meeting to discuss approval pathway of sevabertinib, including data (b) (4) in (b) (4) addition to Group D and Group E, to pursue accelerated approval (b) (4). The Agency did not agree with the inclusion of (b) (4) data to support (b) (4) (b) (4) (b) (4)
11 MAR 2025	Orphan Drug Designation # DRU-2023-9882 was granted for sevabertinib for “treatment of NSCLC harboring EGFR mutations, and/or HER2 activating mutations”.

BTD=Breakthrough therapy designation; CDx=companion diagnostic; ODxET=Oncomine Dx Express Test; ODxTT=Oncomine Dx Express Test; CMC=Chemistry, Manufacturing, and Controls; FDA=Food and Drug Administration; FiH=First-in-human; HER2=Human epidermal growth factor receptor 2; IND=Investigational New Drug; NDA=New Drug Application; NSCLC=Non-small cell lung cancer; PFS=Progression-free survival; USPI=United States Prescribing Information; WRO=Written responses only

The FDA’s Assessment:

FDA agrees with the Applicant's timeline of events.

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

4.1. Office of Scientific Investigations (OSI)

Refer to the Clinical Inspection Summary uploaded in DARRTs on October 21, 2025, for full details. Briefly, three clinical investigators, Dr. Ticiana Leal (Site #14003), Dr. Tae Min Kim (Site #56002), and Dr. Herbert Ho Fung Loong (Site #65001), as well as the General Clinical Imaging Services (GCIS) at Bayer Healthcare Pharmaceuticals, Inc were inspected. The following findings were observed during the inspections.

Inspection of Dr. Kim’s site identified a protocol deviation regarding a patient with mixed histology (sarcomatoid carcinoma with squamous cell and spindle cell components) identified in the pathology report, but histology was identified as squamous cell in the data provided; patients with mixed histology were excluded from the trial per eligibility criteria. This patient was ultimately excluded from the efficacy population and the deviation was determined not to impact the overall assessment of efficacy or safety.

Inspection of Bayer's Clinical Imaging Services identified a data discrepancy for subject (b) (6), which resulted in a patient’s best overall response being reclassified from progressive disease to stable disease; this finding did not affect the calculation of the primary endpoint.

Except for the observations noted above, the inspections did not identify significant concerns regarding study conduct, data discrepancies, Good Clinical Practice (GCP), or regulatory compliance. The data generated by these clinical investigators appear acceptable in support of the proposed indication.

4.2. Product Quality

Please refer to the Office of Pharmaceutical Quality (OPQ) review uploaded to DARRTs on November 4, 2025, for full details. Briefly, OPQ has recommended approval of NDA 219972 for sevabertinib. The review team determined that the Applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

A supplementary PMA (sPMA) application for the Life Technologies Corporation (subsidiary of Thermo Fisher Scientific) Oncomine™ Dx Target Test (ODxTT), P160045/S050 was submitted to the Center for Devices and Radiological Health (CDRH) as a companion diagnostic. It was determined that the data submitted in the sPMA are supportive of approval of the ODxTT as a companion diagnostic device to identify patients with locally advanced or metastatic nonsquamous NSCLC harboring HER2 (ERBB2) TKD activating mutations who may be eligible for treatment with sevabertinib. The following information regarding testing for HER2 (ERBB2) TKD activating mutations will be included in the sevabertinib USPI:

The efficacy population included 70 patients from Group D, and 52 patients from Group E, with advanced non-squamous NSCLC with *HER2 (ERBB2)* tyrosine kinase domain (TKD) activating mutations based on prospective local testing. Of the 122 patients in these combined cohorts, tumor tissue samples from 67.2% (82/122) of patients were retrospectively tested using Oncomine™ Dx Target Test (Life Technologies Corporation). While 92.7% (76/82) of samples were positive for *HER2 (ERBB2)* TKD activating mutations, 7.3% (6/82) were unevaluable, and there were no samples with negative status for *HER2 (ERBB2)* TKD activating mutations.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Sevabertinib is a reversible oral tyrosine kinase inhibitor that targets human epidermal growth factor receptor 2 (HER2), including HER2 exon 20 insertion mutations and HER2 point mutations. It also exhibits activity against wild-type (WT) epidermal growth factor receptor (EGFR) and certain EGFR mutants. The indication is for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. The recommended dose and schedule of sevabertinib for patients is 20 mg orally twice daily (BID).

The established pharmacological class for sevabertinib is kinase inhibitor. Predictive X-ray crystallography showed that sevabertinib noncovalently binds to the HER2 kinase domain. In in vitro kinase activity inhibition assays, sevabertinib inhibited the activity of WT HER2 and WT EGFR with IC_{50} values of 2.94 nM and 0.15 nM, respectively. In cellular assays, sevabertinib inhibited the in vitro proliferation of cells overexpressing WT HER2 ($IC_{50} = 5.30$ nM) and a panel of HER2 exon 20 insertion mutations and activating point mutations ($IC_{50} = 0.54$ to 13.9 nM) at concentrations below the free C_{max} of 88 nM at the recommended dose of 20 mg BID based on ~95% protein binding. Sevabertinib also inhibited phosphorylated HER2 (p-HER2) and downstream signaling in cancer cells harboring an HER2 exon 20 insertion or WT HER2 amplification. In vivo, sevabertinib exhibited antitumor activity against NSCLC patient-derived xenograft (PDX) models harboring the HER2 exon 20 insertion YVMA.

Secondary pharmacology studies showed that sevabertinib exhibited off-target activity in functional in vitro assays at the human adenosine A1 receptor and motilin receptor at concentrations ≥ 46 -fold the free C_{max} of 88 nM at the recommended clinical dose. In kinase activity competition assays, sevabertinib inhibited discoidin domain receptor 2 (DDR2) with an IC_{50} of 53.3 nM, DDR1 with an IC_{50} of 111 nM, and mitogen-activated protein kinase 14 (MAPK14) with an IC_{50} of 132 nM, indicating that sevabertinib has the potential to target these kinases at clinically relevant concentrations. To assess sevabertinib's effects on cardiac function due to the potential off-target activity on human adenosine and motilin receptors, ex vivo rabbit Langendorff heart preparations showed concentration-dependent decrease in left ventricular pressure (LVP), contractility, and coronary flow. Sevabertinib also shortened the QTcF interval and the left ventricular monophasic action potential duration at 90% repolarization (MAPD90) and caused widening of the QRS interval. Effects were noted at doses up to 113-fold higher than the free C_{max} of 88 nM.

In a GLP-compliant study, sevabertinib inhibited hERG potassium current in vitro with an IC_{50} of 2.36 μ M (26-fold the free C_{max} of 88 nM). In other in vitro assays, sevabertinib and its major

metabolite, M1, did not interfere with cardiac ion channels (hNav1.5, hCav1.2, hKir2.1, hKvLQT1), with the exception of the hERG potassium current ($IC_{50} = 2.2 \mu\text{M}$ and $3.5 \mu\text{M}$, respectively). In an in vivo cardiovascular safety pharmacology study, oral administration of up to 15 mg/kg sevabertinib did not increase the mean QT/QTc interval; however, individual animals displayed slightly prolonged (up to ~8 ms) QT/QTc intervals at about 1.5 to 4 post-treatment at ~12-fold the free C_{max} . Cardiac arrhythmia (including QT prolongation) was observed in patients treated with the recommended clinical dose of 20 mg BID and has been reported with other dual EGFR and HER2 inhibitors; refer to analysis and discussion presented in Sections 6, 8.2.3, and 8.2.4.5.. In a central nervous system (CNS) safety pharmacology study in rats, single oral administration of 15 and 45 mg/kg sevabertinib led to increased rearing activity at 1 and 24 hours postdose. There were no effects on respiratory parameters in respiratory safety studies conducted in rats, and sevabertinib did not affect CNS or respiratory parameters in the 4-week repeat-dose toxicity study in rats.

No unique human metabolites were identified. The major human metabolite of sevabertinib, M1 (approximately 31% to 38% of the parent drug), showed weaker cellular activity than sevabertinib and is unlikely to contribute to clinical activity due to the differences in pharmacokinetics, the unbound fraction, and potency. The M1 metabolite exhibited off-target effects on the adenosine A1 and A3 receptors, adenosine transporter, cyclooxygenase-2, and 15-lipoxygenase at concentrations ≥ 2.7 -fold the free C_{max} in humans at the recommended clinical dose. The M1 metabolite was present in rat and monkey plasma. Sevabertinib was rapidly and widely distributed throughout rat tissues with the highest concentrations found in the liver, adrenal cortex, kidney (outer medulla and cortex), and blood vessel wall (aorta), gastrointestinal (GI) tract, and thyroid gland, but brain penetration was low. There was notable distribution of sevabertinib to the melanin-containing tissues of the eye and skin with long-term retention in the eye tissue (see ocular toxicity discussed below). In consultation with the FDA Clinical Pharmacology team, animal to human exposure multiples were calculated using the mean steady state C_{max} and $AUC_{0-12\text{h}}$ of 902 ng/mL and 6640 ng*h/mL, respectively, at the recommended dose in humans. For comparisons with animal AUC_{0-24} , $AUC_{0-12\text{h}}$ in humans were multiplied by 2.

The Applicant evaluated the safety of sevabertinib administered orally once daily in 4- and 13-week good laboratory practice (GLP)-compliant general toxicology studies using rats and cynomolgus monkeys. The oral route of administration is consistent with the intended clinical route of administration. In the 4- and 13-week studies, treatment with sevabertinib caused mortalities. All high-dose (15 mg/kg) females in the 4-week rat study, all high-dose (8 mg/kg) males in the 4-week monkey study, and two high-dose (5 mg/kg) animals in the 13-week monkey study were sacrificed early due to rapid weight loss and diarrhea, as well as poor general condition. Histological findings of GI toxicity included erosion/ulcer, atrophy/degeneration, inflammation, immune infiltrate, and hemorrhage. Additional target organs in both species included the skin (wounds and scab formation; histological findings of up to moderate erosion/ulcer, atrophy, crust, hyperplasia, and inflammation), liver (up to marked fat accumulation), and pancreas (acinar cell atrophy). GI, skin, liver, and pancreatic toxicities are

consistent with clinical experience. Additional target organs in the monkey included the thymus (up to severe atrophy, severe decreased adipose tissue), and mesenteric lymph node (marked decreased adipose tissue, slight increased cellularity).

Ocular toxicity was observed in toxicology studies. In rats, treatment with ≥ 10 mg/kg sevabertinib (≥ 0.2 times the human exposure at the recommended dose of 20 mg BID based on AUC) resulted in slight atrophy of the lacrimal gland and minimal optic nerve hemorrhage. In monkeys, minimal lens degeneration occurred at 5 mg/kg (0.1 times the human exposure at the recommended dose based on AUC). In a non-GLP dose range-finding study in rats, treatment with ≥ 5 mg/kg sevabertinib (0.1 times the human exposure at the recommended clinical dose based on AUC) induced minimal to moderate atrophy/degeneration of the corneal epithelium. In the clinic, most ocular toxicity was characterized as dry eye, and there was one case of unilateral blindness. Ocular toxicity is commonly seen with EGFR inhibitors and has also been seen with dual EGFR and HER2 inhibitors.

Carcinogenicity studies were not conducted for sevabertinib and are not warranted for the proposed indication. Sevabertinib was not mutagenic in an in vitro bacterial reverse mutation assay and was not clastogenic or aneugenic in in vitro and in vivo micronucleus tests. Based on the totality of the data, M1 is not genotoxic. Sevabertinib also did not demonstrate phototoxic potential in a GLP-compliant in vitro assay with mouse fibroblasts.

The Applicant conducted GLP-compliant embryo-fetal development (EFD) studies in pregnant rats to assess the effect of sevabertinib on embryonic and fetal development. Sevabertinib was orally administered once daily to pregnant females during organogenesis (Gestation Days [GD] 6–17) at doses of 3, 7, and 11 mg/kg in the preliminary EFD study and at doses of 1.5, 3, and 6 mg/kg in the pivotal EFD study. Overall, sevabertinib caused dose-dependent maternal and fetal toxicity. Sevabertinib doses ≥ 6 mg/kg (≥ 0.18 times the human exposure at the recommended dose based on AUC) resulted in maternal toxicity characterized by decreases in body weight, body weight gain, and food consumption. Higher doses of sevabertinib (≥ 7 mg/kg) caused more maternal toxicity with additional adverse clinical signs (diarrhea, piloerection, thinness, and hunched posture) and early euthanasia due to morbidity in three animals at 11 mg/kg. Sevabertinib doses ≥ 6 mg/kg (≥ 0.18 times the human exposure at the recommended dose based on AUC) resulted in significantly reduced fetal body weights and decreased placenta and gravid uterine weights. The Applicant was unable to achieve higher exposures due to dose-limiting toxicities in pregnant rats, under the conditions tested, and only limited variations were observed. The Applicant also provided a weight-of-evidence (WOE) assessment, including literature and a new approach methodology (NAM), for reproductive risk to supplement the rat EFD study, consistent with the FDA Guidance for Industry, “Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations.” Animal data from the literature demonstrate that HER2 and EGFR are critically important for reproductive and developmental processes including blastocyst implantation, placental development, cardiac and neural development, and embryofetal/postnatal survival and development (see Section 5.4.4 for detailed assessment). The

Applicant performed a human-induced pluripotent stem cell-based assay (NAM), in which thalidomide/retinoic acid were used as the positive controls for adverse reproductive effects. In this assay, sevabertinib disrupted stem cell differentiation into cardiomyocytes and hepatocytes. Fertility studies were not conducted with sevabertinib nor are they warranted for the advanced cancer indication.

Based on findings in animals and its mechanism of action and consistent with current recommendations for non-genotoxic compounds that are teratogenic and/or embryo-fetal lethal described in the FDA Guidance for Industry, “Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations,” effective contraception use is recommended for male and female patients during treatment with HYRNUO and for 1 week after the last dose, based on five times the half-life of sevabertinib measured in patients (^{(b)(4)} hours). Following administration of [¹⁴C]-sevabertinib to lactating rats, sevabertinib-derived radioactivity was approximately 13- to 26-fold higher in milk than maternal plasma. During the 32-hour monitoring period, approximately 1.3% of the administered dose of sevabertinib was excreted into the milk. Thus, women are advised not to breastfeed during treatment with sevabertinib and for 1 week after the last dose.

Recommendation:

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of HYRNUO for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant’s Position:

This is the initial NDA submission for sevabertinib.

The FDA’s Assessment:

FDA agrees.

5.3. Pharmacology

Primary pharmacology

The Applicant’s Position:

Sevabertinib potently blocks mutant EGFR kinase activity in biochemical assays

The *in vitro* biochemical potency of sevabertinib was assessed in recombinant human *HER2wt*, *EGFRwt*, as well as in different *EGFR* mutant variants (for all *EGFR* mutants tested see Module 4.2.1.1, Report PH-42059). Sevabertinib exerted very strong biochemical activity at a

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physiologically-relevant ATP concentration (ATP=2 mM), with IC₅₀ values of 2.94 nM, 0.15 nM and 0.12 nM for *HER2*wt, *EGFR*wt, and *EGFR* ex20insSVD, respectively. In general, the potency of sevabertinib was at the lower detection limit of the biochemical assays. Therefore, an assessment of the biochemical selectivity of sevabertinib on *EGFR* mutant variants towards *EGFR*wt was technically not feasible (Module 4.2.1.1, Report PH-42059).

Anti-proliferative activity of sevabertinib in a HER2-mutant Ba/F3 cell line panel

The cellular activity profile of sevabertinib was evaluated using proliferation assays on a panel of Ba/F3 murine pro-B cells that stably overexpress a broader panel of mutant variants of the human *HER2* genes.

Sevabertinib showed strong potency in the most frequent *HER2* exon20 insertion mutations (IC₅₀s for the most prevalent exon20 insertion mutations: Ba/F3-*HER2* Y772_A755dup: 8.31 nM; Ba/F3-*HER2* G776delinsVC: 6.73 nM; and Ba/F3-*HER2* G778_P780dup: 2.34 nM). Similarly strong antiproliferative activity was observed in the Ba/F3 cells carrying the most frequent *HER2* activating point mutations: Ba/F3-*HER2* S310F: IC₅₀=2.47 nM; Ba/F3-*HER2* S310Y: IC₅₀=0.98 nM; Ba/F3-*HER2* L755P: IC₅₀=5.29 nM (for additional mutations, see **Table 3**).

Sevabertinib was equipotent on Ba/F3-*HER2*wt vs. the mutant variants, with an IC₅₀ of 5.3 nM (**Table 3**). Additional *HER2* mutations have been profiled and are documented in Module 4.2.1.1, Report B003066.

Table 3. Sevabertinib Potently Inhibits Proliferation in Ba/F3 Cells Lines Expressing HER2 Ex20 Insertion Mutations and Point Mutations

HER2 status	Ba/F3 cell line	Cellular IC ₅₀ [nM]
Ba/F3 parental cells EGFR wildtype HER2 wildtype	Ba/F3 - vector control	>1000
	Ba/F3 - <i>EGFR</i> wt	221
	Ba/F3 - <i>HER2</i> wt	5.3
<i>HER2</i> exon20 insertion mutation	Ba/F3 - <i>HER2</i> Y772_A755dup	8.31
	Ba/F3 - <i>HER2</i> G776delinsVC	6.73
	Ba/F3 - <i>HER2</i> G778_P780dup	2.34
<i>HER2</i> activating point mutation	Ba/F3 - <i>HER2</i> S310F	2.47
	Ba/F3 - <i>HER2</i> S310Y	0.98
	Ba/F3 - <i>HER2</i> S653C	5.85
	Ba/F3 - <i>HER2</i> L755A	6.8
	Ba/F3 - <i>HER2</i> L755P	5.29
	Ba/F3 - <i>HER2</i> V777L	0.54
	Ba/F3 - <i>HER2</i> V842I	2.25

IC₅₀ [nM]=concentration of half-maximal growth inhibition

Antiproliferative effect of sevabertinib was assessed in a Ba/F3 cell line panel stably overexpressing the depicted *HER2* mutant variants.

Source: Module 4.2.1.1, Report B003066.

Anti-proliferative activity of sevabertinib in an EGFR-mutant Ba/F3 cell line panel

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The cellular activity profile of sevabertinib in different *EGFR*- and *HER2* mutational backgrounds was assessed using proliferation assays on a panel of Ba/F3 murine pro-B cells that stably overexpress mutant variants of the human *EGFR* or *HER2* genes.

Sevabertinib showed strong potency in various *EGFR* exon20 insertion mutations and sub-nM potency in the classical activating mutations (*EGFR* ex19del and L858R) (IC_{50} s for the most prevalent exon20 insertion mutation *EGFR* ex20insASV: 4.66 nM; *EGFR* ex19del: 0.16 nM; and *EGFR* L858R: 0.52 nM). Sevabertinib was also highly active in Ba/F3-*HER2* ex20ins cells with an IC_{50} of 8.31 nM. Sevabertinib retained its cellular potency in the presence of the acquired resistance mutation C797S (*EGFR* ex19del/C797S: IC_{50} =0.22 nM), but significantly lost activity in the presence of the gatekeeper mutation T790M (*EGFR* ex19del/T790M: IC_{50} =21.9 nM) (**Table 4**).

Activity of sevabertinib was significantly reduced in Ba/F3-*EGFR*wt cells (IC_{50} =221 nM), resulting in selectivity of the target mutations over *EGFR*wt of ~47-fold for the exon20ins mutations (*EGFR* ex20insASV vs. *EGFR*wt) and of ~1380-fold for the classical activating mutations (*EGFR* ex19del vs. *EGFR*wt). In contrast to the observed selectivity on Ba/F3-*EGFR*wt, sevabertinib was equipotent on Ba/F3-*HER2*wt vs. the mutant variant (**Table 4**). Additional *EGFR* mutations have been profiled and are documented in Module 4.2.1.1, Report PH-42058.

Table 4. Sevabertinib Potently Inhibits Proliferation in Ba/F3 Cells Lines Expressing EGFR- and HER2 Ex20 Insertion Mutations and Classical Activating Mutations; Irrespective of the EGFR-C797S Status

EGFR status	Ba/F3 cell line	Cellular IC ₅₀ [nM]
Ba/F3 parental cells EGFR wildtype	Ba/F3 - vector control	>1000
	Ba/F3 - EGFRwt	221
EGFR exon20 insertion mutation	Ba/F3 - EGFR V769_D770insASV	4.66
	Ba/F3 - EGFR D770_N771insSVD	4.81
	Ba/F3 - EGFR H773_V774insNPH	28.2
EGFR classical activating mutation	Ba/F3 - EGFR E746_A750del	0.16
	Ba/F3 - EGFR L858R	0.52
EGFR acquired resistance mutations	Ba/F3 - EGFR E746_A750del/C797S	0.22
	Ba/F3 - EGFR L858R/C797S	0.60
	Ba/F3 - EGFR E746_A750del/T790M	21.9
	Ba/F3 - EGFR E746_A750del/T790M/C797S	53.9
	Ba/F3 - EGFR L858R/T790M	174
HER2 wildtype	Ba/F3 - HER2wt	5.30
	Ba/F3 - HER2 Y772_A755dup (also known as A775_G776 insYVMA)	8.31

IC₅₀ [nM]=concentration of half-maximal growth inhibition; EGFR E746_A750del = EGFR ex19del.

Antiproliferative effect of sevabertinib was assessed in a Ba/F3 cell line panel stably overexpressing the depicted EGFR- and HER2 mutant variants.

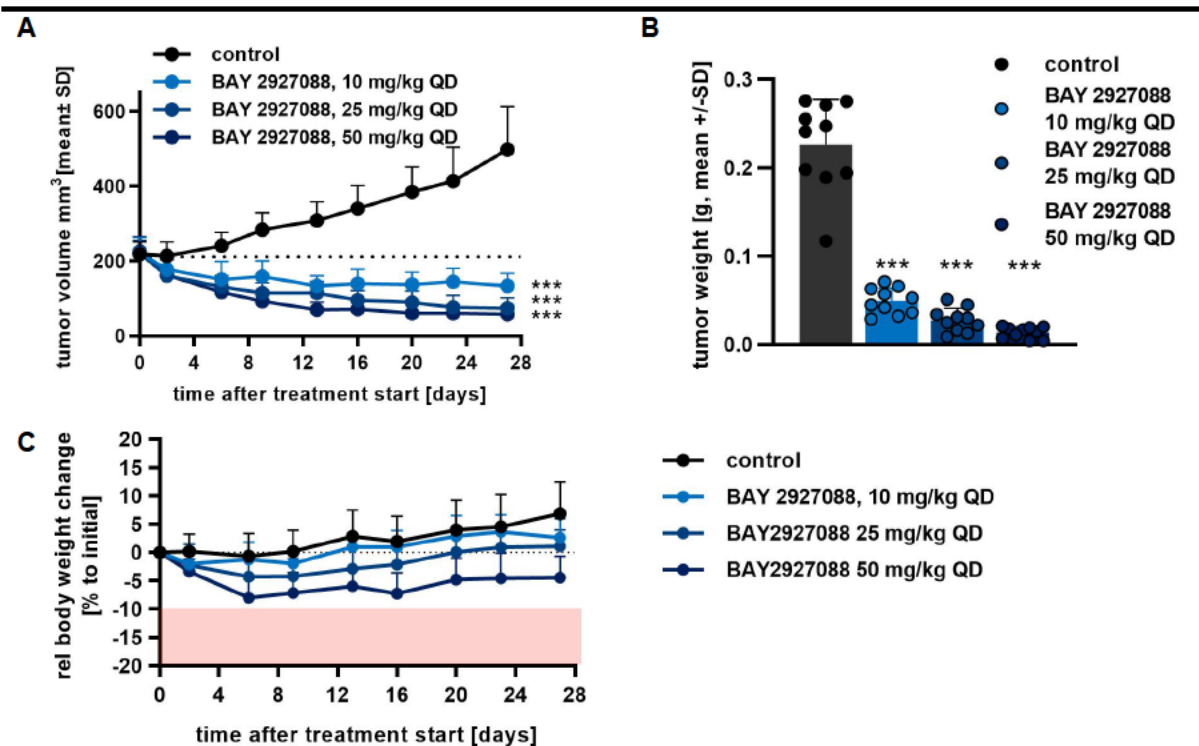
Source: Module 4.2.1.1, Report PH-42058

In vivo antitumor efficacy of sevabertinib in the patient-derived NSCLC xenograft model CTG-2543 (HER2 Y772 A755dup [ex20insYVMA]) in mice

HER2 ex20ins mutations represent the vast majority (96%) of HER2 activating mutations in lung cancer and are found in 2-4% of advanced NSCLC (11). The *in vivo* efficacy of sevabertinib was evaluated in the patient-derived, HER2 Y772_A755dup (ex20insYVMA) positive NSCLC model CTG-2543, to assess the therapeutic potential in HER2 ex20ins mutant patients (25).

Female athymic Nude-*Foxn1tm* mice were subcutaneously transplanted with CTG-2543 tumor fragments. Starting at a tumor size of 150-300 mm³, the animals were treated with either vehicle (control) or sevabertinib at 10 mg/kg, 25 mg/kg, or 50 mg/kg QD for 28 days. Animal body weight and tumor size were measured twice weekly and at study end, the tumors were collected for tumor weight analyses. Treatment with sevabertinib was well tolerated and resulted in significant tumor growth inhibition compared to the vehicle control and tumor regression with final T/C_{vol/weight} values of 0.27/0.22 (10 mg/kg QD), 0.15/0.11 (25 mg/kg QD), and 0.12/0.05 (50 mg/kg QD), respectively (**Figure 1**) (Module 4.2.1.1, Report R-13868).

Figure 1. Efficacy of Sevabertinib in HER2 Y772_A755dup (ex20insYVMA) PDx Model CTG-2543



CTG-2543 tumor fragments were subcutaneously transplanted into female Nude-Foxn1nu mice. At a tumor size of 150 mm³-300 mm³, treatment started for a 28-day treatment period. Animals received either vehicle (Solutol/EtOH/water 40/10/50, pH4) or sevabertinib at 10mg/kg QD, 25mg/kg QD, or 50mg/kg QD po.

(A) Time course of tumor growth

(B) Final tumor weight on Day 27 (study termination). Bar graphs depict the individual tumor weights as well as the mean tumor weight per study group.

(C) Time course of relative body weight change. Asterisks indicate statistical significance (***) p<0.0001).

Source: Module 4.2.1.1, Report R-13868

In vivo antitumor efficacy of sevabertinib in the patient-derived NSCLC xenograft model CTG-2842 (EGFR ex20insASV) in mice

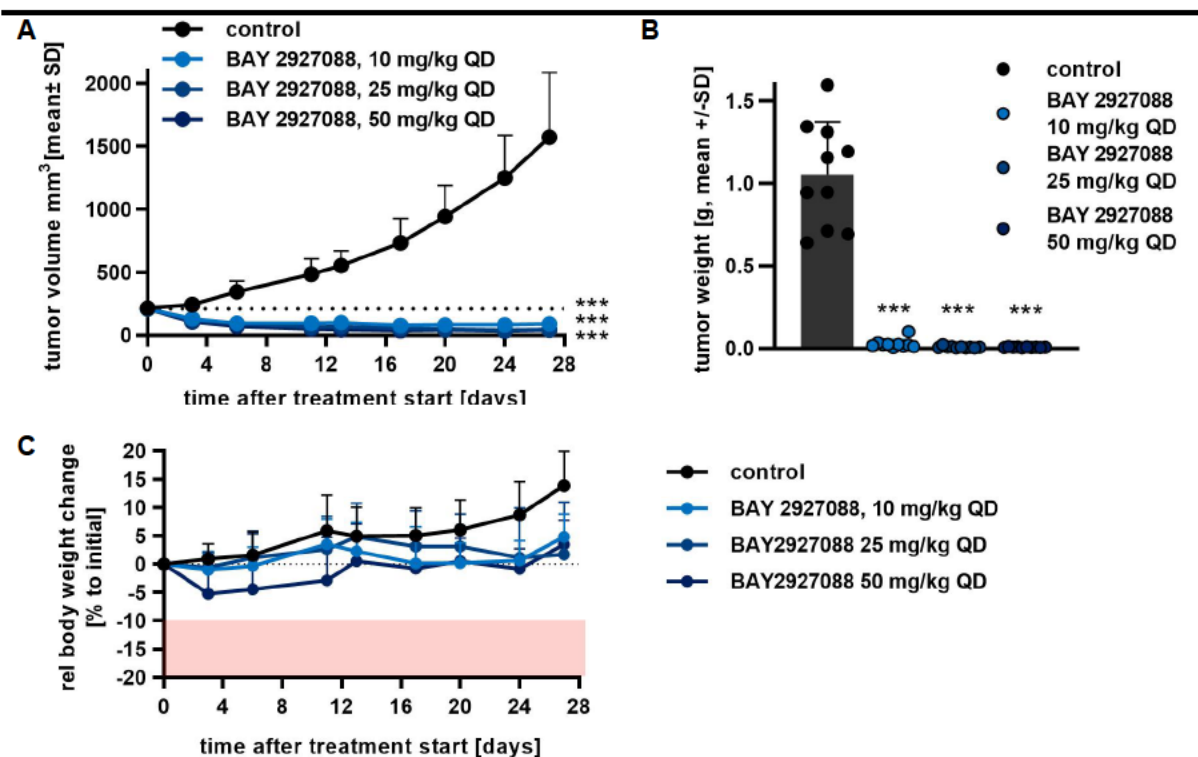
The therapeutic efficacy and tolerability of sevabertinib was assessed in the patient-derived xenograft model, CTG-2842, carrying an *EGFR* V769_D770insASV insertion (ex20insASV) (26). Female athymic Nude-*Foxn1*^{nu} mice were subcutaneously transplanted with CTG-2842 tumor fragments. At a tumor size of 150 mm³-300 mm³, treatment with either vehicle (control) or sevabertinib at 10 mg/kg, 25 mg/kg, or 50 mg/kg QD was initiated and continued for 28 days. Animal body weight and tumor size were measured twice weekly and at study end, tumors were collected for tumor weight analyses.

Treatment with sevabertinib was well tolerated and resulted in significant anti-tumor activity compared to the vehicle control and tumor regression with final T/C_{vol/weight} values of 0.06/0.02

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(10 mg/kg QD), 0.03/0.01 (25 mg/kg QD), and 0.03/0.01 (50 mg/kg QD), respectively (Figure 2) (Module 4.2.1.1, Report R-13868).

Figure 2. Efficacy of Sevabertinib in EGFR ex20insASV PDx Model CTG-2842



CTG-2842 tumor fragments were subcutaneously transplanted into female Nude-*Foxn1^{nu}* mice. At a tumor size of 150 mm³-300 mm³, treatment started for a 28-day treatment period. Animals received either vehicle (Solutol/EtOH/water 40/10/50, pH4) or sevabertinib at 10mg/kg QD, 25mg/kg QD, or 50mg/kg QD po.

(A) Time course of tumor growth

(B) Final tumor weight on Day 27 (study termination). Bar graphs depict the individual tumor weights, as well as the mean tumor weight per study group.

(C) Time course of relative body weight change. Asterisks indicate statistical significance (***) p<0.0001).

Source: Module 4.2.1.1, Report R-13868

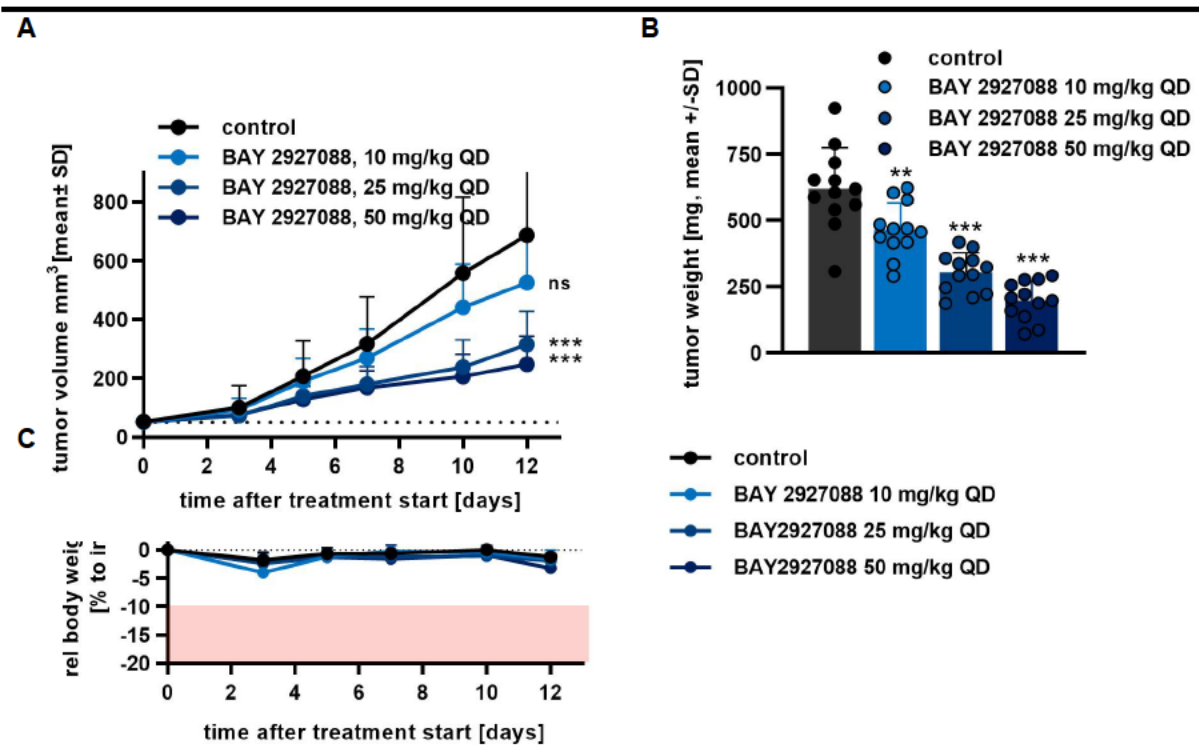
In vivo antitumor efficacy of sevabertinib in the A431 (EGFRwt) human NSCLC xenograft model in mice

In order to evaluate whether the *in vitro* selectivity vs. *EGFRwt* translates into reduced *in vivo* activity in an *EGFRwt* tumor model, sevabertinib was investigated in the A431 (*EGFRwt*) human lung cancer xenograft model. Female CB17-SCID mice, subcutaneously inoculated with A431 (*EGFRwt*) human NSCLC cells, received either vehicle (control) or sevabertinib at 10 mg/kg QD, 25 mg/kg QD, or 50 mg/kg QD. Animal body weight and tumor size were measured 2-3 times weekly and at study end, the tumors were collected for tumor weight analyses.

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Treatments at 25 mg/kg QD and 50 mg/kg QD significantly reduced tumor growth, but to a lesser extent than in the EGFR mutant tumors models tested. The weak to moderate antitumor activity is reflected by the final T/C_{vol/weight} of 0.46/0.49 (25 mg/kg QD) and 0.36/0.32 (50 mg/kg QD), respectively. sevabertinib treatment at 10 mg/kg QD, the dose that has been determined as fully efficacious in the HER2- and EGFR mutant tumor models, shows no significant antitumor activity in the EGFR_{wt} model, A431, with final T/C_{vol/weight} values of 0.77/0.75. All treatments were well tolerated (Figure 3) (Module 4.2.1.1, Report PH-42102).

Figure 3. Efficacy of Sevabertinib in the A431 (EGFR_{wt}) Human NSCLC Xenograft Model in Mice



A431 cells were subcutaneously transplanted into female CB17-SCID mice. At ~52 mm³ tumor size, the animals were randomized into study groups (n=12) and treatment started for a 13-day treatment period. The animals received vehicle (Solutol/EtOH/water 40/10/50, pH4) or sevabertinib at 10 mg/kg QD, 25 mg/kg QD, or 50 mg/kg QD po.

(A) Time course of tumor growth

(B) Final tumor weight on Day 12 (study termination). Bar graphs depict the individual tumor weights, as well as the mean tumor weight per study group.

(C) Time course of body weight change expressed as a percentage of the starting weight of the animal.

Asterisks indicate statistical significance (ns; not significant; * p<0.05; ** p<0.01; *** p<0.001).

Source: M4.2.1.1, Report PH-42102

Anti-proliferative activity of BAY 3306572 (M1 of sevabertinib) in a Ba/F3 EGFRmut and HER2mut cell line panel

BAY 3306572 has been identified as the major human metabolite (M1) of sevabertinib.

The compound was profiled for its *in vitro* anti-proliferative activity in a panel of Ba/F3 EGFR mutant and HER2 mutant cell lines.

BAY 3306572 showed a median activity of 58.6 nM (ranging from 13.3 nM to 100 nM) in all profiled HER2ex20ins mutations and of 29.9 nM (ranging from 2.99 nM to 236 nM) in all profiled HER2 point mutations.

Compared to the parent compound, sevabertinib, the activity of BAY 3306572 was ~ 13-fold weaker in HER2ex20ins mutations and ~6-fold weaker in HER2 point mutations (sevabertinib: median activity in HER2ex20ins: 4.53 nM and HER2 point mutations: 5.09 nM) (Module 4.2.1.1, Report B003066) (see also **Table 5**).

BAY 3306572 also shows weaker activity, as compared to the parent compound sevabertinib, in Ba/F3 cells expressing *EGFR*wt and *HER2*wt. The IC₅₀s are 558 nM and 53 nM for BAY 3306572 (**Table 5**) vs. 221 nM and 5.3 nM (**Table 4**) for sevabertinib, respectively.

Additional EGFR and *HER2* mutations have been profiled and are documented in Module 4.2.1.1, Report B003067.

Table 5. BAY 3306572 Inhibits Proliferation in Ba/F3 Cells Lines Expressing EGFR- or HER2 Ex20 Insertion Mutations and Point Mutations

EGFR/ HER2 status	Ba/F3 cell line	Cellular IC ₅₀ [nM]
Ba/F3 parental cells	Ba/F3 - vector control	>1000
<i>EGFR</i> wildtype	Ba/F3 - <i>EGFR</i> wt	558
<i>HER2</i> wildtype	Ba/F3 - <i>HER2</i> wt	53
<i>EGFR</i> exon20 insertion mutation	Ba/F3 - <i>EGFR</i> V769_D770insASV	61.7
	Ba/F3 - <i>EGFR</i> D770_N771insSVD	61.7
	Ba/F3 - <i>EGFR</i> H773_V774insNPH	235
<i>EGFR</i> classical activating mutation	Ba/F3 - <i>EGFR</i> E746_A750del	2.85
	Ba/F3 - <i>EGFR</i> L858R	7.49
<i>HER2</i> exon20 insertion mutation	Ba/F3 - <i>HER2</i> Y772_A755dup	100
	Ba/F3 - <i>HER2</i> G776delinsVC	95.3
	Ba/F3 - <i>HER2</i> G778_P780dup	21.9
<i>HER2</i> activating point mutation	Ba/F3 - <i>HER2</i> S310F	4.84
	Ba/F3 - <i>HER2</i> S310Y	7.66
	Ba/F3 - <i>HER2</i> S653C	89.7
	Ba/F3 - <i>HER2</i> L755A	25.3
	Ba/F3 - <i>HER2</i> L755P	30.5
	Ba/F3 - <i>HER2</i> V777L	2.99
	Ba/F3 - <i>HER2</i> V842I	29.2

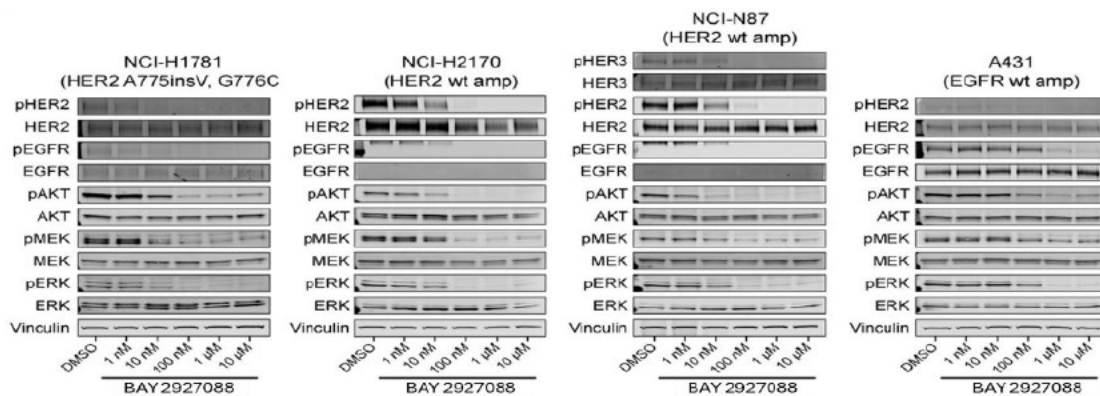
IC₅₀ [nM]=concentration of half-maximal growth inhibition. Antiproliferative effect of BAY 3306572 was assessed in a Ba/F3 cell line panel stably overexpressing the depicted EGFR- and HER2 mutant variants.

Source: Module 4.2.1.1, Report B003067

The FDA's Assessment:

FDA disagrees with the Applicant's use of vague, subjective, and promotional language (b) (4) when describing study results. FDA generally agrees with the Applicant's conclusions, with additional pertinent details below.

- FDA notes that the activity of sevabertinib against WT EGFR and EGFR mutants is not relevant to the proposed clinical indication; however, WT EGFR inhibition may have safety implications and was therefore included in Section 12.1 of the label.
- A homology model of HER2 was built using an X-ray crystallographic structure of EGFR in complex with sevabertinib as a template. The predictive X-ray crystallography showed that sevabertinib noncovalently interacts with the HER2 kinase domain. In addition, it did not interact with the Cys805 in the HER2 kinase domain, which is associated with irreversible binding. A cell viability assay showed that sevabertinib maintained activity in a Ba/F3 cell line expressing a HER2 C805S mutation (Siegel et al., Cancer Discovery, 2025).
- In vitro cellular assays in Ba/F3 murine cells stably expressing WT HER2 and a panel of HER2 exon 20 insertion mutations and activating point mutations showed that sevabertinib exhibited antiproliferative activity against all HER2 mutants tested, with IC₅₀ values generally within 2-fold for WT HER2 (IC₅₀ = 5.30 nM) and the HER2 mutants, with the exception of the activating point mutations S310Y (IC₅₀ = 0.98 nM), V777L (IC₅₀ = 0.54 nM), and T798M (IC₅₀ = 13.9 nM) (Study No. EXP-GDPWI-06962 (ELSA); Report No. B003066). The IC₅₀ concentrations for WT and mutant HER2 are below the free C_{max} of 88 nM at the intended clinical sevabertinib dose of 20 mg based on ~95% protein binding.
- In addition to xenograft models bearing EGFR mutants, the antitumor activity of sevabertinib was evaluated in immunocompromised mice bearing NSCLC patient-derived xenografts expressing the HER2 ex20ins YVMA mutation (Study No. 1212-104; Report No. R-13868). Oral administration of sevabertinib at doses of 10, 25, and 50 mg/kg once daily for 28 days led to tumor growth inhibition of 40%, 67%, and 74%, respectively, compared to the control group. There were 3/10 partial responders (PRs) in the 25 mg/kg group and 6/10 PRs in the 50 mg/kg group. There were no mortalities or adverse effects on body weights.
- Immunoblot analysis showed that treatment of human cancer cell lines with increasing concentrations of sevabertinib (1 nM to 10 μM) led to inhibition of p-HER2 as well as downstream signaling components including p-ERK, p-AKT, and p-MEK in NCI-H1781 lung cancer cells with a HER20 exon 20 insertion, and NCI-H2170 lung cancer cells and NCI-N87 gastric cancer cells with WT HER2 amplification (Study No. STY-25-00593; Report No. B004515).

Figure 4. Sevabertinib Inhibits HER2 Phosphorylation and Downstream Signaling in Cancer Cells Harboring HER2 Alterations

(Excerpted from Applicant's submission: Study STY-25-00593)

Secondary Pharmacology

The Applicant's Position:

Several *in vitro* and *ex vivo* studies were conducted in order to characterize the secondary pharmacodynamic properties of sevabertinib.

The specificity of sevabertinib and its metabolite BAY 3306572, was tested *in vitro* by investigating potential interactions with up to 77 mostly human off-targets, including G protein-coupled and nuclear receptors, ion channels, transporters, and enzymes in radioligand binding and biochemical assays at concentrations up to 10 $\mu\text{mol/L}$ (Module 4.2.1.2, Report R-13832 and Module 4.2.1.2, Report R-14379). Sevabertinib did not display significant effects (>50%) on 72 out of 76 targets at 10 $\mu\text{mol/L}$. Interactions with the following four off-targets were observed: inhibition of binding to the human adenosine A1 ($K_i \sim 0.52 \mu\text{mol/L}$) and A3 receptors ($K_i \sim 1.03 \mu\text{mol/L}$), motilin ($K_i \sim 1.32 \mu\text{mol/L}$), and inhibition of the human PDE4D2 activity ($\text{IC}_{50} \sim 2.77 \mu\text{mol/L}$). In two follow-up functional *in vitro* assays (A1: GTP γ S in CHO cells; motilin: intracellular Ca²⁺ in recombinant CHO cells), sevabertinib displayed functional antagonistic activity at the human adenosine A1 receptor ($\text{IC}_{50} \sim 4.3 \mu\text{mol/L}$) and at the human motilin receptor ($\text{IC}_{50} \sim 4.9 \mu\text{mol/L}$) (Module 4.2.1.2, Report R-13833 and Module 4.2.1.2, Report R-13933). This off-target activity was observed at concentrations ≥ 6 -fold higher than the human plasma concentration ($C_{\text{max,u,ss}} \sim 91 \text{ nmol/L}$) at the clinically relevant dose of 20 mg/patient BID.

The metabolite, BAY 3306572, did not display significant effects (>50%) on 72 out of 77 targets at 10 $\mu\text{mol/L}$. Functional interactions with the following 5 human off-targets were observed: inhibition of the adenosine A1 ($\text{IC}_{50} \sim 4.0 \mu\text{mol/L}$) and A3 receptors ($\text{IC}_{50} \sim 2.7 \mu\text{mol/L}$), adenosine transporter (uptake $\text{IC}_{50} \sim 0.46 \mu\text{mol/L}$), cyclooxygenase-2 ($\text{IC}_{50} \sim 2.2 \mu\text{mol/L}$), and 15-lipoxygenase ($\text{IC}_{50} \sim 0.25 \mu\text{mol/L}$) (Module 4.2.1.2, Report B002421).

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In order to test for interferences with cardiac ion channels *in vitro*, the effects of sevabertinib and its metabolite, BAY 3306572, on the hNav1.5 Na⁺ current (involved in cardiac depolarization), the L-type hCav1.2 Ca²⁺, hKir2.1 K⁺, hKvLQT1 K⁺, and hERG K⁺ currents (involved in cardiac repolarization) were investigated using automated voltage-clamp systems. Sevabertinib and BAY 3306572 did not interfere with these cardiac ion channels, with the exception of the hERG K⁺ current which was inhibited by sevabertinib with an IC₅₀ of 2.2 μmol/L; this concentration is about 24-fold higher than the human plasma concentration (C_{max,u,ss} ~91 nmol/L) at the clinically relevant dose of 20 mg/patient BID. BAY 3306572 inhibited the hERG K⁺ current with an IC₅₀ of 3.5 μmol/L (Module 4.2.1.2, Report PH-42086 and Module 4.2.1.2, Report B002455).

The specificity of sevabertinib was evaluated in the KinaseProfiler panel at (b) (4). Out of 373 kinases tested, sevabertinib (at 1 μM) inhibited 18 kinases by more than 80%, including 3 EGFR kinase family members (EGFR1, ErbB2, and ErbB4). These kinases were included in follow-up studies. The most potently inhibited non-EGFR kinase was DDR2, with an IC₅₀ of 53.3 nM (2 mM ATP) (Module 4.2.1.1, Report R-13813 and Module 4.2.1.1, Report PH-42059).

Ex vivo, sevabertinib, at up to 1 μmol/L, did not alter hemodynamic and electrical parameters in rabbit Langendorff hearts. At 10 μmol/L; however, left ventricular systolic pressure and contractility were markedly reduced, and ECG changes (QTcF shortening and QRS widening) were observed (Module 4.2.1.2, Report PH-42110).

The FDA's Assessment:

FDA generally agrees with the Applicant's conclusions. However, FDA calculated the C_{max} of unbound sevabertinib to be ~88 nM at the recommended dose of 20 mg orally twice daily based on a total C_{max} of 902 ng/mL and fraction unbound of 4.71%. Additional pertinent details are provided below.

- In functional *in vitro* assays assessing off-target activity, sevabertinib exhibited antagonistic effects at the human adenosine A1 receptor and human motilin receptor with IC₅₀ values of 4.3 and 4.9 μM, respectively (≥49-fold the free C_{max} of 88 nM in humans at the recommended clinical dose of 20 mg BID) (Report Nos. R-13833 and R-13933).
- In *in vitro* TR-FRET-based kinase activity inhibition or competition assays, sevabertinib inhibited DDR2 with an IC₅₀ of 53.3 nM, DDR1 with an IC₅₀ of 111 nM, and MAPK14 with an IC₅₀ of 132 nM, indicating that sevabertinib has the potential to target these kinases at clinically relevant concentrations based on a free C_{max} of 88 nM. Sevabertinib inhibited the other seven non-EGFR kinases evaluated with IC₅₀ values ranging from 335 nM to 5.2 μM (Report No. PH-42059).
- In an *ex vivo* study, exposure of spontaneously beating rabbit Langendorff heart to sevabertinib at concentrations of 0.1, 1, and 10 μM resulted in a concentration-dependent decrease in LVP, dP/dt_{max} (contractility), and coronary flow, which reached statistical significance compared to the control at 10 μM (or ≥1 μM for LVP).

Sevabertinib also shortened the QTcF interval and left ventricular MAPD₉₀, and caused widening of the QRS interval. Overall, the largest changes were observed at 10 µM (Study No. T104629-2; Report No. PH-42110), a concentration much higher than the free C_{max} of 88 nM at the recommended clinical dose. These findings also provide relevant safety pharmacology information on vascular effects due to the off-target effects of adenosine and motilin receptors.

Safety Pharmacology

Effects of sevabertinib on vital organ systems, i.e. cardiovascular, respiratory, and the CNS, were investigated in one *in vitro* (hERG assay) and in three *in vivo* studies, according to the ICH S7A and ICH S7B guidelines. The *in vivo* studies were conducted after single oral administration of sevabertinib (i) in rats at doses of 0 (Ethanol/KolliphorHS15®/Water [10/40/50, v/v/v], pH 4), 5, 15, and 45 mg/kg; and (ii) in telemetered dogs at doses of 0 [ethanol/PEG400/water, 1:5:4, pH ~4, 2 mL/kg], 2, 5, and 15 mg/kg body weight. Concordant with the ICH S9 guideline, the effects of sevabertinib on safety pharmacology endpoints of CNS function (detailed clinical observations following dosing) were assessed within a pivotal 4 week, toxicity study in Wistar rats, with once daily oral administration. The studies were conducted in compliance with the OECD Principles of GLP at certified testing facilities in Germany or the United Kingdom, which are member countries of the OECD Mutual Acceptance of Data Agreement.

Sevabertinib, at single oral doses, was devoid of major acute effects (i) on hemodynamic parameters in a dog telemetry study (Module 4.2.1.3, R-14051), (ii) on parameters of CNS function (behavior, locomotor activity, and body temperature) in rats (Module 4.2.1.3, PH-42619), and (iii) on parameters of respiratory function (respiration rate, and tidal and minute volume) in rats (Module 4.2.1.3, Report PH-42756).

Detailed clinical observations as included in the 4-week, repeat-dose, rat toxicity study did not reveal abnormalities in general behavior, posture, and breathing on Days 1 and 2 (Module 4.2.3.2, Report PH-42111).

As shown *in vitro* (hERG K⁺ assay) and *in vivo* (ECG, including QT/QTc intervals in telemetry dogs), sevabertinib has a potential for delayed repolarization at clinically relevant plasma concentrations and above. A hERG IC₅₀ value of 2.4 µmol/L was calculated (Module 4.2.1.3, R-13892), resulting in a no-effect level (defined as 1/30 of the hERG IC₅₀) of 80 nmol/L; this is similar to the human plasma concentration (C_{max,u,ss} ~91 nmol/L) at the clinically relevant dose of 20 mg/patient BID. At the high dose in dogs, the QT/QTc interval in the ECG was slightly (~8 ms), but significantly prolonged at about 1.5 h to 4 h post-treatment. This delayed repolarization was observed at concentrations about 12-fold higher than the human plasma concentration (C_{max,u,ss} ~91 nmol/L) at the clinically relevant dose of 20 mg/patient BID (Module 4.2.1.3, Report R-14051).

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of the cardiovascular safety pharmacology findings. However, FDA notes that the prolonged QT/QTc interval occurred in individual animals (Study No. T104913-8, Report No. R-14051). Sevabertinib showed CNS effects in an in vivo safety pharmacology study in rats (Study No. T105511-3; Report No. PH-42619). After single administration of oral sevabertinib at doses of 5, 15, and 45 mg/kg, animals in the mid- and high-dose groups showed increased rearing activity at 1 and 24 hours postdose compared to the vehicle control group. In addition, animals at the high dose also showed decreased body temperature at 1-hour postdose. In the 4-week repeat-dose toxicity studies in rats, once daily administration of sevabertinib at doses up to 15 mg/kg did not cause CNS or respiratory effects.

5.4. ADME/PK

The Applicant's Position:

The PK of sevabertinib following IV administration was characterized by high systemic clearance in mice and a moderate clearance in rats and dogs. The volume of distribution was high in all three species. Elimination of sevabertinib was bi-phasic with short apparent half-lives in mice, rats and dogs and long terminal half-lives in mice and rats. Following oral administration to rats and dogs, the t_{max} was short. Oral bioavailability was low at 1 mg/kg in rats and moderate at 1 mg/kg in dogs and 10 mg/kg in rats. [^{14}C]sevabertinib (and/or its labelled metabolites) was rapidly and widely distributed from the blood compartment to most peripheral organs and tissues, as shown by QWBA in rats. Brain penetration was very low and testes penetration of radioactivity was moderate. In addition, no radioactivity could be detected in fetal tissues when administered to pregnant rats. In pigmented rats, there was evidence of a specific affinity to melanin bearing tissues. Data from IV and po administration of [^{14}C]sevabertinib to rats suggest that the predominant clearance pathways of sevabertinib can be attributed to metabolic processes. Excretion of [^{14}C]sevabertinib-derived radioactivity after IV dosing to BDC cannulated rats was found in bile, feces, GIT and urine. In addition, radioactivity was detected in the milk of lactating rats.

Binding of sevabertinib and the major human plasma metabolite M1 (BAY 3306572) to plasma proteins was moderate across species, with a stronger binding of M1 to human plasma (sevabertinib: 95.3%; M1: 98.1%). In the whole blood distribution assay, the Cb/Cp ratio for sevabertinib and M1 was more bound to plasma proteins (human), or rather equally distributed (preclinical species). In human hepatocytes *in vitro* and from the mass balance study in humans, the oxidation of sevabertinib leading to metabolite M1, is the most important metabolic pathway, followed by several minor oxidations and oxidations with subsequent secondary reactions. No human specific metabolites were identified. Metabolism of sevabertinib in human hepatocytes was mainly catalyzed by CYP3A4 and to a much lesser extent by CYP1A1 and glucuronidation.

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Absorption**Preclinical PK of sevabertinib after IV dosing in mice, rats and dogs****Table 6. Pharmacokinetics of Sevabertinib After Single Intravenous Administration**

Species		Mouse	Rat	Dog
Sex		Male	Male	Female
Dose	[mg/kg]	1	1	1
AUC	[µg·h/L]	165	587	1070
AUC _{norm}	[kg·h/L]	0.165	0.587	1.07
AUC(0-24)	[µg·h/L]	165	569	n.c.
AUC(0-24) _{norm}	[kg·h/L]	0.165	0.569	n.c.
C _{max}	[µg/L]	834	1060	1320
C _{max, norm}	[kg/L]	0.834	1.06	1.320
t _{max}	[h]	0.0333	0.0333	0.167
CL	[L/(h·kg)]	6.06	1.70	0.935
V _{ss}	[L/kg]	3.30	4.87	1.13
t _{1/2} ^a	[h]	3.85 ^a	15.9 ^a	n.a.
Interval ^b	[h]	2.00-8.00	8.00-48.0	n.a.
t _{1/2 app}	[h]	0.384	1.32	0.911 ^a
Interval ^c	[h]	0.5-2.00	2.00-8.00	0.250-8.00

n.a.=not applicable; n.c.=not calculated

a: used for AUC calculation

b: used for regression to determine half-life

c: used for regression to determine apparent half-life

Study details: mouse: vehicle 2% DMSO, 98% plasma (v/v) at 5 mL/kg, source: Module 4.2.2.2, Report PH-41995, rat: vehicle 2% DMSO, 98% plasma (v/v) at 5 mL/kg, source: Module 4.2.2.2, Report PH-41999, dog: vehicle 10% ethanol, 40% PEG400, 50% aqua demin. (v/v/v) at 1 mL/kg, infusion (T = 0.167 h), source: Module 4.2.2.2, Report R-13842

Preclinical PK of sevabertinib after po dosing in rats and dogs**Table 7. Pharmacokinetics of Sevabertinib After Single Oral Administration**

Species		Rat	Rat	Dog
Sex		Male	Male	Female
Dose	[mg/kg]	1	10	1
AUC	[µg·h/L]	71.3	1950	376
AUC _{norm}	[kg·h/L]	0.0713	0.195	0.376
AUC(0-24)	[µg·h/L]	69.3	1880	n.c.
AUC(0-24) _{norm}	[kg·h/L]	0.0693	0.188	n.c.
C _{max}	[µg/L]	16.0	475	170
C _{max, norm}	[kg/L]	0.0160	0.0475	0.170
t _{max}	[h]	0.750	0.875	0.500
t _{1/2} ^a	[h]	5.28 ^a	10.7 ^a	n.a.
Interval ^b	[h]	6.00 – 24.0 / 30.0	24.0 - 72.0	n.a.
t _{1/2 app}	[h]	1.96	2.14	0.983 ^a
Interval ^c	[h]	2.00-8.00	2.00-8.00	1.00 / 2.00 - 8.00
F ^d	[%]	12.1	33.2	35.1

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n.a. = not applicable; n.c. = not calculated

a: used for AUC calculation

b: used for regression to determine half-life

c: used for regression to determine apparent half-life

d: related to the AUC_{norm} 1 mg/kg IV of rats or dogs

Study details: rat: po vehicle 10% ethanol, 40% Solutol HS15, 50% aqua demin. (v/v/v) at 5 mL/kg, source:

M4.2.2.2, Report PH-41999; dog: po vehicle 10% ethanol, 40% PEG400, 50% aqua demin. (v/v/v) at 1 mL/kg,

source: Module 4.2.2.2, Report R-13842

The results presented in Tables 6 and 7 are derived from the following studies:

- PH-41995: Plasma Pharmacokinetics of Sevabertinib in Male CD1 Mice After Single Intravenous Administration of Sevabertinib.
- PH-41999: Pharmacokinetics of Sevabertinib in Male Wistar Rats After Single Intravenous and Oral Administration of Sevabertinib.
- R-13842: Evaluation of Pharmacokinetic Parameters of Sevabertinib after Single Intravenous and Oral Administration to Dogs

Distribution

Sevabertinib: *In Vitro* Investigations on Binding to Plasma Proteins in Different Species, to Purified Human Plasma Proteins, to Human Liver Microsomes, and on Determination of Blood/Plasma Partitioning (Report PH-41905)

Table 8. Plasma Protein Binding (in Vitro) of Sevabertinib in Different Species and Matrices

Species/Matrix	Concentration [µg-eq/L]	f _u ^a [%]
Human (m)	103 to 1054	4.71
Human (m)	9490	7.64
CD-1 mouse (m)	107 to 10138	9.74
BalbC mouse (f)	117 to 17460	10.5
NMRI mouse (f)	96.0 to 9432	8.46
Wistar rat (m)	107 to 14936	9.14
Wistar rat (f)	112 to 15075	9.97
NZW Rabbit (mix)	55.1 to 5047	9.01
Cynomolgus monkey (f)	98.4 to 12227	11.0
Beagle dog (f)	106 to 10108	9.38
Williams Medium with 10% FCS	102 to 9697	61.5
AGP (0.7 g/L)	945	26.1
HSA (40 g/L)	978	20.7
alpha-globulin (12 g/L)	997	39.4
gamma-globulin (10 g/L)	969	86.8
LDL (3 g/L)	856	38.5
HDL (3 g/L)	992	22.5
Human liver microsomes (0.05 mg/mL)	4209 to 12117	94.3
Human liver microsomes (0.1 mg/mL)	4695 to 12201	92.8
Human liver microsomes (0.5 mg/mL)	4683 to 12290	73.7

a: fraction of free (unbound) drug

Method: equilibrium dialysis.

Source: Module 4.2.2.3, Report PH-41905

Table 9. Blood to Plasma Concentration Ratio (in Vitro) of Sevabertinib in Different Species

Species	Concentration _{blood} [µg-eq/L]	Cb/Cp [%]
Human (m)	124 to 1215	0.637
Human (m)	8745 to 9784	0.837
CD-1 mouse (m)	115 to 8610	0.936
Wistar rat (m)	112 to 8290	1.05
Wistar rat (f)	129 to 8800	1.09
Beagle dog (f)	70.9 to 9027	0.906

Method: Cb/Cp distribution.

Source: Module 4.2.2.3, Report PH-41905

***In Vitro* Protein Binding of BAY 3306572 in Plasma from Various Species, Assay Medium, Protein Solutions, and Human Liver Microsomes, as well as *In Vitro* Distribution in Whole Blood from Human and Mouse (Report B002466)**

Table 10. Plasma Protein Binding (in Vitro) of BAY 3306572 (M1 of Sevabertinib) in Different Species and Matrices

Species / Matrix	Concentration [µg-eq/L]	f _u ^a [%]
Human (m)	100 - 1000	1.85
Human (m)	10000	3.13
NMRI mouse (f)	100 - 10000	3.99
Wistar rat (m)	100 - 10000	8.18
Wistar rat (f)	100 - 10000	4.57
NZW rabbit (f)	100 - 10000	4.39
Cynomolgus monkey (m)	100 - 10000	4.78
Cynomolgus monkey (f)	100 - 10000	4.96
Beagle dog (f)	100 - 10000	4.88
Williams Medium with 10% FCS	100 - 10000	44.9
InVitroGRO HI Medium	100 - 10000	52.7
AGP (0.7 g/L)	1000	6.31
HSA (40 g/L)	1000	8.37
alpha-globulin (12 g/L)	1000	19.6
gamma-globulin (10 g/L)	1000	76.6
LDL (3 g/L)	1000	61.8
HDL (3 g/L)	1000	35.2
Human liver microsomes (0.05 mg/mL)	100 - 10000	98.5
Human liver microsomes (0.1 mg/mL)	100 - 10000	92.0
Human liver microsomes (0.5 mg/mL)	100 - 10000	63.7
Human liver microsomes (1.0 mg/mL)	100 - 10000	43.7

a: fraction of free (unbound) drug

Method: equilibrium dialysis.

Source: Module 4.2.2.3, Report B002466.

Table 11. Blood to Plasma Concentration Ratio (in Vitro) of BAY 3306572 (M1 of Sevabertinib) in Different Species

Species	Concentration _{blood} [µg/L]	C _b /C _p
Human (m)	100 - 1000	0.726
Human (m)	10000	0.910
Mouse NMRI (f)	100 -10000	1.14

Source: Module 4.2.2.3, Report: B002466

R-14142: Quantitative and Qualitative Whole-Body Autoradiography after Oral and Intravenous Administration of [¹⁴C]sevabertinib to Male and Female Rats

[¹⁴C]sevabertinib (and/or its labelled metabolites) was rapidly and widely distributed from the blood compartment to most peripheral organs and tissues, as shown by QWBA in rats. Post-orally, most maximum concentrations in organs/tissues were higher than the blood maximum concentration. This was also reflected in terms of AUCs. However, brain penetration was very low and testes penetration of radioactivity was moderate. In pigmented rats, there was clear evidence of a specific affinity of substance-associated radioactivity to the eye wall and the skin as melanin bearing tissues.

Overall, there was no evidence of retention of radioactivity in the organs and tissues of male and female Wistar rats and of male pigmented rats with the exception of melanin-bearing tissues, in particular the eye wall.

Table 12. Pharmacokinetic Parameters of Radioactivity in Organs, and Tissues of Male Wistar Rats After Single Oral Administration of 2 mg/kg [¹⁴C] Sevabertinib

Organ/Tissue	t _{max} [h]	C _{eq} _{max} [µg-eq/L]	AUC(0-t _{last}) [µg-eq·h/L]	t _{1/2} alpha [h]	Range	t _{1/2} beta [h]	Range [h]
Blood LSC	1	169	413	1.65	2-8	1.65	2-8
Plasma LSC	1	174	509	1.72	2-8	3.63	2-24
Adrenal average	1	1760	4100	1.64	2-8	3.69	2-24
Blood ventricular (QWBA)	1	190	562	1.53	2-8	4.55	2-24
Bone (femur)	1	18.6	18.8	n.a.		n.a.	
Brain (without blood/choroid plexus)	1	3.73	1.87	n.a.		n.a.	
Colon wall	8	2420	35800	7.03	8-24	7.03	8-24
Eye ciliary body	1	129	149	0.815	2-4	2.17	2-8
Kidney (average)	1	812	3440	1.80	2-8	74.8	24-168
Liver ^a	1	3030	18000	3.04	2-8	53.0	24-168
Lung ^b	1	295	608	1.58	2-8	1.58	2-8
Skin (dorsal)	1	290	1030	n.d.		n.d.	
Testis	1	25.6	112	1.83	2-8	1.83	2-8

n.a. = not applicable; n.d. = not determined

Vehicle: 10% ethanol, 40% PEG, 50% distilled water (v/v/v) at 2.33 mL/kg.

a: without large blood vessels and bile ducts

b: without larger blood vessels

Source: Module 4.2.2.3 Report R-14142

Sevabertinib: Qualitative and Quantitative Whole-Body Autoradiography in Timed Pregnant Female Albino Wistar Rats After Single Oral Administration of [¹⁴C]sevabertinib

(Report B003616)

Table 13. Pharmacokinetic Parameters of Radioactivity in Selected Organs, and Tissues of Pregnant Wistar rats After Single Oral Administration of 1 mg/kg BW [¹⁴C] Sevabertinib

Matrix	Ce _q _{max} [µg-eq/g]	t _{max} [h]	AUC(0-24) [µg-eq·h/g]	t _{1/2} [h]	Regression range
Amnion	0.215	4	3.026	11.73	6-48
Amniotic fluid	BQL	n.d.	n.d.	n.d.	n.d.
Blood (cardiac)	0.038	2	0.310	n.d.	n.d.
Bone (femur)	BQL	n.d.	n.d.	n.d.	n.d.
Brain (total)	BQL	n.d.	n.d.	n.d.	n.d.
Heart (myocardium)	0.115	2	0.704	n.d.	n.d.
Eye (vitreous humor)	BQL	n.d.	n.d.	n.d.	n.d.
Kidney (average)	0.233	2	2.081	12.3	4-48
Liver	0.495	2	4.472	7.8	4-48
Mammary gland region	0.277	2	2.969	4.2	4-24
Ovaries	0.037	2	0.294	n.d.	n.d.
Placentae	0.044	2	0.396	n.d.	n.d.
Skeletal muscle	0.054	2	0.340	n.d.	n.d.
Skin	0.137	4	2.090	34.2	6-48
Uterus	0.068	2	0.438	n.d.	n.d.
Fetus (average)	BQL	n.d.	n.d.	n.d.	n.d.
Fetal Adrenal	BQL	n.d.	n.d.	n.d.	n.d.
Fetal Blood	BQL	n.d.	n.d.	n.d.	n.d.
Fetal Brain	BQL	n.d.	n.d.	n.d.	n.d.
Fetal Kidney	BQL	n.d.	n.d.	n.d.	n.d.
Fetal Liver	BQL	n.d.	n.d.	n.d.	n.d.
Fetal Muscle	BQL	n.d.	n.d.	n.d.	n.d.
Fetal Skin	BQL	n.d.	n.d.	n.d.	n.d.

n.d.=not determined; BQL=Below Quantifiable Limits

Vehicle: 10% ethanol, 40% PEG400, 50% Milli-Q water (v/v/v) at 5 mL/kg.

Source: Module 4.2.2.3, Report B003616

Metabolism

Sevabertinib: Metabolite Profiling, Structure Elucidation and species comparison *in vitro* and *in vivo* (Report PH-42600)

Table 14. [¹⁴C] Sevabertinib: Mass Balance of 2 h Incubations With Hepatocytes of Different Species

Species ^a (Sex)	Buffer	HH (m/f)	MH (m)	MH (f)	RH (m)	RH (f)	RbH (f)	DH (m/f)	CMH (f)	MPH (f)
Assignment ^b	%	%	%	%	%	%	%	%	%	%
sevabertinib	95.9	59.8	1.35	1.59	BQL	33.2	BQL	38.4	10.1	4.04
M1	2.10	18.8	12.5	17.2	11.1	14.1	BQL	19.8	22.5	21.8
M2	-	BQL	-	-	-	BQL	BQL	15.8	BQL	16.9
M3	-	BQL	37.8	35.3	9.20	9.69	BQL	-	BQL	-
M4	-	BQL	20.5	19.2	3.86	1.86	-	-	BQL	-
M5	-	2.57	-	-	-	BQL	0.67	BQL	8.85	BQL
M6	-	6.06	BQL	-	BQL	BQL	4.87	BQL	6.44	2.14
M7	-	6.69	BQL	BQL	6.03	5.89	58.1	BQL	19.8	BQL
M8	-	2.34	6.98	6.36	3.30	BQL	14.7	4.35	4.13	5.96
M10	-	BQL	4.30	3.44	26.0	27.0	7.01	3.43	2.00	7.88

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M11	-	-	BQL	2.19	14.2	4.35	-	1.83	-	1.83
M12	-	BQL	BQL	BQL	1.54	0.98	BQL	5.32	3.22	1.14
M13	-	BQL	-	-	-	-	BQL	BQL	BQL	BQL
M14	-	1.49	BQL	BQL	1.80	BQL	-	-	1.47	1.82
M15	-	BQL	BQL	BQL	-	-	1.53	-	7.66	BQL
M16	-	BQL	3.68	6.32	BQL	-	BQL	-	BQL	12.4
M17	-	2.27	1.15	3.11	4.84	BQL	3.56	BQL	8.15	5.61
M18	-	BQL	BQL	BQL	BQL	-	BQL	BQL	5.72	BQL
Sum other	-	-	-	-	3.68	-	5.56	8.81	-	5.67
Sum unknown	2.04	-	11.8	5.21	14.4	2.87	4.00	2.29	-	12.9

a: HH, MH, RH, RbH, DH, CMH, MPH = human, mouse, rat, rabbit, dog, cynomolgus monkey, minipig hepatocytes

b: BQL=below radioactivity quantitation limit, detected by MS only

Source: Module 4.2.2.4, Report PH-42600

Sevabertinib Enzymes involved in the Biotransformation of Sevabertinib *in vitro* (Report PH-42662)

Table 15. Substrate Characteristics of Sevabertinib Towards CYP Isoforms

Species / strain:	Human / n.a. Recombinant CYP isoforms	Route:	In vitro HPLC-LSC-HRMS/MS	Nuclide:	¹⁴ C						
Material:	sevabertinib	Assay:	HRMS/MS	Incubation time:	1 h						
Compound:	sevabertinib	Assay:	HRMS/MS	Incubation time:	1 h						
Human CYP isoform	Recovery [%]	¹⁴ C sevabertinib [%]	M1 [%]	M2 [%]	M9 [%]	M12 [%]	M13 [%]	M14 [%]	Other [%]	Unknown [%]	
Insect Control	124.2	99.4	0.6	-	-	-	-	-	-	-	
1A1	119.4	52.7	11.2	3.5	BQL	2.3	25.4	-	-	4.8	
1A2	108.6	95.2	3.2	0.8	BQL	0.9	BQL	-	-	-	
1B1	127.4	79.0	4.0	BQL	BQL	9.0	4.7	-	2.0	1.3	
2A6	103.7	99.3	0.7	-	-	-	-	-	-	-	
2B6	116.9	99.3	0.7	-	-	-	-	-	-	-	
2C8	140.8	90.2	2.4	-	-	5.9	-	-	0.7	0.7	
2C9	134.5	91.2	2.5	-	-	3.7	-	-	-	2.6	
2C18	122.0	95.8	1.8	-	-	1.7	-	-	-	0.7	
2C19	120.2	97.8	0.8	-	BQL	1.4	-	-	-	-	
2D6	111.4	93.1	2.4	-	BQL	0.9	-	-	-	3.6	
2E1	127.2	98.3	1.7	-	-	-	-	-	-	-	
2J2	138.3	93.0	2.0	-	-	3.6	-	-	0.6	0.8	
3A4	109.2	11.3	44.8	-	5.9	10.6	0.8	4.4	17.0	5.2	
3A5	116.5	70.1	20.5	-	3.0	2.2	1.2	BQL	2.0	1.0	
3A7	103.8	93.0	3.7	-	BQL	0.9	1.5	BQL	-	0.9	
4A11	104.3	95.9	1.4	-	-	-	-	-	-	2.8	
4F2	107.3	97.0	1.1	-	-	0.6	-	-	-	1.3	
4F3A	103.6	98.2	1.1	-	-	-	-	-	-	0.6	
4F3B	120.4	95.3	1.2	-	-	-	0.8	-	-	2.7	
4F11	97.4	94.9	1.1	-	-	1.1	-	-	-	2.9	
4F12	108.0	97.3	1.4	-	-	-	-	-	-	1.2	
19A1	97.0	43.0	36.5	4.9	3.7	-	5.2	-	3.2	3.5	

- = Not detected; BQL = below quantitation limit.

Source: Module M4.2.2.6, Report PH-42662

Excretion

Version date: March 1, 2024 (ALL NDA/ BLA reviews)

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

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Sevabertinib: Absorption, Biotransformation and Excretion in Rat after Single Administration of [¹⁴C]sevabertinib (Report PH-42767)**Table 16. Metabolic Pattern [% of Dose] in Urine, Feces, Bile and GIT (Prominent Metabolites) After Administration of [¹⁴C] Sevabertinib to Male Wistar Rats**

Species	Intact Rat	BDC Rat
Route	po	iv
Dose [mg/kg]	3	1
Sampling interval [h]	0-120	0-24
% of dose		
Urine	1.40	4.12
Sevabertinib	0.108	0.273
Other (M1, M3/13, M5, M6, M12, M14)	0.526	1.834
Feces	93.0	14.7
sevabertinib	51.0	8.54
M1	12.5	3.09
M5/M16	7.70	0.138
M6	3.12	0.718
Other (M9/M12, M13, M15)	6.77	1.04
Bile	n.a.	73.9
sevabertinib		1.08
M1		2.41
M3/M8		6.56
M4/M18		3.74
M7		3.84
M10		18.4
M11		4.69
Other (M12, M14, M17)		3.69
GIT	n.a.	4.34
sevabertinib		1.08
Other (M1, M5/M16, M6, M13)		1.87
Residues	0.0574^a	0.563^c
Recovery^b	94.4	98.8

n.a.=not applicable; GIT=gastrointestinal tract

a: total body including GIT

b: recovery calculated including cage wash

c: total body excluding GIT.

Source: Module 4.2.2.4, Report PH-42767.

Sevabertinib: Determination of Lacteal Excretion and Plasma Pharmacokinetics in Postpartum Female Albino Wistar Rats Following a Single Oral Administration of [¹⁴C]sevabertinib (Report B003512)

Mean milk to plasma concentration ratios determined for each time point ranged from 12.6 at 1 h to 26.1 at 6 h. The cumulative sum percent of administered dose secreted into milk from 0 to 32 h was 1.3%, suggesting that [¹⁴C]sevabertinib-derived radioactivity penetrates from circulating blood into milk of lactating female rats.

Summary PK parameters from pharmacokinetic studies

Please refer to Table 7 Pharmacokinetics of sevabertinib after single oral administration.

Table 17. Toxicokinetics – Summary of Exposure in Steady State (Day 79) in Male & Female Rats

Sex	Dose	[mg/kg/d]	Male			Female		
			2.5	5	10	2.5	5	10
	AR_AUC(0-24)	%	NC	NC	107	NC	109	92.0
	AR_AUC(0-7)	%	140	121	113	98.5	105	101
	AR_C _{max}	%	105	66.9	70.7	112	110	78.1
	AUC(0-24)	µg*h/L	245	NC	1480	NC	1540	3020
	AUC(0-24) _{norm}	kg*h/L	0.0980	NC	0.148	NC	0.308	0.302
	AUC(0-7)	h*µg/L	184	461	1230	417	1190	2510
	AUC(0-7) _{norm}	kg*h/L	0.0737	0.0922	0.123	0.167	0.238	0.251
	C _{max}	µg/L	44.4	92.7	271	132	375	645
	C _{max_norm}	kg/L	0.0178	0.0185	0.0271	0.0529	0.0750	0.0645
	C _{tint_C_{max}}	%	0.917	NC	0.827	NC	0.725	0.436
	RA_MF_AUC(0-24)	%	NC	NC	49.0			
	RA_MF_AUC(0-7)	%	44.2	38.8	48.7			
	RA_MF_C _{max}	%	33.6	24.7	42.0			
	t _{last}	h	24.0	7.00	24.0	7.00	24.0	24.0
	t _{max}	h	1.00	1.00	1.00	2.00	1.00	1.00

NC=not calculated; RA_MF= Ratio Male/Female

RA_M/PAUC_norm: Ratio metabolite/parent for dose normalized AUC

RA_M/PC_{max_norm}: Ratio metabolite/parent for dose normalized C_{max}

Parameters calculated from the geometric mean plasma concentrations.

AUC_{tint} is displayed as AUC(0-24) to indicate the start and end time point for AUC calculation.

AUC_{tlast} is displayed in the same way as AUC(0-7). For the rest of the report, the nomenclature

AUC_{tint} and AUC_{tlast} is utilized. For calculation of the AUC after repeated administration,

concentration at time point zero was set to the concentration value at 24 hours.

Source: Module 4.2.3.2, Report B002293

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Table 18. Toxicokinetics – Summary of Exposure in Steady State (Day 28 and 91) to Sevabertinib in Male & Female Monkeys

Day Dose	[mg/kg/day]	28		91	
		2.5	5.0	2.5	5.0
Geometric Means (gMean)					
AUC _{last}	[µg·h/L]	416	1240	482	1290
AUC _{last_norm}	[kg·h/L]	0.166	0.247	0.193	0.259
t _{last}	[h]	24.0	24.0	24.0	24.0
C _{max}	[µg/L]	68.9	250	93.8	247
C _{max_norm}	[kg/L]	0.0276	0.0500	0.0375	0.0494
t _{max}	[h]	4.00	2.00	3.00	2.00
C _{tint_Cmax}	[%]	2.89	1.43	1.13	0.537
AR_AUC _{last}	[%]	201	244	233	205
AR_C _{max}	[%]	166	239	226	201
RA_M/P_AUC _{last_norm}	[%]	83.1	87.4	94.8	92.7
RA_M/P_C _{max_norm}	[%]	78.3	75.0	78.9	75.9
N	-	6	7	6	5

N=number of animals

AR_AUC: Ratio of accumulation for AUC ((AUC on Day X)/(AUC on Day 1) *100)

AR_C_{max}: Ratio of accumulation for C_{max} ((C_{max} on Day X)/(C_{max} on Day 1) *100)

RA_M/P_AUC_{last_norm}: Ratio metabolite/parent for AUC_{last_norm}

RA_M/P_C_{max_norm}: Ratio metabolite/parent for C_{max_norm}

Source: Module 4.2.3.2, Report B002504

Table 19. Toxicokinetics – Summary of Exposure in Steady State (Day 28 and 91) to BAY 3306572 (M1 of Sevabertinib) in Male & Female Monkeys

Day Dose	[mg/kg/day]	28		91	
		2.5	5.0	2.5	5.0
Geometric Means (gMean)					
AUC _{last}	[µg·h/L]	346	1080	457	1200
AUC _{last_norm}	[kg·h/L]	0.138	0.216	0.183	0.240
t _{last}	[h]	24.0	24.0	24.0	24.0
C _{max}	[µg/L]	54.1	188	74.1	188
C _{max_norm}	[kg/L]	0.0216	0.0375	0.0296	0.0375
t _{max}	[h]	4.00	4.00	4.00	4.00
C _{tint_Cmax}	[%]	3.45	2.41	1.42	1.16
AR_AUC _{last}	[%]	169	234	224	193
AR_C _{max}	[%]	156	256	213	205
N	-	6	7	6	5

N=number of animals

AR_AUC: Ratio of accumulation for AUC ((AUC on Day X)/(AUC on Day 1) *100)

AR_C_{max}: Ratio of accumulation for C_{max} ((C_{max} on Day X)/(C_{max} on Day 1) *100)

Source: Module 4.2.3.2, Report B002504

Table 20. Overview of Toxicokinetics Data and Multiples of Exposure of Sevabertinib in Pivotal Studies

Daily dose	Unit	Sex	Total exposure				Unbound exposure				Report No.	Module
			C _{max}		AUC ₍₀₋₂₄₎		C _{max, u}		AUC _{0-24, u}			
			[µg/L]	MoE	[µg·h/L]	MoE	[µg/L]	MoE	[µg·h/L]	MoE		
Rat												
1.5	mg/kg	F	45.3	0.05	216	0.02	4.5	0.11	22	0.04	B003632	M4.2.3.5
2.5	mg/kg	F	132	0.15	n.c.	-	13	0.32	-	-	B002293	M4.2.3.2
2.5	mg/kg	M	44.4	0.05	245	0.02	4.4	0.11	22	0.04	B002293	M4.2.3.2
3	mg/kg	F	110	0.13	636	0.05	11	0.27	63	0.10	B003632	M4.2.3.5
3	mg/kg	F	102	0.12	697	0.05	10	0.24	69	0.11	B003097	M4.2.3.5
5	mg/kg	F	375	0.43	1540	0.12	37	0.90	154	0.25	B002293	M4.2.3.2
5	mg/kg	M	92.7	0.11	n.c.	-	8.5	0.21	-	-	B002293	M4.2.3.2
5	mg/kg	F	440	0.50	1580	0.12	44	1.07	158	0.26	PH-42111	M4.2.3.2
5	mg/kg	M	161	0.18	664	0.05	15	0.36	61	0.10	PH-42111	M4.2.3.2
6	mg/kg	F	346	0.40	2450	0.19	35	0.85	244	0.40	B003632	M4.2.3.5
7	mg/kg	F	681	0.78	2790	0.22	68	1.65	278	0.46	B003097	M4.2.3.5
10	mg/kg	F	645	0.74	3020	0.23	59	1.43	301	0.50	B002293	M4.2.3.2
10	mg/kg	M	271	0.31	1480	0.12	27	0.66	135	0.22	B002293	M4.2.3.2
10	mg/kg	F	949	1.09	4820	0.37	95	2.31	481	0.79	PH-42111	M4.2.3.2
10	mg/kg	M	354	0.41	1960	0.15	32	0.78	179	0.29	PH-42111	M4.2.3.2
11	mg/kg	F	1010	1.16	6420	0.50	101	2.45	640	1.05	B003097	M4.2.3.5
15*	mg/kg	F	1390	1.59	8410	0.65	139	3.37	838	1.38	PH-42111	M4.2.3.2
15	mg/kg	M	608	0.70	2500	0.19	56	1.36	229	0.38	PH-42111	M4.2.3.2
Cynomolgus Monkey												
2.5	mg/kg	M+F	93.8	0.11	482	0.04	10	0.24	53	0.09	B002504	M4.2.3.2
3	mg/kg	M+F	137	0.16	520	0.04	15	0.36	57	0.09	R-13937	M4.2.3.2
5	mg/kg	M+F	247	0.28	1290	0.10	27	0.66	142	0.23	B002504	M4.2.3.2
6	mg/kg	M+F	412	0.47	1533	0.12	45	1.09	169	0.28	R-13937	M4.2.3.2
8	mg/kg	M	887	1.02	2380	0.18	98	2.38	262	0.43	R-13937	M4.2.3.2
10	mg/kg	F	854	0.98	3390	0.26	94	2.28	373	0.61	R-13937	M4.2.3.2
Human exposure			873.6		12920		41.2		608.5			
MoE=margins of exposure (when compared to the human plasma levels after administration of the highest daily dose of 2 x 20 mg/patient); n.c.= not calculated												
M+F = exposure data of males and females were pooled, since there were no sex-related differences												
Fraction unbound: monkey 11.0%; rat 9.14 % (male), 9.97 % (female); man 4.71 %												
*15 mg/kg: only day 1 exposure levels available for females												

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusions; however, these studies were not reviewed in detail by the nonclinical review team. Notable findings include that following oral administration of 2 mg/kg radiolabeled sevabertinib to rats, the greatest concentration was observed in the eye (ciliary body, choroid, and iris) and skin of pigmented animals. In albino rats, sevabertinib showed poor distribution in the eye. At 168 hours, postdose radioactivity in the skin declined; however, in the eyes of pigmented rats, a high concentration of radioactivity was observed at 672 hours postdose, suggesting not only affinity of sevabertinib for melanin-containing tissue but also retention of the drug in the eye. Additional organs that retained radiolabeled drug up to 168 hours postdose included the thyroid, intestine, and liver. In addition, results from lactating rats administered a single dose of [¹⁴C] sevabertinib demonstrating sevabertinib-derived radioactivity was measured in milk was included in the label. Studies of drug–drug interactions were reviewed under the Clinical Pharmacology section.

5.5. Toxicology

5.5.1. General Toxicology

The nonclinical safety testing strategy for sevabertinib was developed in accordance with the ICH S2(R1), M3(R2), S3A, S5(R3), S7A, and S9 guidelines. All nonclinical studies were conducted in accordance with the best scientific principles. Pivotal nonclinical studies were conducted in conformance with GLP; 21 Code of Federal Regulations (CFR), Part 58 and/or the principles of OECD GLP in countries that are part of the OECD Mutual Acceptance of Data process. Rats and cynomolgus monkeys were used in the toxicology program; both species are considered to be pharmacologically active and have a metabolism of sevabertinib comparable to that of humans. Dogs could not be used because of insufficient exposure due to enzyme induction after repeated dosing.

The toxicity, the reversibility of effects, and exposures of sevabertinib were assessed in repeat dose, toxicology studies, up to 13 weeks duration in rats and monkeys. Daily oral administration of sevabertinib to rats and monkeys over 2, 4, or 13 weeks revealed adverse effects characterized by general signs of toxicity, such as reduced food intake, changes in laboratory parameters, diarrhea, and degenerative and inflammatory processes in epithelial and mucosal tissues. The highest doses tested in the 13-week studies correspond to MoEs slightly less than 1 for unbound AUC and greater than 2 for unbound C_{max} compared to exposures at the maximum therapeutic dose of 2 x 20 mg per day.

Most relevant histopathological findings in the dose range finder studies, and the pivotal 4- and 13-week studies in rats were degenerative and inflammatory processes in epithelial and mucosal tissues, such as forestomach (erosion/ulcer, atrophy, cyst, and inflammation), glandular stomach (atrophy), duodenum (villous atrophy), jejunum (villous atrophy and Paneth cell hypertrophy), ileum (villous atrophy and lymphangiectasis), cecum/colon (degeneration/atrophy, inflammatory cell infiltrates, and dilation), and rectum (degeneration/atrophy). In addition, thymus atrophy and

to a lesser extent epidermal atrophy were recorded. Severity of findings showed a clear dose dependency. In monkeys, daily oral administration of sevabertinib in dose range finder studies and in pivotal studies up to 13 weeks led to significant gastrointestinal adverse effects, including strong diarrhea and marked body weight loss across all dose groups. Notably, clinical signs began at 2.5 mg/kg/day, with altered feces consistency observed. Microscopic examination revealed inflammation in the stomach and ileum at the highest doses with clear interindividual variability and dose dependency. Some animals experienced severe weight loss, necessitating dose reduction or premature sacrifice.

The morphological changes are typical for responses of a small molecule EGFR TKI in rats and monkeys. These effects were fully or partially reversible with a recovery period.

Repeat-dose, 13-week, toxicity study in Wistar rats (Module 4.2.3.2, Report B002293, pivotal study, GLP)

Key Drug-related Adverse Findings:

- There were no sevabertinib-related mortalities
- The main clinical observations were wounds and scab formation at low incidences, slightly decreased body weight development in female high dose animals and increase in neutrophil and monocyte counts in all dose groups
- Histopathology revealed epidermal atrophy (males only)

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 mg/kg (vehicle control), 2.5 mg/kg, 5 mg/kg, and 10 mg/kg once daily for 13 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	Ethanol/Kolliphor HS15®/Water for Injection (10/40/50 v/v/v) adjusted to pH 4
Species/Strain:	Rat, Wistar (Cr:WI (Han))
Number/Sex/Group:	Main groups (10/sex/group)
Age:	8-9 weeks
Satellite groups:	TK satellite control group (3/sex/group)

Parameters	Major findings
Mortality	There were no sevabertinib-related mortalities.
Clinical Signs	After dosing with sevabertinib hairless areas, wounds and scab formation were observed at low incidences in male and female animals. At 5 mg/kg/day, one male displayed a head wound and scab formation during the dosing phase, starting on dosing day 65. The wound and scab formation persisted for 26 days. A second male animal dosed with 10 mg/kg/day, showed wound and scab formation on its shoulder starting at dosing day 15 and on its neck for 16 days. Four female and one male animal dosed at 10mg/kg/day

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	displayed fur thinning or some hairless areas on the forelegs or fur thinning at the neck.
	In the open field observation, the animals did not show any relevant clinical symptoms up to the highest dose level of 10 mg/kg/day.
Body Weight	Body weight development within the main groups was mostly comparable to the respective control groups up to the dose of 10 mg/kg/day sevabertinib in males and up to 5 mg/kg/day in females during the dosing period. A slight reduction in body weight gain was observed in female animals dosed with 10 mg/kg/day. During the recovery period, an increased body weight was observed in both sexes when compared to controls indicating reversibility.
Feed Consumption	The food intake profiles were roughly comparable between the main groups and their respective control groups up to the high dose of 10 mg/kg/day sevabertinib. Statistically significant increases in water consumption were observed in males and females dosed with sevabertinib. But due to the low quantity of deviations and lack of a dose dependency, the changes in water intake are not related to the test item.
Ophthalmoscopy	No adverse findings
Hematology	A statistically significant increase in mean neutrophil counts and monocyte counts starting at 2.5 mg/kg were observed in male and female animals. No increase in neutrophils and monocytes was noted at the end of the recovery period in males and females, indicating full reversibility. Several parameters (erythrocytes, hematocrit, mean corpuscular hemoglobin concentration, hemoglobin concentration, thromboplastin time, and lymphocytes) displayed statistically significant deviations from the controls. However, due to an absence of dose dependency and/or all individual values lying within the historical control range, these alterations are not considered toxicologically relevant.

Red Blood Cell Parameters (Group Means) – Main Groups

Dose mg/kg/d	ERY T/L	HB g/L	HCT L/L	MCV fl	MCH pg	MCHC g/L Ery	RETI %
Males				Day 93			
0	8.993	153.6	0.4744	52.75	17.09	323.9	2.42
2.5	8.576*	149.9	0.4592*	53.62	17.50	326.7	2.54
5	8.891	152.9	0.4665	52.52	17.20	327.7	2.31
10	8.570*	148.8	0.4586*	53.53	17.36	324.6	2.49
Females				Day 93			
0	7.969	147.1	0.4433	55.65	18.51	332.0	2.66
2.5	7.951	145.4	0.4435	55.79	18.28	327.7	2.71
5	7.956	144.3	0.4398	55.31	18.16	328.1	2.60
10	7.720	143.2*	0.4311*	55.89	18.58	332.1	2.82

* = p ≤ 0.05; ** = p ≤ 0.01; *** = p ≤ 0.001

White Blood Cell Parameters (Group Means) – Main Groups

Dose mg/k	LEUCO G/L	NEUTRO G/L	LYM G/L	MONO G/L	EOS G/L	BASO G/L	ATYP G/L
Males				Day 93			
0	5.448	0.833	4.404	0.066	0.121	0.005	0.018
2.5	5.997	1.102*	4.622	0.104*	0.138	0.004	0.023
5	6.170	1.206**	4.682	0.091	0.160	0.005	0.025
10	5.900	1.188**	4.463	0.125**	0.104	0.004	0.020
Females				Day 93			
0	4.126	0.594	3.360	0.068	0.085	0.001	0.018
2.5	5.146	0.894*	4.010	0.116**	0.098	0.001	0.022
5	5.131	0.814	4.076	0.112	0.110	0.004	0.018
10	4.967	1.496**	3.248	0.103	0.102	0.003	0.018

* = $p \leq 0.05$; ** = $p \leq 0.01$; *** = $p \leq 0.001$

Coagulation

No adverse findings

Clinical chemistry

A slight statistically significant reduction in protein and albumin levels was noted in males starting at a dosage of 2.5 mg/kg/day up to the dosage of 10 mg/kg/day. A statistically significant decrease in protein and albumin levels was still noted at the end of the recovery period in males dosed with 10 mg/kg/day. Among females, only the animals administered a dosage of 5 mg/kg/day showed a statistically significant deviation in protein levels compared to the respective control group. At the end of the recovery period, a slight increase in GGT and LDH levels was observed. However, these changes were minimal and lacked biological relevance. In addition, all other liver enzymes remained within the normal ranges, indicating no toxicological relevance.

Several other parameters (Glucose, P, and CA) displayed statistically significant deviations from the controls. Due to an absence of dose dependency and/or just minimal changes within the biological range, these alterations are not considered toxicologically relevant. A statistically significant reduction in creatine kinase levels was observed among females in the main group who received a dosage of 10 mg/kg/d sevabertinib. Usually, a decrease in creatine kinase activity is not typically associated with toxicity.

Substrate Concentrations (Group Means) – Main Groups

Dose mg/kg/d	TG mmol/L	CREA μmol/L	UREA mmol/L	TBIL μmol/L	PROT g/L	ALBUMIN g/L	CHOL mmol/L	GLUCOSE mmol/L
Males				Day 93				
0	2.011	49.6	6.905	0.53	61.85	41.94	1.597	10.005
2.5	2.003	48.9	6.921	0.72	59.34*	40.26**	1.597	11.582
5	2.243	48.2	6.731	0.82*	59.16*	40.10**	1.664	9.716
10	2.032	48.2	6.632	0.64	58.77**	39.74***	1.514	9.763

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Females		Day 93						
0	1.454	51.1	6.701	0.67	65.33	44.76	1.236	9.308
2.5	2.119	49.2	6.871	0.72	65.37	45.04	1.584*	8.373
5	1.728	49.4	7.381	0.64	61.60*	42.46	1.445	9.441
10	1.676	48.0**	7.196	0.62	63.52	43.09	1.310	8.653

* = $p \leq 0.05$; ** = $p \leq 0.01$; *** = $p \leq 0.001$

Electrolyte Concentrations (Group Means) – Main Groups

Dose mg/kg/d	Cl mmol/L	P mmol/L	NA mmol/L	K mmol/L	CA mmol/L
Males		Day 93			
0	104.4	0.915	142.9	4.83	2.530
2.5	103.6	0.946	142.3	4.74	2.534
5	103.3	1.118*	143.2	4.93	2.612***
10	104.2	1.033	143.0	4.69	2.536
Females		Day 93			
0	104.7	0.983	142.1	4.11	2.536
2.5	103.8	0.995	142.1	4.42	2.620*
5	103.3	1.068	142.2	4.41	2.577
10	103.4	0.866	142.1	4.18	2.543

* = $p \leq 0.05$; ** = $p \leq 0.01$; *** = $p \leq 0.001$

Urinalysis	No adverse findings
Gross Pathology	Necropsy did not reveal any test item related findings up to the dose of 2.5 mg/kg/day. A crust on the head was recorded for one male animal from the 5 mg/kg/day group, during necropsy in animals from the main group. In addition, wounds in the cervical or flank region were recorded for 2 males dosed at 10 mg/kg/day from the recovery groups.
Organ weights	The animals from the main group showed a statistically significant increase in relative thymus weight (% body weight); more specifically there was an approximately +21% increase in females dosed at 10 mg/kg/day. The mean relative thymus weights were also slightly increased in the groups of females dosed at 2.5 mg/kg/day (approximately +12 %) and 5 mg/kg/day (approximately +13 %). When compared to brain weight, an increase of mean relative thymus weight (approximately + 21%) was observed for females dosed at 10 mg/kg/day, but this was not statistically significant. Organ weight determination in animals from the recovery group showed a statistically significantly decrease in mean absolute kidney weight in the group of females dosed at 10 mg/kg/day. Due to the minor quantity of the deviation (- 8.9 % compared to control mean) and the slight reduction of body weights in this dose group the deviation was not regarded as toxicologically relevant.
Histopathology	At terminal sacrifice, minimal epidermal atrophy was recorded in the skin of the back region in males from the main group starting at 5 mg/kg/day (5 mg/kg/day: 2 out of 10 animals; 10 mg/kg/day: 8 out of 10 animals). Epidermal atrophy was characterized by a thinner appearance of the epidermis and less kerato-hyaline

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globules in the stratum granulosum. A full recovery was observed for epidermal atrophy 4 weeks post treatment. However, two recovery males, dosed at 10 mg/kg/day, revealed findings of the skin. Minimal epidermal hyperplasia and slight dermal inflammatory cell infiltration in the flank region were recorded in one male animal. Another male animal showed moderate multifocal epidermal hyperplasia and ulceration, crust formation and dermal inflammation in the cervical region at recovery necropsy. In addition, one male main group animal, dosed at 5 mg/kg/day, was diagnosed with crust formation at terminal sacrifice. The corresponding histopathological findings were similar to those observed in the previously mentioned animals. Due to the low incidences of ulcerative skin lesions, the association with treatment with sevabertinib is questionable, as they can also represent a background change. A relation to treatment with sevabertinib, however, cannot be excluded. Minimal epidermal atrophy was also recorded for sevabertinib-treated Wistar rats in the previous 4-week systemic toxicity study. The effects on the skin are considered to be related to the mode of action (inhibition of EGFR and HER2) of sevabertinib.

The panel of organs and tissues from the control and all dose groups scheduled for histotechnical processing and histopathological examination is shown in the Table below.

Scope of Organ Weight Determination, Tissue Preservation and Histopathological Evaluation

Organ / Tissue	Organ Weight Determination	Fixative	Histopathological Evaluation (Main Groups = Subgroup 1)				Histopathological Evaluation (Recovery Groups = Subgroup 3)		
			AG	1	2	3	4	1	4
			Abnormalities		Fo	X			
Adrenal Glands	X	Fo	X				X	X	
Aorta		Fo		X		X	X	X	
Bone Marrow, Femur		Fo		X		X	X	X	
Bone Marrow, Sternum		Fo		X		X	X	X	
Brain	X	Fo		X		X	X	X	
Coagulating glands	X ^c	Fo		X		X	X	X	
Epididymides	X	D		X		X	X	X	
Esophagus		Fo	X				X	X	
Eyes		D		X		X	X	X	
Eyelids		Fo							
Femur		Fo		X		X	X	X	
Harderian glands		Fo		X		X	X	X	
Head		Fo							
Heart	X	Fo		X		X	X	X	
Iliac lymph nodes		Fo		X		X	X	X	
Intestine		Fo							
- Duodenum				X		X	X	X	
- Jejunum				X		X	X	X	
- Ileum				X		X	X	X	

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- Cecum				X	X	X	X
- Colon				X	X	X	X
- Rectum				X	X	X	X
Kidneys	X	Fo ^a /D	X			X	X
Lacrimal glands		Fo		X	X	X	X
Larynx		Fo		X	X	X	X
Liver	X	Fo	X			X	X
Lung		Fo ^b	X			X	X
Mammary gland		Fo		X	X	X	X
Mandibular lymph nodes		Fo		X	X	X	X
Mesenteric lymph node		Fo		X	X	X	X
Mesentery		Fo					
Nasal cavities		Fo					
Optic nerves		Fo		X	X	X	X
Ovaries	X	Fo		X	X	X	X
Oviducts	X ^d	Fo		X	X	X	X
Pancreas		Fo		X	X	X	X
Parathyroid glands		Fo	X			X	X
Peyer's patches		Fo		X	X	X	X
Pharynx		Fo					
Physical Identifier (Transponder)		Fo					
Pituitary gland		Fo		X	X	X	X
Prostate gland	X	Fo		X	X	X	X
Salivary glands		Fo					
- Sublingual glands				X	X	X	X
- Mandibular glands				X	X	X	X
- Parotid glands				X	X	X	X
Sciatic nerve		Fo		X	X	X	X
Seminal vesicles	X	Fo		X	X	X	X
Skeletal muscle		Fo		X	X	X	X
Skin mammary region		Fo		X	X	X	X
Skin back region		Fo	X			X	X
Spinal cord		Fo					
- cervical				X	X	X	X
- thoracic				X	X	X	X
- lumbar				X	X	X	X
Spleen	X	Fo		X	X	X	X
Sternum		Fo		X	X	X	X
Stomach		Fo					

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- forestomach			X	X	X	X
- glandular stomach			X	X	X	X
Tooth/Teeth		Fo				
Testes	X	D	X	X	X	X
Thymus	X	Fo	X	X	X	X
Thyroid gland		Fo	X		X	X
Tongue		Fo	X	X	X	X
Trachea		Fo	X		X	X
Ureters		Fo	X	X	X	X
Urethra		Fo				
Urinary bladder		Fo ^b	X	X	X	X
Uterus	X	Fo				
- corpus			X	X	X	X
- cervix			X	X	X	X
Vagina		Fo	X	X	X	X
Zymbal's glands		Fo				

AG=all groups

X: Conducted

D: Davidson's fixative

Fo: Formalin 10% neutral buffered

a: one kidney pole fixed in formalin

b: fixation by instillation

c: weighed together with seminal vesicles

d: weighed together with ovaries

Results of the histopathological evaluation:								
Repeat-Dose Toxicity - 13-Week Toxicity Study				Test Article: Sevabertinib			Report No.: B002293	
Daily Dose [mg/kg]	0 Control	2.5 D1	5 D2	10 D3	0 Control	2.5 D1	5 D2	10 D3
	M	M	M	M	F	F	F	F
Number of Animals Main Group	10	10	10	10	10	10	10	10
Histopathology Main Group								
Skin, back region	10	10	10	10	10	10	10	10
Atrophy								
Grade 1	0	0	2	8	-	-	-	-

Toxicokinetics

The toxicokinetic evaluation revealed a marked sex-related difference in exposure. The exposure was clearly lower in the male than in the female rats. The exposure of sevabertinib in terms of AUC(0-24) was 3020 µg*h/L for female animals and 1480 µg*h/L for male animals. The corresponding C_{max} was 645 µg/L for female animals and 271 µg/L for male animals. C_{max} was observed

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at 1 hour in males and between 1 and 2 hours in female rats. Thereafter, concentrations decreased to concentrations at the end of the observation interval at 24 hours below 1% of the respective C_{max}.

On Day 79, the exposure, in terms of AUC_{tlast}, was slightly higher than on Day 1 in male animals dosed at 2.5 mg/kg/day and similar to Day 1 in males dosed at 5 and 10 mg/kg/day. The C_{max} on Day 79 was similar to Day 1 in males dosed at 1.5 mg/kg/day and moderately lower than on Day 1 in animals dose at 5 and 10 mg/kg/day. In female animals, the exposure in terms of AUC_{tlast} and C_{max} on Day 79 was almost unchanged in comparison to Day 1.

The exposure of BAY 3306572, the M1 metabolite, was clearly lower than the exposure of the unchanged drug sevabertinib. In males, the metabolic ratio ranged between 29% and 41% and in females between 9% and 15% for both AUC and C_{max}.

For the summary of exposure in steady state (Day 79) in male & female rats, please refer to Table 17.

Repeat-dose 13-week toxicity study in Cynomolgus Monkeys (Module 4.2.3.2, Report B002504, pivotal study, GLP)

Key Drug-related Adverse Findings

- Mortality was observed at the high dose of 5 mg/kg per day; two animals dosed at 5 mg/kg/day, showed a significant body weight loss resulting in premature sacrifice
- The main clinical observations were slight to severe changed feces consistency/diarrhea at all doses.
- Target organs included the GI tract (stomach, small and large intestine), thymus, lymph node (mesenteric) and liver (fat accumulation).

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 mg/kg (vehicle control), 2.5 mg/kg, and 5 mg/kg once daily for 13 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	Ethanol/Kolliphor HS15®/Water for Injection (10/40/50 v/v/v) adjusted to pH 4
Species/Strain:	Monkey, Cynomolgus
Number/Sex/Group:	3 male and 3 female (control and low dose) and 4 male and 4 female (high dose)
Age:	4 to 5 years
Satellite groups:	-

Parameters	Major findings

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Mortality	Premature euthanasia of two high dose animals on day 11 and day 85, respectively, due to pronounced weight loss (-14.8% and -16.4%) and watery feces and transiently reddish feces color/occasionally reddish or mucous admixtures. Euthanasia of one high dose male due to scrotal herniation of the small intestine (not considered test item related).
Clinical Signs	Slight to severe changed feces consistency/diarrhea small amounts of reddish or mucous admixtures and a reddish color of feces
Body Weight	Slight weight loss (individual animals) at 2.5 mg/kg/day Up to marked body weight loss (individual animals) at 5 mg/kg/day
Feed Consumption	Reduced food intake (up to severe)
Ophthalmoscopy	No findings
Hematology	In animals no. 8 (male) and 20 (female) dosed at 5 mg/kg/day and who were prematurely sacrificed due to body weight loss accompanied by changed feces consistency, the erythrocyte counts, hemoglobin concentration, hematocrit and thrombocyte counts (only animal no. 20) were slightly increased at blood collection on day 11 (for animal no. 20) or 85 (for animal no. 8) compared to previously determined individual values of these parameters. For all other animals that underwent scheduled necropsy, hematology and coagulation parameters were inconspicuous and no statistically significant deviations were recorded for groups dosed at 2.5 and 5 mg/kg/day.
Coagulation	-
Clinical chemistry	The prematurely euthanized animal no. 08 (male, 5 mg/kg/day) had an increase of alkaline phosphatase at blood collection on day 85. In animal no. 20 (female, 5 mg/kg/day), an increase in total bilirubin was recorded on day 11 prior to premature sacrifice of this animal: On day 11, total bilirubin was approximately 2.5-times higher compared to the individual total bilirubin value during the predose phase. No further deviations of clinical chemistry parameters were regarded as related to treatment with sevabertinib.
Urinalysis	No findings
Gross Pathology	Small intestine showed distension, discoloration, obstruction
Organ weights	At the 2.5 mg/kg/day dose level, a statistically significant decrease in mean relative liver weight was recorded in males; however, without any histopathological correlate.
Histopathology	Histopathological evaluation revealed a marked to massive atrophy of mediastinal and mesenteric adipose tissue and predominantly mononuclear inflammation of marked severity in the stomach and slight severity in the large intestine in one animal dosed at 5 mg/kg/day, who was prematurely sacrificed on dosing day 11. In Peyer's patches and the mesenteric lymph node of this animal, a reactive increase in cellularity was recorded. The small intestine showed a slight increase in mononuclear cell infiltrates, only. Similar gastrointestinal histopathological findings were observed in a male animal dosed at 5 mg/kg/day, who was prematurely sacrificed on day 85: slight inflammation was found in the stomach, cecum, colon and rectum, and cellularity was slightly reactively increased in Peyer's patches. Moreover, a massive atrophy was present in the thymus. Testes showed minimal germ cell degeneration. Moderate sperm decrease and slight cell debris was found in the epididymides. Prostate gland and seminal vesicles were markedly atrophic. This effect was considered as secondary to the reduced general condition of this prematurely sacrificed animal. Thymic atrophy was observed in males and females at 5 mg/kg/day and in one female at 2.5

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mg/kg/day. In the liver, Oil Red O staining for fat accumulation was increased in females at 5 mg/kg/day. One male animal, that was prematurely sacrificed on day 66 showed marked congestion and hemorrhage in the jejunum in line with grossly observed scrotal herniation. This finding was considered not-related to the test item administration.

The panel of organs and tissues from the control and all dose groups scheduled for histotechnical processing and histopathological examination is shown in the Table below.

Scope of Organ Weight Determination, Tissue Preservation, Histotechnique and Histopathological Evaluation

Organs	Determination of Organ Weight	Fixative	Histotechnique and Histopathology
Abnormalities		Fo	X
Adrenal gland	X	Fo	X
Aorta		Fo	X
Brain (7 regions)	X	Fo	X
Epididymides	X	D	X
Esophagus		Fo	X
Eyes (with Nervus Opticus)		D	X
Femur (with Bone Marrow)		Fo	X
Gallbladder		Fo	X
Heart	X	Fo	X
Intestine		Fo	
- Duodenum			X
- Jejunum			X
- Ileum			X
- Peyer’s Patches			X
- Caecum			X
- Colon			X
- Rectum			X
Kidneys	X	D ^b	X
Larynx		Fo	X
Liver	X	Fo	X
Lung	X	Fo ^a	X
Lymph Node, mandibular		Fo	X
Lymph Node, mesenteric		Fo	X
Lymph Node, iliac		Fo	X
Mammary Gland		Fo	X
Mesentery		Fo	
Nasal Cavity with Teeth		Fo	
Ovaries	X	Fo	X
Oviducts	X ^c	Fo	X

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Pancreas	X	Fo	X
Pituitary Gland	X	Fo	X
Prostate	X	Fo	X
Salivary Glands		Fo	
- Sublingual Gland			X
- Submandibular Gland			X
- Parotid Gland			X
Sciatic Nerve		Fo	X
Seminal Vesicles		Fo	X
Skeletal Muscle (M. adductor magnus)		Fo	X
Skin (Mammary and Lumbar Region)		Fo	X
Spinal Cord		Fo	
- cervical			X
- thoracic			X
- lumbar			X
Spleen	X	Fo	X
Sternum (with Bone Marrow)		Fo	X
Stomach		Fo	X
Testes	X	D	X
Thymus		Fo	X
Thyroid Gland with Parathyroid Glands	X	Fo	X
Tongue		Fo	X
Tonsils		Fo	X
Trachea		Fo	X
Ureters		Fo	X
Urinary Bladder		Fo	X
Uterus	X	Fo	
- Cervix			X
- Corpus			X
Vagina		Fo	X
Physical Identifier (Transponder Chip)		Fo	

X:	Conducted
a:	Fixation by instillation of one lung lobe
b:	A transversally cut piece of kidney tissue fixed in formalin
c:	Weighed together with uterus/cervix
D:	Davidson's fixative
Fo:	10 % formalin

Results of histopathological investigation:

Repeat-Dose Toxicity - 13-Week Toxicity Study			Test Article: Sevabertinib			Report No.: B002504	
Daily Dose [mg/kg]	0 Control	2.5 D1	5 D2	0 Control	2.5 D1	5 D2	
	M	M	M	F	F	F	
Number of Animals Main Group	3	3	4	3	3	4	
Histopathology							
Large Intestine, Cecum	3	3	4	3	3	4	
Inflammation							
Grade 2	0	0	1	0	0	1	
Large Intestine, Colon	3	3	4	3	3	4	
Inflammation							
Grade 2	0	0	1	0	0	1	
Large Intestine, Rectum	3	3	4	3	3	4	
Inflammation							
Grade 2	0	0	1	0	0	1	
Liver red oil o stain	3	3	4	3	3	4	
Positive staining							
Grade 1	1	0	1	-	-	-	
Grade 2	2	2	4	3	2	1	
Grade 3	0	1	1	0	1	1	
Grade 4	-	-	-	0	0	1	
Lymph Node, Mesenteric	3	3	4	3	3	4	
Adipose tissue, decreased							
Grade 4	-	-	-	0	0	1	
Cellularity, increased,							
Grade 2	-	-	-	3	2	1	
Payer's Patch	3	3	4	3	3	4	
Increased number and size, germinal centers							
Grade 2	0	1	1	-	-	-	
Cellularity, increased							
Grade 2	-	-	-	0	0	1	
Small Intestine, Duodenum	3	3	4	3	3	4	
Infiltrate, inflammatory cell							

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Grade 2	-	-	-	0	0	1
Small Intestine, Ileum	3	3	4	3	3	4
Infiltrate, inflammatory cell						
Grade 2	-	-	-	0	0	1
Small Intestine, Jejunum	3	3	4	3	3	4
Infiltrate, inflammatory cell						
Grade 2	-	-	-	0	0	1
Stomach	3	3	4	3	3	4
Inflammation						
Grade 2	0	0	1	-	-	-
Grade 4	-	-	-	0	0	1
Thymus	3	3	4	3	3	4
Adipose tissue, decreased						
Grade 5	-	-	-	0	0	1
Atrophy						
Grade 2	1	0	1	-	-	-
Grade 3	0	0	1	0	0	1
Grade 4	-	-	-	0	1	1
Grade 5	0	0	1	0	0	1

Toxicokinetics

The toxicokinetic evaluation revealed no sex-related differences in exposure. For sevabertinib, C_{max} was reached 2 to 4 h after administration. For its metabolite, BAY 3306572, C_{max} was reached 4 h after administration. At 24 hours after administration, the concentrations of both analytes were below 3.5% of the respective C_{max} with a trend towards lower values for the metabolite. On days 28 and 91, the exposure in animals from both dose groups in terms of AUC_{last} and C_{max} was moderately to markedly higher than on day 1. Exposure in terms of both, AUC_{last} and C_{max} was at least 1.5-fold higher than on day 1.

The exposure of sevabertinib on day 91, in terms of AUC(0-24), was 1290 $\mu\text{g}\cdot\text{h}/\text{L}$ for females and males and the corresponding C_{max} was 247 $\mu\text{g}/\text{L}$ for both sexes.

Under steady state conditions (day 28 and 91), the exposure of BAY 3306572, the M1 metabolite, represented between approximately 80% to 95 % of the exposure to the unchanged drug sevabertinib in terms of AUC_{last} and between 75% to approx. 79 % in terms of C_{max} .

For the summary of exposure in steady state (Day 28 and 91) to sevabertinib in male & female monkeys, please refer to Table 18.

For the summary of exposure in steady state (Day 28 and 91) to BAY 3306572 (M1 of sevabertinib) in male & female monkeys, please refer to Table 19.

The FDA's Assessment:

FDA generally agrees with the Applicant’s conclusions, with additional pertinent findings described below. FDA notes that animal:human exposure comparisons were made using total AUC, as it is not our standard practice to consider protein binding when making AUC comparisons.

Study title/ number: 13-Week Repeat Dose Systemic Toxicity Study in Rats with Once Daily Oral Administration followed by a 4-Week Recovery Period / Study No. T105912-8, Report No. B002293

- Skin toxicity was observed in males at ≥ 5 mg/kg and in females at 10 mg/kg, as evidenced by clinical signs, gross pathology, and histologic findings that did not recover (crust, hyperplasia, inflammation, ulceration, and atrophy).
- Mild hemorrhage in the eye at 10 mg/kg and minimal degeneration and infiltrate in the lacrimal gland in recovery animals at 10 mg/kg were observed.

Observations and Results: changes from control

Parameters	Major findings
Mortality	No sevabertinib-related deaths. • One female in the vehicle control group developed a tumor and was euthanized prematurely in accordance with animal welfare protocols. • One animal in the high-dose group died accidentally during the gavage procedure.
Hematology	% Change in Hematology Parameters from Vehicle-Treated Control Group in Rats Treated with Sevabertinib

Sex	Males			Females			
	Dose (mg/kg)	2.5	5	10	2.5	5	10
Monocytes							
Day 93		57.58*	37.88	89.39**	70.59**	64.71	51.47
Day 121				-2.35			2.56
Neutrophils							
Day 93		32.29*	44.78**	42.62***	50.51*	37.04	151.85**
Day 121				25.97			-5.89

% relative to controls on Days 93 (day of necropsy) and 121 (Recovery group); *p $\leq$ 0.05, **p $\leq$ 0.01, ***p $\leq$ 0.001

Clinical Chemistry

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

Sex	Males			Females		
Dose (mg/kg)	2.5	5	10	2.5	5	10
Albumin						
Day 93	-4.01**	-4.39**	-5.25***	0.63	-5.14	-3.73
Day 121			-5.46			-0.74
Creatine						
Day 93	-1.41	-2.82	-2.82	-3.72	-3.33	-6.07
Day 121			4.29			2.81
Protein						
Day 93	-4.06*	-4.35*	-4.98**	0.06	-5.71*	-2.77
Day 121			-4.87			1.55

% relative to controls on Days 93 (day of necropsy) and 121 (Recovery group); *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001

Urinalysis

Increased protein/creatinine ratio in males at ≥2.5 mg/kg and in females at 10 mg/kg. Findings did not recover in males.

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Histopathology

Adequate
battery: Yes

Sex	Males				Females				
	Dose (mg/kg)	0	2.5	5	10	0	2.5	5	10
Terminal Sacrifice									
EYE									
HEMORRHAGE (focal, associated/surrounding tissue, unilateral)	Mild	1	0	0	3	0	0	0	0
GLAND, ADRENAL									
CYSTIC DEGENERATION	Mild	0	0	0	1	0	0	0	1
GLAND, HARDERIAN									
DEGENERATION/REGENERATION (multifocal, bilateral)	Minimal	0	0	0	1	0	0	0	1
	Moderate	1	0	0	1	0	0	0	2
SKIN									
CRUST	Mild	0	0	1	0	0	0	0	0
HYPERPLASIA (epidermis)	Mild	0	0	1	0	0	0	0	0
INFLAMMATION (mixed cell)	Mild	0	0	1	0	0	0	0	0
ULCER	Moderate	0	0	1	0	0	0	0	0
ATROPHY (diffuse, epidermis)	Minimal	0	0	2	8	0	0	0	0
INFILTRATE (mononuclear cell)	Minimal	0	0	0	0	0	0	0	1
Recovery Sacrifice									
EYE									
HEMORRHAGE (multifocal, associated/surrounding tissue, unilateral)	Mild	0	n/a	n/a	1	0	n/a	n/a	1
GLAND, LACRIMAL									
CYTOPLASMIC ALTERATION	Minimal	0	n/a	n/a	1	0	n/a	n/a	0
DEGENERATION	Minimal	0	n/a	n/a	1	0	n/a	n/a	0
INFILTRATE (mononuclear cells)	Minimal	0	1	0	1	0	n/a	n/a	0
PANCREAS									
ATROPHY (acinar cell, diffuse)	Minimal	0	n/a	n/a	1	0	n/a	n/a	0
INFILTRATE (mononuclear cells)	Minimal	0	n/a	n/a	1	0	n/a	n/a	0
SKIN									
CRUST	Moderate	0	n/a	n/a	1	0	n/a	n/a	0
HYPERPLASIA (epidermis)	Minimal	0	n/a	n/a	1	0	n/a	n/a	0
	Moderate	0	n/a	n/a	1	0	n/a	n/a	0
INFILTRATE (mixed cells)	Minimal	0	n/a	n/a	1	0	n/a	n/a	2
INFILTRATE (mononuclear cells)	Minimal	0	n/a	n/a	0	0	n/a	n/a	2
INFILTRATE (mononuclear cells)	Mild	0	n/a	n/a	1	0	n/a	n/a	0
INFLAMMATION (mixed cells)	Mild	0	n/a	n/a	1	0	n/a	n/a	0

Version date: March 1, 2024 (ALL NDA/BLA reviews)

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INFLAMMATION (pyogranulomatous)	Moderate	0	n/a	n/a	1	0	n/a	n/a	0
ULCER	Moderate	0	n/a	n/a	1	0	n/a	n/a	0

Study title/ number: 13-Week Repeat Dose Systemic Toxicity Study in Monkeys with Once Daily Oral Administration by Gavage/ Study No. T105960-1, Report No. B002504

- Minimal to mild degeneration of the lens in the eye was observed in one main study animal and one recovery animal at 5 mg/kg.

Observations and Results: changes from control

Parameters

Major findings

Clinical Signs

- Soft/thin or watery feces with reddish or mucous admixtures were observed during treatment at doses ≥ 2.5 mg/kg, with more severe changes noted in males.
- White discharge of the mammary gland was observed in females at 5 mg/kg.

Body Weights

In addition to the two preterm decedents, one female in the 5 mg/kg group showed decreased body weight of 18% on Day 92 compared to the pre-dose weight.

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Histopathology

Adequate battery:

Yes

Treatment	Sevabertinib					
	Sex			Sex		
	Males		Females			
Dose (mg/kg)	0	2.5	5	0	2.5	5
BONE, STERNUM						
DEGENERATION (focal, cartilage)	Mild	0	0	0	0	1
EYE, LENS						
DEGENERATION (focal, lens fiber, unilateral)	Minimal	0	0	0	0	1
GLAND, ADRENAL						
HYPERTROPHY (focal/multifocal, cortex, unilateral)	Mild	0	0	2	0	0
VACUOLATION (focal/multifocal, cortex, unilateral)	Minimal	0	0	1	0	0
LIVER						
POSITIVE STAINING (lipid accumulation)	Moderate	0	1	0	0	1
	Marked	0	0	0	0	2
VACUOLATION (diffuse)	Mild	0	0	0	0	1
LARGE INTESTINE, CECUM						
PARASITE	Minimal	1	1	2	2	2
	Mild	0	1	0	0	0
LARGE INTESTINE, COLON						
PARASITE	Minimal	1	1	2	1	2
	Mild	0	0	0	0	1
LARGE INTESTINE, RECTUM						
PARASITE	Minimal	1	1	2	1	2

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Histopathology

Adequate battery:
Yes

Early Sacrifice				
		Sex	Male	Female
		Dose (mg/kg)	5	5
EPIDIDYMIS				
CELL DEBRIS	Mild		1	n/a
SPERM, DECREASED	Moderate		1	n/a
EYE, LENS				
DEGENERATION (focal, lens fiber, unilateral)	Mild		0	1
GLAND, ADRENAL				
HYPERTROPHY/HYPERPLASIA (zona glomerulosa, diffuse)	Mild		1	1
GLAND, PARATHYROID				
ACCUMULATION, ADIPOCYTES (diffuse)	Minimal		1	0
GLAND, PROSTATE				
ATROPHY (diffuse)	Marked		1	n/a
GLAND, SEMINAL VESICLE				
ATROPHY (diffuse)	Moderate		1	n/a
CELL DEBRIS (diffuse)	Mild		1	n/a
LARGE INTESTINE, CECUM				
INFLAMMATION (diffuse)	Mild		1	1
LARGE INTESTINE, COLON				
INFLAMMATION (diffuse)	Mild		1	1
LARGE INTESTINE, RECTUM				
HEMORRHAGE (focal/multifocal)	Minimal		1	0
INFLAMMATION (diffuse)	Mild		1	1
LIVER				
GLYCOGEN DEPLETION (diffuse, periportal)	Mild		1	0
POSITIVE STAINING (lipid accumulation)	Mild		2	1
LYMPH NODE, MESENTERIC				
ADIPOSE TISSUE, DECREASED (diffuse)	Marked		0	1
CELLULARITY, INCREASED (diffuse)	Mild		0	1
PANCREAS				
ATROPHY (acinar cell, diffuse)	Mild		1	0
VACUOLATION (diffuse)	Mild		1	0
PEYER'S PATCH				
CELLULARITY, INCREASED	Mild		0	1
↑ NUMBER and SIZE OF GERMINAL CENTERS (multifocal)	Mild		1	0

SMALL INTESTINE, DUODENUM			
INFILTRATE (inflammatory cell, diffuse)	Mild	0	1
SMALL INTESTINE, ILEUM			
CONGESTION/HEMORRHAGE (diffuse)	Mild	1	0
INFILTRATE	Mild	0	1
SMALL INTESTINE, JEJUNUM			
CONGESTION/HEMORRHAGE (diffuse)	Marked	1	0
INFILTRATE (inflammatory cell, diffuse)	Mild	0	1
STOMACH			
INFLAMMATION (diffuse)	Mild	1	0
INFLAMMATION (diffuse)	Marked	0	1
TESTIS			
GERM CELL DEGENERATION	Minimal	1	0
HYPOPLASIA/ATROPHY (focal/multifocal)	Minimal	1	0
THYMUS			
ADIPOSE TISSUE, DECREASED	Severe	0	1
	Moderate	1	0
ATROPHY (diffuse)	Severe	1	1

In the GLP-compliant 4-week repeat-dose toxicity study in rats (reviewed under IND 155685), sevabertinib was orally administered at 5, 10, or 15 mg/kg once daily. All females in the 15 mg/kg group were euthanized prematurely due to significant weight loss, abnormal feces (liquid), and poor general condition (e.g., piloerection, reduced motility, and high-stepping gait). In animals that survived to scheduled necropsy, treatment with 15 mg/kg resulted in $\leq 14\%$ decreases in mean body weight and a 38% decrease in mean food consumption compared to controls. Similar to the 13-week toxicity study, skin was a target organ with histologic findings of up to moderate atrophy, slight erosion/ulcer, and minimal hyperplasia. Additionally, histologic findings of up to slight lacrimal gland atrophy and minimal optic nerve hemorrhage were observed in both sexes at doses ≥ 10 mg/kg. Sevabertinib induced extensive histologic findings in the GI tract (small and large intestines, stomach, esophagus) of up to moderate degeneration/atrophy and erosion/ulcer, and up to slight inflammation. Additional target organs included the pancreas (acinar atrophy), salivary gland, thyroid gland (atrophy, colloid alteration, hemorrhage, hypertrophy), lung (increased alveolar macrophages, hypertrophy, metaplasia), thymus (increased tangible body macrophages), kidney (tubule atrophy, dilatation, hyperplasia, inflammation), tongue (atrophy), liver (periportal cytoplasmic alteration, glycogen depletion, periportal fatty change), cervix (degeneration/vacuolation), epididymis (sperm granuloma), and mammary gland (vacuolation).

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In the GLP-compliant 4-week repeat-dose toxicity study in monkeys (reviewed under IND 155685), sevabertinib was orally administered at 3, 6, or 10/8 mg/kg once daily. Due to severe liquid and/or soft feces associated with body weight loss that did not respond to preventative care, the high dose level was reduced from 10 to 8 mg/kg in males beginning on Day 11. Since the health status of these animals did not improve, all monkeys at 8 mg/kg were euthanized prematurely on Day 18. Target organs included the GI tract (parasite, up to mild infiltrate, mild inflammation, minimal atrophy), skin (mild crust, moderate ulcer) thymus (up to mild atrophy), eye (up to mild infiltrate), and bone marrow (sternum; minimal lymphoid aggregate).

FDA limited the review of the 2-week non-GLP-compliant dose-range finding study in rats to ocular effects (Study No. T104669-6, Report No. PH-41998). Rats were orally administered sevabertinib at doses of 5, 15, or 30 mg/kg once daily. Treatment with ≥ 5 mg/kg sevabertinib induced minimal to moderate atrophy/degeneration of the corneal epithelium

5.4.2 Genetic Toxicology

The Applicant's Position:

Sevabertinib was not mutagenic in a GLP-compliant bacterial reverse mutation assay (Ames assay) in the presence and absence of Aroclor 1254-induced rat liver S9 fractions at concentrations up to 5,000 $\mu\text{g}/\text{plate}$.

The aneugenic and clastogenic potential of sevabertinib was assessed *in vitro* in a GLP-compliant micronucleus test. Based on toxicity, the limit concentrations for assessment were set at 75 $\mu\text{g}/\text{mL}$ (without S9 mix, 4 hours treatment) and 85 $\mu\text{g}/\text{mL}$ (with S9 mix, 4 hours treatment). In addition, concentrations up to 30 $\mu\text{g}/\text{mL}$ were chosen for assessment of the extended treatment without the S9 mix. Evaluation of the data indicate that sevabertinib is not genotoxic in the micronucleus test *in vitro*, when tested up to cytotoxic concentrations in the absence or presence of metabolic activation.

In addition, there was no evidence of a biologically relevant or statistically significant genotoxic effect of orally administered test item in the peripheral blood of the micronucleus test in the male and female rats when tested in assessable doses up to the MTD in the course of the pivotal 4-week toxicology study.

The FDA's Assessment:

FDA confirmed the Applicant's results of the submitted genotoxicity assays and agrees with the conclusions. Standard positive controls confirmed the sensitivity and validity of these GLP-compliant assays. The genotoxic potential for metabolite M1 was not investigated by the Applicant; however, we note that M1 was present following incubation of sevabertinib with hepatocytes from rat and monkey and measured in plasma of animals in the 13-week repeat-dose studies. Additionally, M1 is structurally similar to sevabertinib, which was not genotoxic in *in vitro* and *in vivo* assays. Therefore, M1 is not genotoxic based on the totality of data with active pharmaceutical ingredient and metabolite (genotoxicity, ADME, and structure).

5.5.2. Carcinogenicity

Carcinogenicity studies have not been conducted. Consistent with the guideline ICH S9, carcinogenicity studies are not warranted to support clinical trials for therapeutics intended to treat patients with advanced cancer.

The FDA's Assessment:

FDA agrees.

5.5.3. Reproductive and Developmental Toxicology

Dedicated fertility and early embryonic development studies were not conducted and are not warranted per ICH S9 guidance for nonclinical safety assessment of pharmaceuticals intended for the treatment of advanced cancer. Reproductive organs were weighed and/or examined microscopically in repeat-dose rat and monkey toxicity studies.

A preliminary embryo-fetal development study in rats was conducted. Oral (gavage) administration of 0, 3, 7, or 11 mg/kg/day sevabertinib to pregnant female Wistar rats during organogenesis resulted in test item-related effects at all dose levels, including three mortalities following administration of 11 mg/kg/day. A dose level of 7 or 11 mg/kg/day was considered excessive due to the severity of the test item-related body weight loss, reduced food consumption, adverse clinical observations, and reduced fetal weights, however no fetal malformations or variations were noted. Test item-related effects following administration of 3 mg/kg/day were confined to initial reduced body weight gain and small reductions in food consumption and considered not to represent an adverse effect to the pregnant animals. The marginal reductions in fetal weight were not classified as adverse. A no observed adverse effect level (NOAEL) of sevabertinib was established as 3 mg/kg/day as a result.

In the pivotal EFD study in rats, sevabertinib-related effects observed after administration of 1.5 or 3 mg/kg/day were limited to marginal reductions in body-weight gain and food consumption. This resulted in slightly lower absolute body weights at GD 21 compared with controls and did not adversely affect maternal health or fetal development. Fetal effects were limited to slightly reduced fetal weights (combined and individual sexes), resulting in a slight reduction in gravid uterine and placental weights; however, mean values were within the historical control data range. A dose level of 6 mg/kg/day was considered excessive due to the severity of the sevabertinib-related body weight changes, reduced food consumption, and reduced fetal and placental weights. In summary it can be stated that no fetal malformations or adverse fetal variations were noted at unbound exposures of sevabertinib at multiples of exposure below or in the range of 1 compared to the therapeutic human unbound exposure. Based on these findings, the NOAEL is 3 mg/kg/day.

Rabbit did not qualify as a test species for embryo-fetal development assessment, as no relevant exposure to sevabertinib could be achieved.

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In order to complement the rat EFD studies, the ReproTracker assay (Study T106172-7) was conducted. In this assay, differentiation of hiPSCs into cardiomyocytes, hepatocytes, and neural rosettes was investigated using morphology. Biomarker gene expression was assessed using qRT-PCR. The ReproTracker assay’s validity was established by exposing hiPSCs to known teratogenic (thalidomide/retinoic acid) and non-teratogenic (saccharin) compounds. Sevabertinib did not significantly affect the mesodermal marker but decreased MYH6 expression in a concentration-dependent manner. Changes in MYH6 expression were noted starting at 1.0 μM, indicating disrupted cardiomyocyte differentiation. Sevabertinib also decreased AFP expression from 0.2 μM, disrupting hepatocyte differentiation and morphology at 2.0 μM. Additionally, it exhibited a U-shaped response in neural rosette markers and disrupted their morphology at higher concentrations. Ultimately, ReproTracker classified sevabertinib as a teratogen due to its effects on stem cell differentiation.

Prenatal and postnatal development studies were not conducted and are not warranted per ICH S9 guidance for nonclinical safety assessment of pharmaceuticals intended for the treatment of advanced cancer.

Sevabertinib: Oral (Gavage) Enhanced Range-Finding Study of Embryo-Fetal Development in the Rat (Module 4.2.3.5, Report B003097, GLP)

Key Drug-related Adverse Findings:

- There were three sevabertinib-related mortalities in the high dose group.
- The main clinical observations were piloerection, reduced body weight, liquid feces.
- Only marginal increase in post-implantation loss and early resorptions were noted for animals administered 11 mg/kg/day. This dose was considered excessive due to severe maternal toxicity.
- No test item-related fetal malformations or variations were noted.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (vehicle control), 3, 7 and 11 mg/kg daily from GD6-GD17
Route of administration:	Oral gavage
Formulation/Vehicle:	Ethanol/Kolliphor HS15®/Water for Injection (10/40/50 v/v/v) adjusted to pH 4
Species/Strain:	Rat, Wistar
Number/Sex/Group:	9 animals/group
Age:	9 weeks
Satellite groups:	-

Parameters	Major findings
Mortality	Mortality was observed at the highest dose of 11 mg/kg per day.
Clinical Signs	Body weight loss, reduced food consumption, and adverse clinical observations, such as piloerection, liquid feces, hunched posture, and a thin appearance were observed following administration of 11 mg/kg/day. Test item-related effects observed following administration of 7 mg/kg/day included body weight loss, reduced body weight gain, and food consumption. Clinical observations included piloerection and a hunched posture. At 3 mg/kg/day initial reduced body weight gain and small reductions in food consumption were observed, which did not adversely impact the health of the maternal animal.
Body Weight	Reduced body weight and reduced body weight gain were observed starting with the lowest dose tested.
Feed Consumption	Food consumption was reduced.
Gross Pathology/Cesarian section	

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Reproductive and Developmental Toxicity - Embryo-Fetal Developmental Toxicity Study in Rats **Test Article: Sevabertinib** **Report No.: B003097**

Dose Level (mg/kg/day)	0	3	7	11
Number of Females	9	9	9	9
Pregnant Females	9	8	9	7
Moribund Sacrifice	0	0	0	3
Non-Pregnant Females	0	1	0	2
Pregnant with Total litter loss	0	0	0	0
Summary of Cesarean Section Data				
Number of females pregnant at cesarean section	9	8	9	4
Mean No. Corpora Lutea	11.3	12.4	12.2	12.0
Mean No. Implantation Sites	10.2	11.9	11.0	11.0
Mean No Pre-implantation Loss	1.1	0.5	1.2	1.0
Pre-implantation Loss (%)	9.22	3.76	9.56	8.11
Mean No. Early Resorptions	0.2	0.6	0.3	1.0
Mean No. Late Resorptions	0.0	0.0	0.0	0.0
Mean No. Total Resorptions	0.2	0.6	0.3	1.0
No. of Dead Fetuses	0.0	0.0	0.0	0.0
Mean No Postimplantation Loss	0.2	0.6	0.3	1.0
Postimplantation Loss (%)	1.78	5.36	3.13	10.00
Mean Live Fetuses	10.0	11.3	10.7	10.0
Mean Gravid Uterine Weight (g)	71.76	74.34	67.04	60.33
Mean Corrected Body Weight (Carcass Weight) (g)	243.91	230.29	225.07	218.93
Mean Corrected Weight Change, Day 4 to 21 (g)	34.36	27.29	19.62	15.68

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

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Mean Total Weight Change (Weight Change) Day 4 to 21 (g)	106.11	101.63	86.67	76.00
Summary of Mean Fetal Data				
Number of Females with Live Fetuses	9	8	9	4
Mean Number of Male Fetuses per Litter	5.0	5.6	5.8	4.8
Mean Number of Male Fetuses per Litter Fetuses (% Males)	5.0	5.6	4.9	5.3
	49.3	50.7	54.5	48.2
Mean Fetal Weight (g)	5.426	5.091	4.740	4.626
Mean Weight, Male Fetuses (g)	5.565	5.285	4.848	4.756
Mean Weight, Female Fetuses (g)	5.318	4.889	4.609	4.524
Summary of Cesarean Section Data including Decedent Females				
Number of females pregnant at cesarean section	9	8	9	7
Mean No. Corpora Lutea	11.3	12.4	12.2	13.0
Mean No. Implantation Sites	10.2	11.9	11.0	11.7
Mean No Pre-implantation Loss	1.1	0.5	1.2	1.3
Pre-implantation Loss (%)	9.22	3.76	9.56	9.61
Mean No. Early Resorptions	0.2	0.6	0.3	0.7
Mean No. Late Resorptions	0.0	0.0	0.0	0.0
Mean No. Total Resorptions	0.2	0.6	0.3	0.7
No. of Dead Fetuses	0.0	0.0	0.0	0.0
Mean No Postimplantation Loss	0.2	0.6	0.3	1.0 ^a
Postimplantation Loss (%)	1.78	5.36	3.13	10.00 ^a

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Mean Live Fetuses	10.0	11.3	10.7	11.0
Mean Gravid Uterine Weight (g)	71.76	74.34	67.04	60.33 ^a
Mean Corrected Body Weight (Carcass Weight) (g)	243.91	230.29	225.07	218.93 ^a
Mean Corrected Weight Change, Day 4 to 21 (g)	34.36	27.29	19.62	15.68 ^a
Mean Total Weight Change (Weight Change) Day 4 to 21 (g)	106.11	101.63	86.67	76.00 ^a
Summary of Mean Fetal Data				
Number of Females with Live Fetuses	9	8	9	7
Mean Number of Male Fetuses per Litter	5.0	5.6	5.8	2.7
Mean Number of Male Fetuses per Litter	5.0	5.6	4.9	3.0
Fetuses (% Males)	49.3	50.7	54.5	27.6
Mean Fetal Weight (g)	5.426	5.091	4.740	4.626 ^a
Mean Weight, Male Fetuses (g)	5.565	5.285	4.848	4.756 ^a
Mean Weight, Female Fetuses (g)	5.318	4.889	4.609	4.524 ^a
Macroscopic Observations				
Adrenal				
Large, left, collected	0	0	0	1
Animal				
Thin, not collected	0	0	0	1
Summary of Fetal Observations	-	-	-	-

- No noteworthy findings

a: N=4

* - $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$

GD = Gestation day

Statistics = ANOVA and Dunnett's

Sevabertinib (BAY 2927088) – Version 2.0

Toxicokinetics

After repeated dosing, on Gestation Day 17, the exposure of sevabertinib in terms of AUC_{tint}, increased in a moderately higher than dose proportional manner over the dose range from 3 to 11 mg/kg/day. C_{max} increased in a markedly higher than dose proportional manner from 3 to 7 mg/kg/day and in an approximately dose proportional manner from 7 to 11 mg/kg/day.

C_{max} for sevabertinib was observed at 2 hours following administration of sevabertinib on Gestation Day 17. The exposure of sevabertinib in terms of AUC_{tint} and C_{max} on Gestation Day 17 was almost unchanged in comparison to the AUC_{tint} and C_{max} on Gestation Day 6 across the dose range of 3 to 11 mg/kg/day, except for C_{max} in animals dosed at 7 mg/kg/day, which showed a moderately higher exposure on Gestation Day 17 than on Gestation Day 6.

Systemic exposure summary of sevabertinib after repeated dosing in female pregnant rats on GD 17 (Study T105411-2)

Dose Parameter	Unit	Day 17		
		3 mg/kg/day	7 mg/kg/day	11 mg/kg/day
AUC _{all}	h·µg/L	697	2790	6420
AUC _{all, norm}	kg·h/L	0.232	0.398	0.584
C _{max}	µg/L	102	681	1010
C _{max, norm}	kg/L	0.0339	0.0972	0.0917
t _{max}	h	2.00	2.00	2.00
C _{tint} /C _{max}	%	1.58	0.252	1.25
R _A AUC _{all}	%	86.3	98.1	104
R _A C _{max}	%	92.3	169	103
t _{last}	h	24.0	24.0	24.0

Sevabertinib: Oral (Gavage) Toxicity and Toxicokinetic Study of Embryo-Fetal Development in the Rat (Module 4.2.3.5, Report B003632, pivotal, GLP)

Key Drug-related Adverse Findings:

- There were no sevabertinib-related mortalities
- Sevabertinib-related reductions in mean body weight gain and food consumption were noted at all dose levels and a dose response was evident.
- Reductions in mean fetal and placenta weights were noted following administration of 6 mg/kg/day.
- No sevabertinib-related macroscopic observations were noted.
- No test item-related fetal malformations were noted.
- Non-adverse variations were confined to increased incidences of incomplete ossification of the mandible following administration of all doses, compared with controls.

GLP compliance: Yes

Sevabertinib (BAY 2927088) – Version 2.0

Methods	
Dose and frequency of dosing:	0 (vehicle control), 1.5, 3, or 6 mg/kg daily from GD6 to GD17
Route of administration:	Oral gavage
Formulation/Vehicle:	Ethanol/Kolliphor HS15@/Water for Injection (10/40/50 v/v/v) adjusted to pH 4
Species/Strain:	Rat, Wistar
Number/Sex/Group:	20 animals/group
Age:	9 weeks
Satellite groups:	-

Parameters	Major findings
Mortality	No sevabertinib-related mortalities.
Clinical Signs	No sevabertinib-related clinical observations were noted.
Body Weight	Sevabertinib -related reduced body weight gain was noted from GD 6 following administration of 3 or 6 mg/kg/day, and from GD 9 following administration of 1.5 mg/kg/day, compared with controls.
Feed Consumption	Reduced food consumption was noted throughout the dosing period following administration of 1.5, 3, or 6 mg/kg/day, with statistically significant reductions noted from GD 6 to 9 and from GD 9 to 12, and from GD 15 through 18, following administration of 6 mg/kg/day compared with controls.
Gross Pathology/Cesarian section	A slight reduction in total and corrected maternal weight change was noted following administration of 1.5, 3, or 6 mg/kg/day, compared with controls, when corrected for the gravid uterus weight. Values did not attain statistical significance; however, the reduced total and corrected maternal weight change reflected the body weight changes observed in life. Reduced mean fetal weights (combined and individual sexes) were noted for sevabertinib-treated groups, with statistically significant reductions noted following administration of 6 mg/kg/day. Mean combined and mean male fetal weight values were within the Historical Control Data (HCD) range, while mean female fetal weight values were marginally below the HCD range. Upon review of the individual litters, multiple litters maternally exposed to 6 mg/kg/day had combined fetal weights below the HCD range. These changes were considered sevabertinib-related and reflected the individual body weight changes observed in life. No fetal malformations were observed at any dose level, and no adverse sevabertinib-related fetal variations were observed. Increased incidences of the variation, incomplete ossification of the mandible, were noted following administration of 1.5, 3, or 6 mg/kg/day, compared with controls. A dose relationship was observed, and although the percentage litter and fetal incidence values were outside the HCD range, no adverse effects on the developing fetus were observed. Therefore, these findings were considered sevabertinib-related but not adverse.

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Reproductive and Developmental Toxicity - Embryo-Fetal Developmental Toxicity Study in Rats	Test Article:	Sevabertinib	Report No.:	B003632
Daily Dose [mg/kg]	0 (Control)	1.5	3	6
Number of Females	20	20	20	20
Total Females	20	20	20	20
Pregnant Females	20	19	19	16
Non-Pregnant Females	0	1	1	4
Pregnant with Total litter loss (no viable fetuses)	1	0	0	0
Females with Live Fetuses at GD 21	19	19	19	16
Summary of Cesarean Section Data - Excluding Females with no viable Fetuses				
Number of females pregnant at cesarean section	19	19	19	16
Mean No. Corpora Lutea	12.4	11.5	11.6	12.0
Mean No. Implantation Sites	11.7	10.9	10.8	11.3
Mean No Pre-implantation Loss	0.7	0.5	0.8	0.8
Pre-implantation Loss (%)	5.28	4.17	7.32	6.38
Mean No. Early Resorptions	0.3	0.5	0.4	0.6
Mean No. Late Resorptions	0.0	0.0	0.1	0.1
Mean No. Total Resorptions	0.3	0.5	0.4	0.6
Mean Resorption rate per animal (%)	2.7	4.9	4.0	5.1
No. of Dead Fetuses	0.0	0.0	0.0	0.0
Mean No Postimplantation Loss	0.3	0.5	0.4	0.6
Postimplantation Loss (%)	2.69	4.88	3.96	5.09
Mean Live Fetuses	11.4	10.4	10.4	10.6

Reproductive and Developmental Toxicity - Embryo-Fetal Developmental Toxicity Study in Rats	Test Article:	Sevabertinib	Report No.:	B003632
Daily Dose [mg/kg]	0 (Control)	1.5	3	6
Number of Females	20	20	20	20
Mean Placenta Weight (g)	0.489	0.483	0.471	0.436
% change from controls	Not applicable	-1.2	-3.7	-10.6
Mean Gravid Uterine Weight (g)	77.79	71.58	69.17*H	67.83*H
Mean Corrected Body Weight (Carcass Weight) Day 6 to 21 (g)	244.89	237.99	234.04	231.29
Mean Corrected Weight Change , Day 6 to 21 (g)	37.42	35.42	30.14	31.04
Summary of Mean Fetal Data				
Mean Total Weight Change (Weight Change) (g)	115.21	107.00	99.32	98.88
Number of Females with Live Fetuses	19	19	19	16
Mean Number of Male Fetuses per Litter	5.8	5.7	5.6	5.6
Mean Number of Male Fetuses per Litter	5.6	4.7	4.8	5.1
% Males Fetuses	51.0	54.9	52.8	52.7
Mean Fetal Weight (g)	5.261	5.237	5.142	4.973
Adjusted Mean	5.280	5.229	5.133	4.971+H
Mean Weight, Male Fetuses (g)	5.382	5.384	5.299	5.097
Adjusted Mean	5.415	5.368	5.287	5.091+H
Mean Weight, Female Fetuses (g)	5.145	5.066	4.979	4.831
Adjusted Mean	5.157	5.061	4.973	4.830+H
Macroscopic Observations	-	-	-	-
Fetal Malformations	-	-	-	-
- No noteworthy finding GD = Gestation day *H = Dunnett Exact Homogeneous Test Significant: 0.05 level +H = Dunnett Exact Homogeneous Test Significant: 0.01 level				

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Toxicokinetics

After repeated dosing, on GD 17, the exposure of sevabertinib in terms of AUC(0-7) increased in a moderately higher than dose proportional manner over the dose range 1.5 to 6 mg/kg/day. C_{max} increased in an approximately dose proportional manner from 1.5 to 3 mg/kg/day and in a moderately higher than dose proportional manner from 3 to 6 mg/kg/day. On Gestation Day 17, the exposure of sevabertinib in terms of AUC(0-7) and C_{max} was almost unchanged in comparison to AUC(0-7) and C_{max} on Gestation Day 6 in animals dosed from 1.5 to 6 mg/kg/day with accumulation ratios between 85.6% and 129%.

Summary of Mean Pharmacokinetic Parameters after Daily Oral (Gavage) Administration of sevabertinib on Gestation Day 17 (Study T106047-8)

Dose	Unit	Day 17		
		1.5 mg/kg/day	3 mg/kg/day	6 mg/kg/day
AUC _{last}	h·µg/L	216	636	2450
AUC _{last, norm}	kg·h/L	0.144	0.212	0.409
AUC (0-7)	h·µg/L	216	636	1820
AUC(0-7)norm	kg·h/L	0.144	0.212	0.304
C _{max}	µg/L	45.3	110	346
C _{max, norm}	kg/L	0.0302	0.0366	0.0576
t _{max}	h	1.00	2.00	4.00
t _{last}	h	7.00	7.00	24.0

Discussion on Reproductive Toxicology

A preliminary EFD study in rats was conducted. Oral (gavage) administration of 0, 3, 7, or 11 mg/kg/day sevabertinib to pregnant female Wistar rats during organogenesis resulted in test item-related effects at all dose levels, including three mortalities following administration of 11 mg/kg/day. A dose level of 7 or 11 mg/kg/day was considered excessive due to the severity of the test item-related body weight loss, reduced food consumption, adverse clinical observations, and reduced fetal weights, however no fetal malformations or variations were noted. Test item-related effects following administration of 3 mg/kg/day were confined to initial reduced body weight gain and small reductions in food consumption and considered not to represent an adverse effect to the pregnant animals; and non-adverse marginal reductions in fetal weights.

In the pivotal EFD study in rats, sevabertinib-related effects observed after administration of 1.5 or 3 mg/kg/day were limited to marginal reductions in body-weight gain and food consumption. This resulted in slightly lower absolute body weights at GD 21 compared with controls and did not adversely affect maternal health or fetal development. Fetal effects were limited to slightly reduced fetal weights (combined and individual sexes), resulting in a slight reduction in gravid uterine and placental weights, but mean values were within the historical control data range. A

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dose level of 6 mg/kg/day was considered excessive due to the severity of the sevabertinib-related body weight changes, reduced food consumption, and reduced fetal and placental weights; however, no fetal malformations or adverse fetal variations were noted.

An evaluation in rabbits was not possible. Several studies in rabbits with oral application of sevabertinib in different formulations did not lead to any relevant systemic exposure. The reason for the poor exposure is probably due to a low absorption in the intestine in combination with a very fast metabolism and rapid clearance of the test substance. *In vitro* experiments with rabbit hepatocytes suggest rapid metabolism. In order to achieve an exposure that corresponds to the therapeutic exposure in humans, slow-bolus intravenous application in rabbits was tried as an alternative. This study ultimately had to be discontinued because intravenous application led to unacceptable local effects, which finally resulted in the premature euthanasia of the animals.

Although there is no evidence of developmental toxicity from the rat EFD studies, there is a clear concern that EGFR and HER2 inhibition may have adverse effects on embryo-fetal development. These concerns include target expression (EGFR and HER2) in reproductive organs and the pharmacological pathway, along with its critical role in cell growth, survival, and differentiation within development. Additionally, effects observed in EGFR and HER2 knock-out animals and an *in vitro* study performed with human inducible pluripotent stem cells suggest potential teratogenic effects. After discussion between the FDA and Bayer, a weight-of-evidence based assessment of the potential for sevabertinib to cause reproductive and embryofetal toxicity is provided.

The EGFR and the HER2 (ERBB2) receptor are widely expressed throughout the body in various tissues and organs, such as the skin, nerves, lungs, breast, prostate, bladder and gastrointestinal tract ((27) and in house data). Notably, they are also present in reproductive organs, including the ovaries and uterus, where they play important roles in cell growth and differentiation.

The EGFR plays a crucial role in embryogenesis and organogenesis, especially with its expression observed in the placenta, uterus, and nervous system. Studies involving knockout models reveal that mice lacking EGFR suffer from significant developmental issues, leading to mid-gestation death due to placental dysfunction and abnormal organ formation (28-31).

Specifically, the absence of EGFR results in fewer spongiotrophoblast layers in the placenta, which negatively impacts fetal growth and survival. Newborns lacking EGFR display underdeveloped features, such as immature lungs and skin defects, which align with EGFR expression patterns. Underdeveloped lungs with collapsed alveoli, preventing newborns from beginning or maintaining respiration, resulted in mortality due to respiratory distress syndrome and respiratory failure. Mice also showed significant growth retardation, along with eye defects (born with open eyes) and hair abnormalities (30, 32). Progressive neurodegeneration began shortly after birth in areas such as the frontal cortex, olfactory bulb and thalamus. This effect was characterized by increased cellular apoptosis and a near absence of viable neurons (33).

Zhang et al. (2013) (34) underscores the critical role of EGFR in the regulation of cartilage matrix degradation and secondary ossification center formation, which is essential for normal skeletal development. EGFR regulates these processes through both β -catenin-dependent and -independent pathways. The findings reveal that while chondrocyte hypertrophy occurs normally, there is impaired mineralization and apoptosis of hypertrophic chondrocytes in the absence of EGFR signaling. Research by Large et al. (2014) (35) explored the role of EGFR in endometrial function during early pregnancy. Using conditional knockout models in mice and siRNA in human endometrial stromal cells, the study found that EGFR is essential for successful decidualization and overall fertility. Mice with conditional EGFR ablation experienced significant subfertility, with pregnancy failures occurring shortly after the implantation of the blastocyst. The findings also extended to primary human endometrial stromal cells, highlighting EGFR as a critical regulator of human decidualization.

Similarly, the HER2 is vital for the development of cardiac and neural tissues, particularly in forming cardiac trabeculae and cranial sensory ganglia. Knockout studies show that mice deficient in HER2 face severe cardiac and neural developmental defects, leading to embryonic lethality (28, 36, 37). In addition, HER2/HER4 heterodimers have been implicated in the development of mammary glands (38). The absence of HER2 results in significant neural defects and a loss of Schwann cells, which are essential for peripheral nerve development. Overall, these knockout studies underscore the importance of HER2 for proper cardiac development, as defects can lead to severe malformations (39).

In order to complement the literature search, the results of the ReproTracker assay were submitted to the authorities. In this assay, the differentiation of hiPSCs into cardiomyocytes, hepatocytes, and neural rosettes was investigated by assessing morphology and biomarker gene expression using qRT-PCR. The ReproTracker assay's validity was confirmed in every differentiation experiment via exposure to a human teratogenic compound (thalidomide/retinoic acid) and a non-teratogenic compound (saccharin). Thalidomide exposure significantly decreased expression of cardiomyocyte-specific marker MYH6 and liver-specific markers FOXA2 and AFP, disrupted cardiac contractions, and altered hepatocyte morphology. Retinoic acid exposure led to a concentration-dependent decrease in neural rosette markers PAX6 and NESTIN and affected their morphology. Saccharin had no impact on differentiated cells' morphology, functionality, or biomarker gene expression, confirming ReproTracker's validity. Sevabertinib did not significantly affect mesodermal marker expression but caused a concentration-dependent decrease in MYH6, with significant changes starting at 1.0 μ M, indicating disrupted cardiomyocyte differentiation. This aligns with the loss of cardiac contraction ability at this concentration. This result could be explained by the high expression of HER2 in cardiomyocytes. Sevabertinib did not significantly affect the endodermal marker, FOXA2, but caused a decrease in the hepatocyte-specific marker, AFP, starting at 0.2 μ M, indicating disrupted hepatocyte differentiation and morphology at 2.0 μ M. It also showed a U-shaped response in the neural rosette markers PAX6 and NESTIN, disrupting their morphology at 2.0 μ M in one biological replicate. Based on the assay criteria, ReproTracker identified sevabertinib as a teratogen, disrupting proper stem cell differentiation into cardiomyocytes and hepatocytes.

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Even though sevabertinib has a rather high selectivity with respect to the mutated EGFR receptor, there is no relevant selectivity with respect to the mutated HER2 receptor and consequently an interaction with wild-type HER2 cannot be avoided. Based on the comprehensive evaluation of potential impact of EGFR and/or HER2 inhibition on embryo-fetal development, it is clear that the existing data raises significant concerns regarding its potential teratogenic effects. The absence of developmental toxicity in rat studies does not mitigate the risks associated with EGFR and HER2 inhibition, particularly given their critical roles in reproductive organ development and overall embryogenesis. The findings from knockout studies and *in vitro* assays further suggest that sevabertinib may disrupt essential processes in fetal growth and differentiation. Therefore, conducting another study in a non-rodent species on embryo-fetal development is unlikely to alleviate these concerns, as the underlying mechanisms of action and potential adverse effects have already been substantiated through various lines of evidence.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the data, with additional pertinent details. In the GLP-compliant preliminary EFD study (Study No. T105411-2, Report No. B003097), sevabertinib was orally administered to pregnant females during organogenesis at doses of 3, 7, and 11 mg/kg once daily from GD 6 to 17. Three animals at 11 mg/kg (0.5 times the human exposure at the recommended dose of 20 mg BID based on AUC) were sacrificed in moribund condition on GD 14 or GD 15 due to body weight loss up to -16% and severe clinical signs including piloerection, cool to the touch, liquid feces, hunched posture, and/or thin appearance. Similar clinical findings were observed in animals at 11 mg/kg that survived to scheduled necropsy, in addition to observations of decreased general activity, labored respiration, and partially closed eyes in individual animals. Decreased body weight was observed on GD 18 by -9% and -15% at 7 and 11 mg/kg, respectively (≥ 0.2 times the human exposure at the recommended dose based on AUC), compared with concurrent controls, and only slightly recovered following dosing cessation between GD 18 and GD 21 (-7% and -11%, respectively). In addition, mean body weight gains during the dosing period at 7 and 11 mg/kg were significantly lower than the controls (-33% and -56%, respectively), but were higher than the controls (6% and 14%, respectively) following dosing cessation (GD 18 to GD 21). Overall food consumption decreased by -17% and -30% at 7 and 11 mg/kg, respectively (≥ 0.2 times the human exposure at the recommended dose based on AUC) from GD 6 through GD 18 compared with controls, but fully recovered between GD 18 and GD 21. The Applicant was unable to achieve higher exposures due to dose-limiting toxicities in pregnant rats, under the conditions tested, and only limited variations were observed; however, they were close to the historical control data (HCD) and not dose-dependent.

In the GLP-compliant pivotal EFD study (Study No. T106047-8, Report No. B003632), sevabertinib was orally administered to pregnant females at doses of 1.5, 3, and 6 mg/kg once daily from GD 6 to 17. There were no mortalities or clinical signs. During the dosing phase, mean body weight gains at 1.5, 3, and 6 mg/kg (≥ 0.02 times the human exposure at the

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recommended dose based on AUC) were significantly lower than the controls (-13%, -18%, and -21%, respectively), but partially recovered (-3%, -8%, and -5%, respectively) following dosing cessation (GD 18 to GD 21). Overall food consumption decreased by -13% at 6 mg/kg (approximately 0.18 times the human exposure at the recommended dose based on AUC) compared with controls during the dosing period but recovered between GD 18 and GD 21. Significant reductions in mean fetal weights (combined and individual sexes) were observed at 6 mg/kg compared with controls, but only the decrease in mean female fetal weight (-6%) was slightly below the HCD. Reduced mean placenta weight by -11% was observed at 6 mg/kg compared with controls. The reduced fetal and placental weights resulted in statistically significant decreases in mean gravid uterine weights by -11% and -13% at 3 and 6 mg/kg, respectively, compared with the controls; however, these values were within the HCD.

The M1 metabolite was present in rat plasma. The toxicokinetic parameters for M1 in both EFD studies are shown in the tables below.

Toxicokinetic Parameters for the M1 Metabolite (BAY 3306572); Preliminary Embryo-Fetal Development Study

Dose Parameter	Unit	Day 17		
		3 mg/kg/day	7 mg/kg/day	11 mg/kg/day
AUC _{all}	h·µg/L	nc	nc	981
AUC _{all, norm}	kg·h/L	nc	nc	0.0892
C _{max}	µg/L	10.9	52.2	107
C _{max, norm}	kg/L	0.00362	0.00746	0.00971
t _{max}	h	2.00	2.00	2.00
C _{int} /C _{max}	%	-	-	4.35
R _A AUC _{all}	%	nc	nc	166
R _A C _{max}	%	67.5	168	208
t _{last}	h	7.0	7.0	24.0

Excerpted from the Applicant's submission: Study No. T105411-2, Report No. B003097

Toxicokinetic Parameters for the M1 Metabolite (BAY 3306572); Pivotal Embryo-Fetal Development Study

Dose Parameter	Unit	Day 17		
		1.5 mg/kg/day	3 mg/kg/day	6 mg/kg/day
AUC _{last}	h·µg/L	28.4	69.8	166
AUC _{last, norm}	kg·h/L	0.0189	0.0233	0.0277
AUC (0-7)	h·µg/L	28.4	69.8	166
AUC(0-7) _{norm}	kg·h/L	0.0189	0.0233	0.0277
C _{max}	µg/L	5.12	11.9	32.4
C _{max, norm}	kg/L	0.00341	0.00397	0.00540
t _{max}	h	4.00	4.00	4.00
t _{last}	h	7.00	7.00	7.00

Excerpted from the Applicant's submission: Study No. T106047-8, Report No. B003632

The Applicant provided a WOE assessment, including published literature and a NAM (human-induced pluripotent stem cell-based assay) for reproductive risk to supplement the rat EFD study. The referenced published literature shows that HER2 and EGFR are critically important for reproductive and developmental processes including blastocyst implantation, placental development, and embryofetal/postnatal survival and development. The human-induced pluripotent stem cell-based assay showed that sevabertinib disrupted stem cell differentiation into cardiomyocytes and hepatocytes. Fertility studies were not conducted with sevabertinib nor are they warranted for the advanced cancer indication.

Based on findings in animals and the mechanism of action of sevabertinib, FDA recommends a warning for embryo-fetal toxicity and advising females of reproductive potential to use effective contraception during treatment with sevabertinib and for 1 week after the last dose, based on five times the human half-life of sevabertinib (^{(b) (4)} hours).

5.5.4. Other Toxicology Studies

The Applicant's Position:

The phototoxic potential of sevabertinib was assessed in a GLP-compliant *in vitro* 3T3 NRU assay, with concentrations up to 50 µg/mL sevabertinib in the presence or absence of UVR. The average PIF was 1.0; thus, sevabertinib was identified as a non-phototoxic compound.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions regarding phototoxicity. In a GLP-compliant phototoxicity study (Study No. T105051-2, Report No. PH-41909), the Applicant evaluated the phototoxic potential of sevabertinib by measuring the relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to sevabertinib in the presence or absence of ultraviolet radiation. Sevabertinib did not demonstrate phototoxic potential (photoirritancy factor [PIF] = 1) compared to the positive control chlorpromazine hydrochloride (PIF = 36.7) under the conditions of this *in vitro* assay. The criterion for "phototoxic" is PIF > 5.

Impurity levels

The CMC review team consulted the pharmacology/toxicology review team regarding the qualification threshold for ^{(b) (4)}. The Applicant proposed a qualification limit of ^{(b) (4)} based on the nonclinical data and the fact that this is a ^{(b) (4)}. Toxicology studies in rats qualified ^{(b) (4)} at ^{(b) (4)}; thus, the proposed qualification threshold for this impurity is acceptable from the pharmacology/toxicology perspective.

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6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking accelerated approval of sevabertinib for the treatment of adult patients with advanced NSCLC whose tumors have HER2 (ERBB2) mutations and who have received prior systemic therapy. The Applicant's proposed recommended dosage is sevabertinib 20 mg twice daily (BID) taken with food.

The clinical pharmacology review addressed the following key review issues:

Dosage Acceptability:

The proposed recommended dosage of sevabertinib 20 mg BID taken with food is supported by available pharmacokinetics (PK), pharmacodynamics (PD), activity, and safety data from the ongoing first-in-human (FIH) study 21607. The dosage of 20 mg BID showed a higher overall response rate (ORR) in the targeted patients compared to the lower dosage of 10 mg BID (64% vs 36%). Although 20 mg BID was also associated with higher rates of Grade ≥ 3 TEAEs and TEAEs leading to dose modifications (i.e., dose reductions and interruptions), the overall safety profile at this dose level is considered acceptable in the context of the observed activity. FDA exposure-response (E-R) analyses identified a positive trend of ORR with higher exposure and a significant positive E-R relationship for the safety endpoints (i.e., any Grade rash, any Grade and Grade ≥ 3 diarrhea, AEs leading to dose modification). Further analysis using activity and safety data of individual patients suggested that the dosage of 20 mg BID resulted in earlier response and steeper tumor reduction as compared to 10 mg BID; diarrhea was generally manageable and did not necessarily lead to dose reduction, regardless of severity and recurrence of diarrhea, patient age, and dose level. Taken together, FDA agrees that the favorable benefit-risk profile supports the proposed sevabertinib dosage of 20 mg BID in adult patients with NSCLC with HER2 mutations.

Specific populations:

Population PK analyses found no clinically meaningful effects on the PK of sevabertinib for the following covariates, including age (18 to 91 years), sex, race (27% White, 65% Asian), body weight (29 to 155 kg), smoking status, renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (AST $>$ ULN and total bilirubin $\leq$ ULN; or total bilirubin $>$ 1 to 1.5x ULN and any AST).

Hepatic Impairment: Patients with hepatic impairment may have serious risk of increased exposure to sevabertinib as sevabertinib is eliminated primarily through hepatic metabolism. The PK and safety of sevabertinib in patients with moderate or severe hepatic impairment have not been evaluated. Given the rarity of the target patient population, a Post Marketing Requirement (PMR) will be issued for a study to evaluate the potential serious risk of increased drug exposure

and determine a safe and appropriate dosage of sevabertinib in patients with moderate hepatic impairment. The dosage recommendation in patients with severe hepatic impairment will be determined based on the PK results in patients with moderate hepatic impairment or a subsequent PMR study if needed.

Drug-drug interactions (DDIs):

Sevabertinib is a substrate for CYP3A4. Clinical DDI studies were conducted with itraconazole (P-gp and strong CYP3A4 inhibitor) and carbamazepine (strong CYP3A4 inducer). The labeling recommends avoidance of concomitant use of strong CYP3A4 inhibitors and dose reduction if concomitant use cannot be avoided. Moderate CYP3A4 inhibitors may be used with safety monitoring for increased adverse reactions. Given the significant changes in exposure of sevabertinib following concomitant use of a strong CYP3A4 inducer, the labeling recommends avoidance of concomitant use of strong or moderate CYP3A4 inducers.

Sevabertinib displays a net inhibitory effect on PK of CYP3A4 substrates. The clinical DDI study conducted with midazolam (CYP3A4 substrate) showed approximately 2-fold increase in midazolam exposure following concomitant use of sevabertinib 20 mg twice daily. The labeling recommends avoid concomitant use of CYP3A4 substrates where minimal concentration changes may lead to serious adverse reactions.

Sevabertinib is an inhibitor of P-gp. Based on clinical DDI results with dabigatran etexilate (P-gp substrate), the labeling recommends referring to the Prescribing Information of P-gp substrates where minimal concentration changes may lead to serious adverse reactions for recommended dosage modification and/or monitoring.

The inhibitory effect of sevabertinib on CYP1A1 cannot be ruled out based on in vitro DDI studies. However, given that CYP1A1 is not a typical enzyme with generally low expression, a post-marketing study will not be required. Instead, the labeling recommends referring to the Prescribing Information of CYP1A1 substrates when concomitant use of sevabertinib with these substrates.

Based on the results of in vitro DDI studies, a PMR will be issued to conduct a clinical drug interaction trial to assess the effect of sevabertinib on the PK of MATE1/2-K substrates and to inform an appropriate drug interaction management strategy for coadministration with sevabertinib.

QT Interval Prolongation:

Based on data from study 21607, sevabertinib does not demonstrate mean QTcF interval prolongation ≥ 20 msec. The observed largest mean increase in the QTc interval was 3.9 msec (upper confidence interval of 5.8 msec) at steady state C_{max} after administration of 60 mg QD, which covers the anticipated therapeutic sevabertinib C_{max} by 2.2-fold.

Recommendations:

The Office of Clinical Pharmacology has reviewed the information contained in NDA 219972. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized in **Table 21**. Clinical pharmacology PMRs are summarized in **Table 22**.

Table 21 FDA Key Clinical Pharmacology Review Issues, Recommendations, and Comments

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of efficacy is provided by Study 21607 (SOHO-1) Group D and E (See Section 8.1.1). The primary endpoint of overall response rate (ORR) was 71% (95% CI: 59, 82) at 20 mg BID in HER2 targeted therapy naïve patients who had received prior platinum therapy, and 38% (95% CI: 25, 53) at 20 mg BID in patients who had received prior platinum therapy and HER2-targeted ADCs. E-R analysis for efficacy identified positive trends for ORR and best tumor response (BTR) with higher exposure (See Section 19.4.4).
General dosing instructions	The proposed dosage of sevabertinib is 20 mg BID taken with food. The dosage is supported based on the PK, PD, activity, and safety data from patients receiving 10 mg BID and 20 mg BID in Study 21607 and the supportive E-R analyses. Given the decreased exposure with food intake determined from a dedicated food effect study, the identified positive E-R relationship for safety, and the observed high rate of gastrointestinal (GI) adverse events (e.g., diarrhea), the proposed fed dosing condition is reasonable with the potential for toxicity mitigation.
Dosing in patient subgroups (intrinsic and extrinsic factors)	<u>Renal impairment:</u> Per population PK analysis, no dosage adjustment is recommended in patients with eGFR 30 to < 90 mL/min. Since renal elimination only accounts for 10% of the administered dose with 1.3% as the parent drug, the effect of severe renal impairment on sevabertinib exposure is not expected to be clinically meaningful, and therefore a dedicated renal impairment study in patients with severe renal impairment is not needed. <u>Hepatic impairment:</u> Per population PK analysis, no dosage adjustment is recommended in patients with mild hepatic impairment (per NCI -ODWG). The PK and safety of sevabertinib 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 sevabertinib in patients with moderate hepatic impairment. The dosage recommendation in patients with severe hepatic impairment will be determined based on the results in patients with moderate hepatic impairment or a subsequent PMR study if needed.

Review Issue	Recommendations and Comments
Drug Interactions	Per population PK analysis, no dosage adjustment is required based on age (18 to 91 years), sex, race (27% White, 65% Asian), body weight (29 to 155 kg), or smoking status. <u>HER2 genetic alternations</u>: Sevabertinib treatment response was generally observed across <i>HER2</i> alterations assessed. CYP3A is the primary CYP450 enzyme involved in sevabertinib metabolism. Sevabertinib AUC increased 2.3-fold and C_{max} 1.6-fold following concomitant use of itraconazole (strong CYP3A4 inhibitor) 200 mg once daily. Sevabertinib AUC decreased by 79% and C_{max} by 57% following concomitant use of carbamazepine (strong CYP3A inducer) 600 mg once daily. Sevabertinib displays a net inhibitory effect on PK of CYP3A4 substrates. Midazolam (CYP3A4 substrate) AUC increased 2-fold and C_{max} 1.8-fold following concomitant use of sevabertinib 20 mg twice daily. Sevabertinib is an inhibitor of P-gp. Dabigatran etexilate (P-gp substrate) AUC increased 1.4-fold following concomitant use of sevabertinib 20 mg twice daily. Based on the above clinical DDI results, the review team agrees with the proposed labeling recommendations to avoid concomitant use with strong CYP3A inhibitors and inducers (dose reduction if concomitant use of strong CYP3A inhibitors cannot be avoided), revises the instructions for certain substrates of CYP3A4 and P-gp, and recommends additional instructions for moderate CYP3A inhibitors and inducers based on the anticipated drug interactions. • Monitor patients for increased HYRNUO-associated adverse reactions when used with a moderate CYP3A4 inhibitor. • Avoid concomitant use with a moderate CYP3A4 inducer. • Avoid concomitant use with certain CYP3A4 substrates where minimal concentration increase may lead to serious adverse reactions. • Refer to the Prescribing Information of P-gp substrates where minimal concentration increase may lead to serious adverse reactions. Based on the <i>in vitro</i> DDI results, the review team agrees with the proposed labeling recommendations to refer to the Prescribing Information for CYP1A1 substrates when concomitant use of sevabertinib with these substrates.

Review Issue	Recommendations and Comments
QT	Based on data from Study 21607, the observed largest mean increase in the QTc interval for sevabertinib was 3.9 msec (upper confidence interval of 5.8 msec) at steady state C _{max} after administration of 60 mg QD, which covers the anticipated therapeutic sevabertinib C _{max} by 2.2-fold. According to FDA’s QT-IRT analysis (DAARTS ID: 5634071), given the absence of a positive control and a placebo group in Study 21607, there is reluctance to conclude a lack of an effect of sevabertinib on the QTc interval. FDA proposes to describe the observation from Study 21067 in the label, i.e., at 2 times the maximum recommended dose, a mean increase in the QTc interval >20 ms was not observed.
Labeling	FDA provided labeling revisions following the guidance and current labeling practice. Overall, the proposed labeling language in the Clinical Pharmacology pertinent sections are generally acceptable upon the Applicant’s agreement to the FDA revisions.

Table 22. Post-Marketing Requirements

PMR	Rationale	PMR language
PMR #1 Hepatic impairment	The PK and safety of sevabertinib in patients with moderate hepatic impairment have not been evaluated. Given the hepatic elimination pathway of sevabertinib and the positive E-R relationship for safety, a hepatic impairment study is warranted.	Conduct a clinical hepatic impairment trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dosage of sevabertinib in patients with moderate hepatic impairment.
PMR #2 DDI	In vitro studies showed that sevabertinib inhibited MATE1/2-K. The potential inhibitory effects of sevabertinib 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 sevabertinib on the pharmacokinetics of sensitive substrates of MATE1/2-K in healthy subjects and inform appropriate drug interaction management strategy for coadministration of sevabertinib with these transporter substrates.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

An overview of general pharmacology and PK characteristics is provided in Section 6.3.1.

The Applicant's Position:

The pharmacology and clinical PK of sevabertinib have been extensively studied both *in vitro* and *in vivo*. *In vitro* studies using human biomaterials focused on aspects like protein binding, blood cell/plasma partitioning, metabolism in human hepatocytes, and potential DDIs. Clinical data comprise of PK properties from 6 clinical studies which included participants with advanced NSCLC harboring *HER2* or *EGFR* mutations as well as healthy participants.

The clinical program started with the FiH dose escalation/expansion Study 21607 in participants with advanced NSCLC harboring *HER2* or *EGFR* mutations. Clinical studies conducted in healthy participants included the mass balance Study 22249, the DDI Studies 22250 (DDI with itraconazole and carbamazepine), 22251 (DDI with midazolam), and 22252 (DDI with dabigatran etexilate and rosuvastatin), as well as Study 22253 which investigated the effect of food and an acid reducing agent on sevabertinib PK.

Additional analyses were conducted to evaluate population PK, exposure-response correlations, and the effect of sevabertinib concentration on QTcF.

The FDA's Assessment:

FDA generally agrees with the Applicant's position on the pharmacology and clinical PK of sevabertinib. Refer to Sections 6.3.1, 6.3.2, and 19.4.3 for additional details.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The proposed dose for sevabertinib is 20 mg BID, equal to a total daily dose of 40 mg.

The maximum tolerated dose (MTD) of sevabertinib was determined to be 60 mg TDD in the FiH Study 21607, and 20 mg BID was selected as the RP2D. Data from this study demonstrated that treatment with sevabertinib 20 mg BID resulted in rapid, deep, and durable responses in participants with advanced NSCLC harboring *HER2* activating mutations, who had received prior systemic therapy, but are naïve to *HER2* ex20ins-targeted therapy, as assessed by ORR by BICR (see Section 8.1.2). In addition, sevabertinib was generally well tolerated up to a 40 mg TDD, with the most common drug-related TEAEs being low grade and manageable (see Section 8.2.3). Out of 268 participants treated with 20 mg BID (Whole Study 20 mg BID), 6 (2.2%) discontinued treatment due to a TEAE, 73 (27.2%) experienced TEAEs leading to a dose reduction, and 113 (42.2%) had TEAEs leading to dose interruption/delay.

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Based on the integrative analyses including PK-PD analyses/modeling, the clinical efficacy and safety data presented, and exposure-response evaluations, a dose of 20 mg BID was selected as the optimal dosage. While exposure of doses >20 mg BID was in the upper/flat part of the exposure-response curve for ORR and maximal change in tumor size, more participants are expected to reach >80% reduction in pEGFR over 24 hours with doses >20 mg BID and patients might further benefit from these higher doses. On the other hand, exposure of doses >20 mg BID showed a steep increase in the incidence of diarrhea Grade ≥ 3 and TEAEs leading to dose modifications, which may limit the clinical application of these higher doses. While exposure of doses <20 mg BID showed a decrease in AE incidence, as exposure was in the steep phase of the exposure-response relationship for safety, exposure was also in the steep phase of the exposure-response for efficacy, suggesting lower probability of efficacy (ORR and maximal change in tumor size) compared to the 20 mg BID dose.

Simulations using a translational PK-PD model of pEGFR reduction after daily doses of 10 mg to 80 mg, administered either QD or BID, based on the estimated PK variability in participants in Study 21607, showed that BID dosing provides more sustained pEGFR reduction compared to QD dosing of the same daily dose. As previously published preclinical and clinical data suggest pEGFR levels should be reduced below a threshold of 80% reduction over 24 hours for clinical efficacy, BID dosing was selected as the optimal dosing schedule.

Thus, data from the ongoing Study 21607, PK-PD, and exposure-response analyses collectively support a favorable benefit/risk profile of the sevabertinib 20 mg BID regimen.

The Applicant's Position:

The available data support the proposed dosing regimen of 20 mg BID for the treatment of advanced NSCLC patients with *HER2* activating mutations who have received prior systemic therapy.

The FDA's Assessment:

Based on PK, PD, and efficacy and safety results obtained from Study 21607, along with E-R analyses, FDA agrees that the favorable benefit-risk profile supports the proposed dosage of sevabertinib 20 mg BID in patients with advanced NSCLC harboring *HER2* activating mutations. Refer to Section 6.3.2.1 for details.

6.2.2.2. Therapeutic Individualization

Data:

The impact of intrinsic and extrinsic factors on the PK of sevabertinib was evaluated during clinical development. The main findings are summarized below:

Intrinsic (and extrinsic) factors

The population PK analysis demonstrated that age (18 to 91 years), sex (120 male and 215 female), race (216 Asian, 91 White, 9 Black or African American, and 1 American Indian or

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Alaska Native), geographic region (214 from Asia, 91 from Western Europe and Israel, 29 from North America, 1 from South America, 36 from Japan, and 83 from Mainland China), body weight (29.3 kg to 155 kg), mild or moderate renal impairment (146 mild and 25 moderate), mild hepatic impairment (73 mild), and smoking status (8 current smokers, 224 non-smokers, and 103 ex-smokers) do not affect the PK of sevabertinib (see Section 19.4.3.2). Therefore, no dose adjustment is required for these intrinsic and extrinsic factors.

Extrinsic factors

Food: Light low fat or high fat/high calorie meals were found to reduce the C_{max} of sevabertinib (20 mg) by 27.8% and 55.7%, respectively, and resulted in a delay of time to reach C_{max} (t_{max}) from approximately 1 hour to 2 and 4 hours, and reduced overall exposure (AUC) by 16.1 and 27.6% in comparison with intake in fasted state. Comparing the effect of a high-fat, high-calorie meal with the effect of a light, low-fat meal, AUC was decreased by 14% and C_{max} was decreased by 39%. ANOVA revealed that the LSM ratios [90% CI] of the C_{max} and AUC of sevabertinib for a low-fat meal vs fasted were 0.7225 [0.6295; 0.8293] and 0.8390 [0.7620; 0.9238], respectively. The LSM ratios [90% CI] of the C_{max} and AUC of sevabertinib for a high-fat/high-calorie meal vs fasted were 0.4432 [0.3861; 0.5087] and 0.7242 [0.6578; 0.7974], respectively. The LSM ratios [90% CI] of the C_{max} and AUC of sevabertinib for a high-fat/high-calorie meal vs a light, low-fat meal were 0.6134 [0.5344; 0.7041] and 0.8631 [0.7839; 0.9504], respectively.

Acid-reducing agents: Sevabertinib is a lipophilic base showing strong pH-dependent solubility. Despite the pH-dependent solubility, the proton pump inhibitor esomeprazole had no clinically relevant effect on the exposure of sevabertinib after oral administration of 20 mg sevabertinib. The LSM ratios [90% CI] were 0.9034 [0.7921; 1.0302] for AUC and 0.7074 [0.6128; 0.8165] for C_{max} .

Strong cytochrome P450 (CYP) 3A4 inhibitors: *In vitro* studies indicate that sevabertinib is primarily metabolized by CYP3A4. Data from Study 22250 demonstrated that coadministration of multiple oral doses (200 mg daily) of the strong CYP3A4 inhibitor (and P-gp inhibitor) itraconazole significantly increased the PK of a single oral dose of 10 mg sevabertinib. The LSM ratios [90% CI] were 2.2530 [1.9992; 2.5390] for AUC and 1.5973 [1.4701; 1.7356] for C_{max} .

Moderate CYP3A4 inhibitors: Clinical data on moderate CYP3A4 inhibitor use are too limited to evaluate the possible effect of moderate CYP3A4 inhibitor use on exposure, safety, and efficacy of sevabertinib. On the basis of the observed effect of the strong CYP3A4 (and P-gp) inhibitor, itraconazole, it cannot be excluded that sevabertinib exposure may increase when co-administered with moderate CYP3A4 inhibitors.

Weak CYP3A4 inhibitors: Exposure, safety, and efficacy data from Study 21607 did not show clinically meaningful differences between participants with or without concomitant use of weak CYP3A4 inhibitor(s). Sevabertinib may be given concomitantly with weak CYP3A4 inhibitors without clinically relevant DDIs.

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Strong CYP3A4 inducers: Study 22250 demonstrated that coadministration of multiple doses of the strong CYP3A4 (and P-gp) inducer carbamazepine (titrated up from 100 mg BID to 300 mg BID), significantly decreased the PK of a single oral 40 mg dose of sevabertinib. The LSM ratios [90% CI] were 0.2116 [0.1825; 0.2453] for AUC and 0.4294 [0.3617; 0.5098] for C_{max}.

Moderate CYP3A4 inducers: Sevabertinib exposure, safety, and efficacy were similar in participants who used moderate CYP3A4 inducer(s), with/without P-gp inhibitor(s) compared to the reference group of participants who took no inhibitors and/or inducers related to CYP3A4, P-gp, or BCRP during Cycle 1 in Study 21607. No adjustment of the sevabertinib dosage is needed when sevabertinib is dosed concomitantly with a moderate CYP3A4 inducer.

Weak CYP3A4 inducers: Available data on weak CYP3A4 inducer use are too limited to evaluate the possible effect of weak CYP3A4 inducer use on exposure, safety, and efficacy. As the clinical data showed similar exposure, safety, and efficacy profiles for participants who used moderate CYP3A4 inducers, no clinically relevant effect on exposure, safety, and efficacy of concomitant use of weak CYP3A4 inducers is expected. No adjustment of the sevabertinib dosage is needed when sevabertinib is dosed concomitantly with a weak CYP3A4 inducer.

Other inhibitors and inducers of transporters: *In vitro* studies suggest that sevabertinib is a substrate of BCRP and P-gp and is not a substrate of OATP1B1 or OATP1B3.

No clinically relevant interactions with BCRP or P-gp inhibitors are expected due to high permeability and limited unchanged excretion of sevabertinib. Clinical data from Study 21607 confirmed that sevabertinib exposure, efficacy, and safety profiles were similar in participants with or without concomitant use of BCRP inhibitors. The number of participants who took P-gp inhibitors, BCRP inducers, or P-gp inducers in Study 21607 was too low to make inferences on possible differences in exposure, safety and efficacy.

The Applicant's Position:

Therapeutic individualization is not required for the intrinsic (and extrinsic) factors of age, sex, race, geographical region, body weight, mild hepatic impairment, mild or moderate renal impairment, and smoking status.

To reduce the risk of gastrointestinal AEs, sevabertinib should be taken with food. The type of meal (high-fat, high-calorie or light, low-calorie) is not relevant.

Sevabertinib may be given concomitantly with acid-reducing agents.

To prevent potential DDIs, the following dosage adjustments/safety measures are suggested:

- Concomitant use of sevabertinib with strong CYP3A4 inhibitors (including, but not limited to, clarithromycin, itraconazole, ketoconazole, cobicistat, lopinavir/ritonavir, saquinavir/ritonavir, and grapefruit or grapefruit juice) during treatment with sevabertinib is not recommended. If concomitant use cannot be avoided, the current sevabertinib TDD should be reduced by 50%. For patients taking a current total daily dose of 10 mg (one

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10 mg tablet once daily), sevabertinib should be temporarily withheld until treatment with the strong CYP3A4 inhibitor is completed. After the CYP3A4 inhibitor has been discontinued for 3 to 5 elimination half-lives, sevabertinib should be resumed at the dose taken prior to initiating the inhibitor.

- As sevabertinib exposure may be increased when co-administered with moderate CYP3A4 inhibitors it is recommended to closely monitor patients for adverse reactions.
- Use of strong CYP3A4 inducers (including, but not limited to, carbamazepine, phenytoin, rifabutin, rifampicin, and St. John’s Wort) during treatment with sevabertinib is not recommended since decreased sevabertinib plasma concentrations are expected to result in reduced efficacy. Selection of an alternate concomitant medicinal product, with no or less potential to induce CYP3A4, should be considered.

The FDA’s Assessment:

Based on individual population PK analysis, FDA agrees with the Applicant’s assessment that no dosage adjustment is required for age (18 to 91 years), race (27% White, 65% Asian), sex, body weight (29 to 155 kg), smoking status, renal impairment (eGFR 30 to < 90 mL/min), or mild hepatic impairment (AST > ULN and total bilirubin ≤ ULN; or total bilirubin > 1 to 1.5x ULN and any AST).

Given the small sample size of Black/African American patients (n=9) included in the pivotal study 21607, a definitive conclusion of comparable PK cannot be made for this patient population. Therefore, FDA does not agree with Applicant’s assessment that no dosage adjustment is required for Black/African American patients based on current data. FDA anticipates that additional data to inform recommendations may be available from SOHO-02 which is intended to verify the clinical benefit of sevabertinib (refer to Section 13).

In addition, FDA does not agree with the Applicant’s DDI assessment using the population PK model to evaluate the effect of moderate CYP3A4 inhibitors and moderate CYP3A4 inducers on the PK of sevabertinib given these population PK estimates are not robust or reliable. Refer to Section 6.3.2.4 for detailed DDI evaluation.

6.2.2.3. Outstanding Issues

Data:

Not applicable.

The Applicant’s Position:

Data analysis of Study 22249 Part 1 (absolute bioavailability) is still ongoing at the time of submission.

Clinical data are available on the PK of sevabertinib in subjects with mild hepatic impairment. Results from the population PK indicated no differences in exposure between participants with normal hepatic function and participants with mild hepatic impairment. An assessment of the effect of moderate hepatic impairment on the PK of sevabertinib is planned.

Following oral administration to humans, sevabertinib is eliminated primarily by metabolism, mainly by CYP3A4-mediated biotransformation. Urinary excretion of unchanged sevabertinib was only 1.34% of the dose and is thus negligible. Clinical data are available in participants with mild and moderate renal impairment. The population PK indicated no difference in exposure in participants with mild or moderate renal impairment and in participants with normal renal function. A clinical study in subjects with severe renal impairment is therefore not considered necessary.

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, a PMR for DDI evaluation will also be issued. See detailed PMRs below:

- Conduct a clinical hepatic impairment trial to assess the magnitude of change in exposure of sevabertinib and to determine appropriate dosing recommendations of sevabertinib in patients with moderate hepatic impairment.
- Conduct a clinical drug interaction trial to assess the effect of sevabertinib on the pharmacokinetics of MATE1/2-K substrates and to inform an appropriate drug interaction management strategy for coadministration with sevabertinib with these substrates.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Drug product: The to-be-marketed product is provided as a film-coated, immediate release, round, red brown tablet of 6 mm in diameter, containing 10 mg of sevabertinib. Sevabertinib was initially developed as a 20 mg tablet, which was used in the FiH Study 21607. This 20 mg tablet is no longer manufactured or used. The dose strength of 10 mg was additionally included in Study 21607 and was used for subsequent studies during clinical development. In addition, a solution for oral use, with 5 mg sevabertinib per 1 mL (also called LSF in this document), was used in the Dose Escalation and Backfill parts of Study 21607. An exploratory relative bioavailability assessment in Study 21607, comparing the 20 mg tablet formulation (test) with the LSF (reference), showed that the LSM ratio [90% CI] for C_{max} and AUC(0-24) was 2.2699

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[1.5822; 3.2563] and 1.5545 [1.0746; 2.2485], respectively. An additional exploratory relative bioavailability assessment showed similar C_{max} and AUC(0–24) values for the 10 mg tablet formulation compared with the 20 mg tablet formulation, supporting the comparability of the two tablet strengths. The LSM ratios [90% CI] for the comparison of the 10 mg tablet formulation vs the 20 mg tablet formulation were 1.0491 [0.6995; 1.5733] for AUC and 0.9300 [0.594; 1.456] for C_{max} .

ADME: After single oral administration of 20 mg sevabertinib to participants with NSCLC, together with a light meal, maximum plasma concentrations were generally reached approximately 2 hours (range: 0.5–8.2 hours) after administration (t_{max}). A t_{max} of 1.5 hours (CV: 33.7%) was estimated based on the population PK model. Geometric mean apparent volume of distribution (V_z/F) was 28.1 L (CV: 42.2%). The apparent volume of the central compartment (V_c/F) was estimated to be 30 L (CV: 31%) based on all data using the population PK model. Sevabertinib is bound to human plasma proteins at 95.3%. The blood-to-plasma ratio is 0.61, indicating that sevabertinib is more bound to plasma proteins than to blood cells. *In vitro* studies suggest that sevabertinib is a substrate of P-gp and BCRP and is not a substrate of OATP1B1 or OATP1B3.

In the human mass balance Study 22249 sevabertinib and the major metabolite M1 were the main circulating moieties in plasma, constituting 59.3% and 38.5% of the total radioactivity, respectively. M1 has less potent cellular activity in most of the evaluated *HER2*- and *EGFR*-mutant variants. M1 is also bound to plasma proteins to a larger extent (98.1% vs 95.3%) compared with the parent compound. Based on systemic exposure, relative potency, and PK properties, M1 is unlikely to significantly contribute to the clinical activity of sevabertinib.

The geometric mean apparent clearance of sevabertinib is 3.6 L/hour (CV: 55.2%,). The population PK analysis estimated a typical CL/F of 3.1 L/h (CV: 38%). The half-life is approximately (b) (4) hours. The estimated geometric mean effective half-life in the population PK analysis of Study 21607 was 8.3 hours (CV: 32.6%). After oral administration of [¹⁴C]-sevabertinib, mean total radioactivity recovered in urine and feces was approximately 94.1% of the administered dose, with 83.6% of the radioactivity excreted via feces and 10.4% via urine. Only 14.0% of the dose was excreted in feces as unchanged sevabertinib, and approximately 70% of the dose was excreted as metabolites. Excretion of unchanged sevabertinib in urine was 1.34% of the administered radiolabeled dose and approximately 9% was excreted as metabolites.

Dose- and time dependencies: Dose-proportional increase in exposure was observed following administration of sevabertinib as an LSF in the doses of 10, 20, and 40 mg, and as tablet(s) in TDDs of 20, 40, 60, and 80 mg. the population PK analysis confirmed that sevabertinib PK is linear over the evaluated TDD range of 10 mg to 80 mg.

Steady state exposure is achieved within approximately 3 days of BID dosing and accumulation is low (1.65) and as expected, based on the half-life and dosing interval.

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Time-dependent PK of sevabertinib cannot be excluded based on the population PK analysis of Study 21607, but the identified decrease in PK remains within the bioequivalence range and is not considered clinically relevant.

Inter-individual variability: The inter-subject variability at steady state for sevabertinib exposure [AUC(0–12)] was 50.2%, following administration of 20 mg BID sevabertinib in Study 21607. This is consistent with the inter-subject variability in predicted exposure [AUC(0-24)_{ss}] of 51% in the population PK analysis.

Pharmacokinetics in target population: Sevabertinib exposure in participants with advanced NSCLC harboring *HER2* or *EGFR* mutations was approximately 2 times the exposure in healthy participants based on the observed range of systemic exposure.

Effect on QTc: The mean change from baseline in QTcF interval was well below 10 ms, and the upper limit of the 90% CI of the predicted baseline corrected QTcF (Δ QTcF) remained well below the threshold of regulatory concern of a Δ QTcF of 20 ms, at doses up to 2 times the recommended TDD.

The Applicant’s Position:

The clinical pharmacology of sevabertinib has been adequately assessed via *in vitro* studies, dedicated clinical studies, and model-based population PK and exposure-response analyses.

The FDA’s Assessment:

Pharmacology

Mechanism of Action

Sevabertinib is a kinase inhibitor of human epidermal growth factor receptor 2 (*HER2*). It also exhibits activity against epidermal growth factor receptor (*EGFR*). *In vitro*, sevabertinib inhibited the proliferation of tumor cells expressing wild-type *HER2* and *HER2* mutations. *In vivo*, sevabertinib demonstrated antitumor activity in subcutaneous mouse xenograft models derived from human NSCLC tumors harboring an activating *HER2* exon 20 mutation.

Administration, formulation type, strengths

The to-be-marketed sevabertinib formulation is tablets in strength of 10 mg. The recommended dosage is 20 mg administered orally BID with food.

QT Prolongation

At 2 times the maximum recommended dose, a mean increase in the QTc interval >20 ms was not observed.

General Information

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Bioanalysis	Bioanalytical information for sevabertinib is provided in Section 19.4.1.
Dose range tested in clinical trials	10 mg to 60 mg (QD), 20 mg to 40 mg (BID)
Dose proportionality	Sevabertinib showed dose proportional increase in AUC and Cmax across the dose range of 10 mg to 80 mg total daily dose.
Accumulation	Approximately 1.7-fold for AUC and 1.3-fold for Cmax at the approved recommended dosage.
Absorption	Sevabertinib median (min, max) time to maximum concentrations (Tmax) is approximately 2 hours (0.5, 8.2 hours). Sevabertinib Cmax decreases 56% and AUC decreases 28% with a high-fat meal (1000 calories, 50% fat) in healthy subjects. No clinically significant differences in sevabertinib pharmacokinetics were observed following administration of a low-fat meal (400 calories, 25% fat), as compared to a high-fat meal or overnight fasting.
Distribution	Sevabertinib apparent (oral) volume of distribution is 28 L (42%). Sevabertinib plasma protein binding is 95%. The blood-to-plasma concentration ratio is 0.6.
Metabolism	Sevabertinib is primarily metabolized by CYP3A4 (major), CYP1A1 (minor), and glucuronidation (minor).
Elimination	Based on population PK analysis, sevabertinib effective half-life is approximately 8 hours (33%) with an apparent clearance of 3.1 L/hour (38%).
Excretion	After a single oral dose of radiolabeled sevabertinib 40 mg to healthy subjects, approximately 84% of the dose was recovered in feces (14% unchanged) and 10% in urine (1.3% unchanged).
DDI potentials	Effect of Other Drugs on HYRNUO • Effect of Strong and Moderate CYP3A4 Inhibitors on HYRNUO: ○ Sevabertinib AUC increased 2.3-fold and Cmax increased 1.6-fold following concomitant use of itraconazole (strong CYP3A4 inhibitor) 200 mg once daily.

- The effect of concomitant use of moderate CYP3A inhibitors on sevabertinib C_{max} and AUC are unknown. Monitor patients for increased HYRNUO-associated adverse reactions.
- Effect of Strong and Moderate CYP3A4 Inducers on HYRNUO:
 - Sevabertinib AUC decreased by 79% and C_{max} decreased by 57% following concomitant use of carbamazepine (strong CYP3A4 inducer) 600 mg once daily. Avoid concomitant use with a strong or moderate CYP3A4 inducers with HYRNUO.

Effect of HYRNUO on Other Drugs

- Midazolam (CYP3A4 substrate) AUC increased 2-fold and C_{max} increased 1.8-fold following concomitant use of HYRNUO 20 mg twice daily. Avoid concomitant use of HYRNUO with CYP3A4 substrates where minimal increases in the concentration may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information of the CYP3A substrate.
- Dabigatran etexilate (P-gp substrate) AUC increased 1.4-fold following concomitant use of HYRNUO 20 mg twice daily. Refer to the Prescribing Information of P-gp substrates where minimal increases in the concentration may lead to serious adverse reactions.
- Sevabertinib is an inhibitor of CYP1A1 *in vitro*. Refer to the Prescribing Information of CYP1A1 substrates when concomitant use with these substrates (see Section 6.3.2.4).

The above DDI information and instructions are described in the label. Additional clinical DDI studies were conducted to evaluate the effect of acid-reducing agents on PK of sevabertinib or the effect of HYRNUO on BCRP substrates:

- Rosuvastatin (BCRP substrate) AUC increased by 1.2-fold and C_{max} by 1.4-fold following concomitant use of HYRNUO 20 mg twice daily. No clinically significant differences in sevabertinib pharmacokinetics were

observed when used concomitantly with esomeprazole (proton pump inhibitor).

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Data from Study 21607 demonstrated that a sevabertinib dose of 20 mg BID was effective at achieving clinically meaningful and durable responses in advanced NSCLC patients with *HER2* activating mutations. Details regarding efficacy are provided in Section 8.1.2.

Exposure-response analyses for ORR were conducted based on all participants with an ORR observation and exposure estimate in Study 21607 (n=326), and a sub-set of participants from Groups D and D1 only (n=115). Mutational status showed a considerable and statistically significant effect on ORR based on investigator and BICR assessments and based on all data, with participants with *HER2* ex20ins mutations (n=217) showing an approximate 3- to 4-fold higher ORR compared with participants with other mutations (n=109; odds ratio based on investigator assessment: 2.94, 95% CI: [1.73, 4.98], odds ratio based on BICR: 3.59, 95% CI: [2.1, 6.14]). Exposure did not show a statistically significant (p<0.01) association with ORR based on both investigator and BICR assessments. The exposure-response for participants with *HER2* activating mutations in Groups D and D1 also showed no statistically significant (p<0.01) association between exposure and ORR based on both investigator and BICR assessments. The effect of sevabertinib on ORR in participants with activating mutations was not affected by any of the baseline covariates tested (age, sex, body weight, race, geographical region, serum albumin, smoking status, ALP, LDH, neutrophil to lymphocyte ratio, ECOG status, AJCC grading at initial diagnosis, tumor stage, tumor size, number of metastatic sites, brain/liver metastases, time since diagnosis, previous lines of anti-cancer therapy, and prior platinum/immunotherapy/trastuzumab deruxtecan/*HER2* ex20ins-targeted therapy/EGFR ex20ins-targeted therapy). Exposure-response analyses for BTR in participants with *HER2* activating mutations in Groups D and D1 showed increasing BTR, i.e. a more pronounced decrease in tumor size from baseline, with increasing exposure. None of the pre-selected baseline covariates showed a statistically significant effect on BTR.

Overall, the results indicate that the efficacy benefit of sevabertinib was highest in the targeted patient population, i.e. patients with advanced NSCLC whose tumors have activating *HER2* mutations, and that the effect in these patients is consistent regardless of a variety of demographic and clinical baseline characteristics.

The Applicant’s Position:

The clinical pharmacology program provides supportive evidence of the effectiveness of 20 mg sevabertinib for the treatment of patients with advanced NSCLC harboring *HER2* activating mutations as demonstrated in Study 21607. The results of the exposure-response analyses support the effectiveness in the proposed indication.

The FDA’s Assessment:

FDA agrees with the Applicant’s proposed dosage of sevabertinib 20 mg BID for the targeted indication given the following reasons:

- 1) In Study 21607 dose escalation phase, multiple dosages have been studied using different formulations (LSF: 10 mg, 20 mg, or 40 mg QD, and tablets: 40 mg QD, 60 mg QD, 20 mg BID, 30 mg BID, and 40 mg BID). The PK linearity range was established over the dose range of 20 mg to 80 mg total daily with the determined MTD of 60 mg total daily dose. The tablet formulation was selected due to higher bioavailability over the LSF formulation. The PD estimate suggested that BID regimens could achieve more sustained pEGFR reduction as compared to QD dosing, and dosages ≥ 20 mg BID are likely to achieve $>80\%$ pEGFR reduction. In addition, a higher ORR (i.e., 38%) was reported at 20 mg BID over other dosages evaluated in the dose escalation phase, which supported further evaluation of 20 mg in the expansion phase.
- 2) Expansion/extension Groups D and E in Study 21067 evaluated 20 mg BID in patients who were naïve to *HER2* ex20ins-targeted therapy (N=81) and who progressed to *HER2*-targeted ADCs (N=52), respectively. In addition, a separate expansion Group D1 evaluated 10 mg BID in the same patient population as Group D (N=36), which allowed for a comparison of activity and safety data between the two dosages.

Activity: As shown in **Table 23**, 20 mg BID exhibited higher ORR (64% vs 36%) and longer median DOR (9 months vs 7 months) as compared to 10 mg BID in the dose expansion and extension phase. In addition, E-R analysis for efficacy also identified positive trends for ORR and BTR with higher exposure (refer to Section 19.4.4 for details).

Table 23. Activity in Dose Expansion/Extension of Study 21607

	10 mg BID (N=36)	20 mg BID (N=81)
ORR (% [95% CI])	36 [21, 54]	64 [53, 75]
Median DoR (months [95% CI])	6.9 [4.1, 15]	9.2 [5.8, 15]

Source: Updated efficacy data submitted 06/27/2025 based on data cutoff on 03/28/2025

Safety: Higher rates of Grade ≥ 3 TEAEs, TEAEs leading to dose modifications (i.e., dose reductions and interruptions) were observed at 20 mg BID compared to 10 mg BID in the dosage expansion/extension part (**Table 24**). Particularly, higher rates of all grade and Grade 3/4 diarrhea and earlier onset of diarrhea were reported at 20 mg BID (**Table 25**). In alignment with the safety observations, FDA analysis identified significant positive E-R relationships for rash, any Grade and Grade ≥ 3 diarrhea and AEs leading to dose reduction or interruption (refer to Section 19.4.4 for details). However, further analysis using safety data of individual patients suggested that diarrhea was generally manageable and did not necessarily lead to dose reduction, regardless of severity and recurrence of diarrhea, patient age, and dose level (see Section 19.4.4 for details).

Table 24. Safety Comparison Between 10 mg and 20 mg

%	10 mg BID (Group D1, N=36)	20 mg BID (Group D, N=81)	20 mg BID (Group E, N=55)	20 mg BID (Whole Study, N=287)
Grade ≥ 3 TEAEs	36	52	46	50
SAE	31	33	29	32
TEAE leading to dose reduction	8	27	33	31
TEAE leading to dose interruption	22	44	51	46
TEAE leading to treatment discontinuation	6	5	2	3

Source: Updated safety data submitted 06/27/2025 based on data cutoff on 03/28/2025

Table 25. Comparison of Diarrhea Events Between Dosages

%	10 mg BID (Group D1, N=36)	20 mg BID (Group D, N=81)	20 mg BID (Group E, N=55)	20 mg BID (Whole Study, N=287)
Any TEAEs	64	86	89	86
Grade 3 or 4	8	24	9	15
Serious TEAEs	3	6	4	4
Dose reduction	3	12	11	12
Dose interruption/ delay	6	15	22	15
Median time to 1st event [days, 95% CI]	25 [7, A*]	4 [3, 7]	3 [2, 5]	4 [3, 6]

Source: Updated safety data submitted 06/27/2025 based on data cutoff on 03/28/2025 (eCTD 0016) and 21607-report.body-1.pdf (eCTD 0001)

A*: Value cannot be estimated due to censored data.

Considering the available efficacy and safety data, FDA agrees that the favorable benefit-risk profile support the proposed sevabertinib dosage of 20 mg BID in adult patients with NSCLC with HER2 mutations.

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

Data:

Sevabertinib 20 mg BID resulted in rapid, deep, and durable responses in advanced NSCLC participants with *HER2* activating mutations, who had received prior systemic therapy, but are naïve to *HER2* ex20ins-targeted therapy, as assessed by ORR by BICR (see Section 8.1.2). In addition, sevabertinib 20 mg BID presented a manageable safety profile. Most common drug-related TEAEs were of low grade (Grade 1 or 2), reversible, and manageable with standard of care (see Section 8.2). Out of 268 participants treated with 20 mg BID, 6 (2.2%) discontinued treatment due to a TEAE, 73 (27.2%) experienced TEAEs leading to a dose reduction, and 113 (42.2%) had TEAEs leading to dose interruption/delay.

Results of exposure-response analyses confirm that the efficacy benefit of sevabertinib was highest in the targeted patient population (see Question 6.3.2.1 above), regardless of baseline demographic and clinical characteristics.

The Applicant's Position:

Taken together, the efficacy and safety data as well the results from exposure-response analyses, support a favorable benefit/risk profile of the 20 mg BID sevabertinib dosing regimen for the general patient population for the proposed indication.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the PK, PD, activity, and safety data as well the results from the E-R analyses, support a favorable benefit/risk profile of the 20 mg BID sevabertinib dosing regimen for the general patient population for the proposed indication. Refer to Sections 6.3.2.1 and 19.4.4 for additional 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 related to the effect of intrinsic (and extrinsic) factors on the PK of sevabertinib are presented in Section 6.2.2.2.

The Applicant's Position:

The population PK analysis demonstrated that age, sex, body weight, race, geographic region, mild or moderate renal impairment, mild hepatic impairment, and smoking status do not affect the PK of sevabertinib. Therefore, no alternative dosing regimen or management strategy is required for these intrinsic (and extrinsic) patient factors.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that no dosage adjustment is required for age (18 to 91 years), race (27% White, 65% Asian), sex, body weight (29 to 155 kg), smoking status, eGFR 30 to < 90 mL/min, or mild hepatic impairment (AST > ULN and total bilirubin ≤ ULN; or total bilirubin > 1 to 1.5x ULN and any AST).

HER2 genetic alternations and treatment effect:

FDA explored the treatment efficacy by HER2 genetic alteration in the primary efficacy population, Group D, in study 21607. In study 21607, group D, 81 patients with activating HER2 mutations were enrolled. HER2 mutations were detected at a laboratory accredited by Clinical Laboratory Improvement Amendments (CLIA) or equivalent standard. The local HER2 results were retrospectively confirmed by the Thermo Fisher OncoPrint™ Dx Target Test (ODxTT) as part of the clinical bridging study for companion diagnostic development. Based on an information request response (dated 05/21/2025), there was no pre-defined list of HER2 variants eligible for enrollment. Variants known to contribute to carcinogenesis and activate the HER2 pathway, based on publications and public databases including ClinVar (<https://www.ncbi.nlm.nih.gov/clinvar/>) and COSMIC (<https://cancer.sanger.ac.uk/cosmic>), were considered as activating HER2 mutations. Consistent with literature (Loeffler et al. 2023), the majority of identified HER2 genetic alterations were exon 20 insertions (N=64, 83%), with HER2 Y722_A775 dup (YVMA) identified as the most common exon 20 insertion (N=48, 59%). Treatment response was observed across HER2 genetic alterations (**Table 26**). Responses were numerically lower in patients with point mutations, compared to patients with exon 20 insertions. However, the results for patients with point mutations need to be interpreted with caution due to small sample size. This analysis suggests sevabertinib treatment is effective for patients with activating HER2 mutations, and did not identify efficacy concerns for any mutation subtypes or specific mutations based on the limited available data.

Table 26. Efficacy by HER2 Genetic Alterations in Study 21607 Group D, by BICR

HER2 Mutations	N	Responders ^a (N)	ORR (%)
HER2 Y722_A775 dup (YVMA)	48	37	77
Other HER2 Exon 20 insertions	19	10	52
G776delinsVC	8	4	50
G778_P780dup	5	2	40
G776delinsLC	4	3	50
G778_S779insCPG	1	0	0
M774dup	1	1	100
HER2 Point Mutations	13	5	39
V659E	3	0	0
S310Y	2	2	100
S310F	2	0	0

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S310P	1	0	0
L755P	1	1	100
L755S	1	1	100
V777L	1	1	0
D769Y+S310Y	1	0	0
G776S	1	0	0
Not Specified ^b	1	0	0
Total	81	52	64

Source: Reviewer's analysis. Abbreviation: HER2 = Human Epidermal Growth Factor Receptor 2; ORR=Objective response rate; BICR = Blinded Independent Central Review; N= Number

a: Responders were defined as participants with confirmed CR or PR.

b: One participant was enrolled by a PCR-based assay that targets multiple activating HER2 exon20ins without specifying the exact variant

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

Data:

Clinical data related to the effect of food, acid-reducing agents, and other drugs (CYP3A4 inhibitors and CYP3A4 inducers, P-gp inhibitors and inducers, and BCRP inhibitors and inducers) on the PK of sevabertinib are provided in Section 6.2.2.2.

Clinical data related to the potential effects of sevabertinib on other drugs are presented below:

CYP3A4 substrates: In Study 22251, co-administration of a single dose of 20 mg sevabertinib with 1 mg midazolam (a CYP3A4 probe substrate) resulted in a mean midazolam AUC and C_{max} ratio of 1.10 compared to administration of 1 mg midazolam alone. The results indicate that a single dose of sevabertinib has only a minor effect on the PK of midazolam. Pre-treatment and co-administration of multiple doses of sevabertinib (20 mg BID) with 1 mg midazolam resulted in an increase in a mean midazolam AUC ratio of 1.95 (reflecting a 95% increase) and a mean midazolam C_{max} ratio of approximately 1.8 (reflecting an 80% increase) compared with administration of 1 mg midazolam alone.

P-gp substrates: In Study 22252, pre-treatment and co-administration of 20 mg sevabertinib BID with 75 mg dabigatran etexilate (a sensitive P-gp substrate) resulted in a mean dabigatran AUC ratio of 1.4 (reflecting a 40% increase) while the C_{max} was unchanged, compared with administration of 75 mg dabigatran etexilate alone.

BCRP substrates: In Study 22252, pre-treatment and co-administration of 20 mg sevabertinib BID with 10 mg rosuvastatin (a sensitive BCRP substrate) resulted in a mean rosuvastatin AUC ratio of 1.25 (reflecting a 25% increase) and a mean rosuvastatin C_{max} ratio of approximately 1.4 (reflecting a 40% increase) compared to administration of rosuvastatin alone.

The Applicant's Position:

Sevabertinib should be taken with food.

No clinically relevant effect of esomeprazole on the PK of sevabertinib was observed. Thus, sevabertinib may be given concomitantly with acid-reducing agents (e.g. proton pump inhibitors, H₂-receptor antagonists, and locally acting antacids).

There are clinically relevant DDIs associated with sevabertinib. The recommended management strategies are outlined below:

Study 22250 demonstrated that strong CYP3A4 inhibitors increase exposure of sevabertinib (see Section 6.2.2.2). Concomitant use of strong CYP3A4 inhibitors (including, but not limited to, clarithromycin, itraconazole, ketoconazole, cobicistat, lopinavir/ritonavir, saquinavir/ritonavir, and grapefruit or grapefruit juice) during treatment with sevabertinib is not recommended. If concomitant use cannot be avoided, the current sevabertinib TDD should be reduced by 50%. For patients taking a total daily dose of 10 mg (one 10 mg tablet once daily), sevabertinib should be temporarily withheld until the strong CYP3A4 inhibitor is completed. After the CYP3A4 inhibitor has been discontinued for 3 to 5 elimination half-lives, sevabertinib should be resumed at the dose taken prior to initiating the inhibitor.

As sevabertinib exposure may be increased when co-administered with moderate CYP3A4 inhibitors, it is recommended to closely monitor patients for adverse reactions. Sevabertinib may be given concomitantly with weak CYP3A4 inhibitors without clinically relevant DDIs.

Strong CYP3A4 inducers decrease the exposure of sevabertinib based on the results of Study 22250 (see Section 6.2.2.2). Use of strong CYP3A4 inducers (including, but not limited to, carbamazepine, phenytoin, rifabutin, rifampicin, and St. John's Wort) during treatment with sevabertinib is not recommended, since decreased sevabertinib plasma concentrations are expected to result in reduced efficacy. Selection of an alternate concomitant medicinal product, with no or less potential to induce CYP3A4 should be considered.

No adjustment of the sevabertinib dosage is required when sevabertinib is dosed concomitantly with a weak or moderate CYP3A4 inducer.

Study 22251 demonstrated that sevabertinib is a weak CYP3A4 inhibitor and that concomitant use of sevabertinib may increase the plasma concentrations of sensitive CYP3A4 substrates. Therefore, the related recommendation in the product information of sensitive CYP3A4 substrates, with a narrow therapeutic window (including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, or tacrolimus), should be followed when co-administered with sevabertinib.

Based on the results from Study 22252, sevabertinib is a P-gp inhibitor and may increase the plasma concentrations of sensitive P-gp substrates. Therefore, related recommendation in the product information of sensitive P-gp substrates, with a narrow therapeutic window (including but not limited to digoxin), should be followed when co-administered with sevabertinib.

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Study 22252 also demonstrated that sevabertinib is an inhibitor of BCRP and that concomitant use of sevabertinib may increase the plasma concentrations of sensitive BCRP substrates. Therefore, the related recommendation in the product information of sensitive BCRP substrates (including but not limited to methotrexate, atorvastatin) should be followed when co-administered with sevabertinib.

No clinical data are available regarding a potential effect of sevabertinib on CYP1A1 substrates. However, sevabertinib is a strong inhibitor of CYP1A1 at clinically relevant concentrations *in vitro*. This indicates that co-administration of sevabertinib may increase the plasma concentrations of CYP1A1 substrates. Therefore, the related recommendation in the product information of these substrates (e.g. riociguat, granisetron) should be followed when co-administered with sevabertinib.

No clinical data are available regarding a potential effect of sevabertinib on CYP2C8 substrates. However, sevabertinib is a weak inhibitor of CYP2C8 at clinically relevant concentrations *in vitro*. The clinical relevance of this finding is unknown.

No clinical data are available regarding a potential effect of sevabertinib on MATE1 or MATE2K. However, sevabertinib is an inhibitor of MATE1 and MATE2-K at clinically relevant concentrations *in vitro*. This indicates that co-administration of sevabertinib may affect renal clearance of substrates of these transporters. Therefore, the related recommendation in the product information of these substrates (including, but not limited to metformin, cisplatin) should be followed when co-administered with sevabertinib.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that sevabertinib should be taken with food and can be given with acid reducing agents. FDA also agrees with the Applicant's assessment regarding concomitant use of sevabertinib with strong CYP3A4 inhibitors, strong CYP3A4 inducers, and certain substrates of CYP3A4 substrates and P-gp.

FDA does not agree with the Applicant's assessment using the population PK model to evaluate the effect of mild and moderate CYP3A4 inhibitors and inducers on the PK of sevabertinib. According to FDA analysis, the population PK estimates are not robust or reliable as the treatment duration of the CYP3A4 inhibitors and inducers is unknown and the mild and moderate categories are not separated. Clinical DDI Study 22250 demonstrated that sevabertinib AUC increased 2.3-fold and C_{max} 1.6-fold following concomitant use of itraconazole (strong CYP3A4 inhibitor). Moderate CYP3A4 inhibitors may also increase the exposure of sevabertinib and thus lead to increased adverse reactions. However, a PMR clinical DDI trial to assess the effect of moderate CYP3A4 inhibitors is not required given the dosage modifications based on adverse reactions have been specified in the label and the outcome of a DDI study with moderate CYP3A4 inhibitors may not change the labeling recommendations as currently recommended. Study 22250 demonstrated that sevabertinib AUC decreased by 79% and C_{max} by 57% following concomitant use of carbamazepine (strong CYP3A4 inducer). Given the significant changes in exposure following concomitant use of a strong CYP3A4 inducer, it is expected that

the moderate CYP3A4 inducers would also significantly alter the exposure of sevabertinib. In addition, there are no sufficient data over a wider dose range at this point to suggest efficacy would maintain with reduced exposure. Therefore, FDA recommends avoid the concomitant use of moderate CYP3A4 inducers as well.

FDA does not consider avoidance of concomitant use of BCRP substrates is necessary. Study 22252 demonstrated that rosuvastatin (BCRP substrate) AUC increased 1.2-fold and C_{max} 1.4-fold following concomitant use of HYRNUO. The limited exposure change of rosuvastatin suggests that there is unlikely a clinically significant impact on other BCRP substrates which usually exhibit lower degree of PK alternation compared to rosuvastatin

FDA agrees with the Applicant's assessment that sevabertinib is a strong inhibitor of CYP1A1 at clinically relevant concentrations in vitro. According to FDA analysis, the inhibitory effect of sevabertinib on CYP1A1 in vivo cannot be ruled out, i.e., the exposure change of CYP1A1 substrates is likely to be more than 3-fold. Therefore, FDA agrees with the Applicant to include relevant DDI instructions in the label. However, a PMR clinical drug interaction trial to assess the effect of sevabertinib on the PK of CYP1A1 substrates is not required given no available PMR examples evaluating the impact on CYP1A1, the overall low expression levels of CYP1A1, and the limited involvement of CYP1A1 in drug metabolism.

FDA agrees with the Applicant's assessment that sevabertinib is an inhibitor of MATE1/2-K at clinically relevant concentrations in vitro. A PMR will be issued to conduct a clinical drug interaction trial to assess the effect of sevabertinib on the PK of MATE1/2-K substrates and to inform an appropriate drug interaction management strategy for coadministration with sevabertinib.

Given the embryo-fetal toxicity of sevabertinib, FDA evaluated the potential impact of sevabertinib on combined oral contraceptives (COCs) via induction effect on CYP enzymes. Study 22251 demonstrated that midazolam (CYP3A4 substrate) AUC increased 2-fold and C_{max} increased 1.8-fold following concomitant use of HYRUNO, indicating a net inhibitory effect of sevabertinib on CYP3A4, which suggests the CYP3A pathway is unlikely to cause efficacy reduction of COCs. The potential induction effect of sevabertinib on other CYP enzymes (e.g., CYP2B6 and CYP2C19) that may also contribute to metabolism of COCs was evaluated by the Applicant using two analytical models, i.e., relative induction score (RIS) method and mechanistic static model (MSM). Despite uncertainties on accuracy of the model prediction, FDA agrees with the low risk of efficacy reduction of COCs via drug interactions with sevabertinib. In addition, majority of the female patients with the targeted indication (NSCLC) are postmenopausal, which further reduces the risk. Therefore, FDA agrees that no specific labeling recommendation for COCs is needed.

X

X

Primary Reviewer

Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data and the Applicant’s Position:

An overview of Study 21607, supporting the efficacy and safety of sevabertinib for the treatment of adult patients with advanced NSCLC whose tumors have activating *HER2* (*ERBB2*) mutations, and who have progressed after at least 1 prior line of systemic therapy, is presented in **Table 27**.

Table 27. Overview of Study 21607 in NSCLC Patients Supporting the Efficacy and Safety of Sevabertinib

Study and Report no.	Study design	Main objectives	Study population	Treatment and dose ^a	No. treated
NCT number					
Countries/regions					
No. of centers					
21607 (SOHO-01) Module 5.3.5.2, Report B003047 NCT05099172 US, Belgium, Brazil, China, France, Hong Kong, Israel, Italy, Japan, Netherlands, South Korea, Singapore, Spain, Taiwan 23 centers in DE/BF part and 75 centers in Expansion/Extension	Non-randomized, open-label, FiH, Phase 1/2 single-arm, multicenter study	Phase 1: Safety and tolerability, MTD/MAD, PK Phase 2: Efficacy and safety	Patients with advanced NSCLC and a mutation in <i>EGFR</i> and/or <i>HER2</i> who have progressed after systemic therapy ^a	Sevabertinib orally: Dose Escalation/ Backfill (Phase 1): Starting dose 10 mg QD up to MTD/MAD Dose Expansion (Phase 1): RDE (20 mg BID) Dose Extension (Phase 2): RP2D (20 mg BID) based on benefit-risk from Dose Expansion	As of 14 OCT 2024: 357 participants As of 28 MAR 2025: 376 participants

BID=Twice daily; EGFR=Epidermal growth factor receptor; FiH=First-in-human; HER2=Human epidermal growth factor receptor 2; MAD=Maximum administered dose; MTD=Maximum tolerated dose; NCT = The National Clinical Trials; NSCLC=Non-small cell lung cancer; PK=Pharmacokinetics; QD=Once daily; RDE=Recommended dose for Expansion; RP2D=Recommended Phase 2 dose; US= United States

a: Treatment with prior systemic therapy is not applicable for Dose Expansion/Extension Group F (see Figure 5).

The efficacy and safety analyses supporting the proposed indication are based on data from the ongoing pivotal Study 21607, a non-randomized, open-label, single-arm, multi-center, FiH, Phase 1/2 study in participants with advanced NSCLC harboring activating mutations in *HER2*

Sevabertinib (BAY 2927088) – Version 2.0

and/or *EGFR*. For completeness, supportive safety data from 5 clinical pharmacology studies, conducted in 89 healthy participants (Studies 22249, 22250, 22251, 22252, and 2253) to evaluate sevabertinib for DDI potential, mass balance, and the effect of food, is provided in the NDA Module 2.7.4. A tabular listing of all clinical studies is provided in Module 5.2.

The FDA's Assessment:

FDA agrees with the Applicant's description. The primary efficacy data used to support the approval are based on patients from Dose Escalation/Backfill, Dose Expansion, and Dose Extension parts of the study who received sevabertinib at the 20 mg BID dose in Groups D and E, as of the updated data cutoff date of March 28, 2025.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 21607 (SOHO-01)

The efficacy analyses in support of the proposed indication are based on data from **Study 21607** to evaluate sevabertinib in participants with locally advanced or metastatic NSCLC harboring *EGFR* and/or *HER2* activating mutations (see **Table 27**). Study 21607 consists of Dose Escalation, Backfill, Dose Expansion, and Dose Extension parts, with the latter representing the Phase 2 part of the study (**Figure 5**).

Populations supporting efficacy

The efficacy of sevabertinib is presented for the following populations of patients with advanced NSCLC harboring *HER2* activating mutations (including ex20ins):

- **Primary efficacy population** is **Group D** (N=81), which includes participants who have received prior systemic therapy but were naïve to *HER2* ex20ins-targeted therapy. Participants who had prior treatment with *HER2* ex20ins-targeted therapy for ≤ 2 months and stopped treatment due to reasons other than progressive disease were also eligible.
- **Supportive efficacy data** are provided by **Group E** (N=55), which includes participants who have received prior systemic therapy and had documented progression to *HER2*-targeted ADCs. Prior treatment with *HER2* ex20ins-TKIs for ≤ 2 months was exclusionary unless treatment lasted for ≤ 2 months and was stopped due to reasons other than progressive disease.

These populations include participants from DE/BF, Dose Expansion, and Dose Extension parts of the study who received sevabertinib at the 20 mg BID dose and who met the eligibility criteria for Groups D and E. Group D included 37 participants from the Dose Extension, 34 from Dose Expansion, and 10 from the DE/BF part of the study. In Group E, 21 participants were from Dose Extension, 31 were from the Dose Expansion, and 3 were from the DE/BF part of the study.

As follow-up was longer and the data are more mature in the DE/BF and Dose Expansion parts compared to the Dose Extension part, efficacy data (ORR, DOR, DCR, and PFS), based on response assessments by BICR, are also presented by study part:

- DE/BF/Expansion (N=44 in Group D and N=34 in Group E).
- Extension (N=37 in Group D and N=21 in Group E).

Trial Design

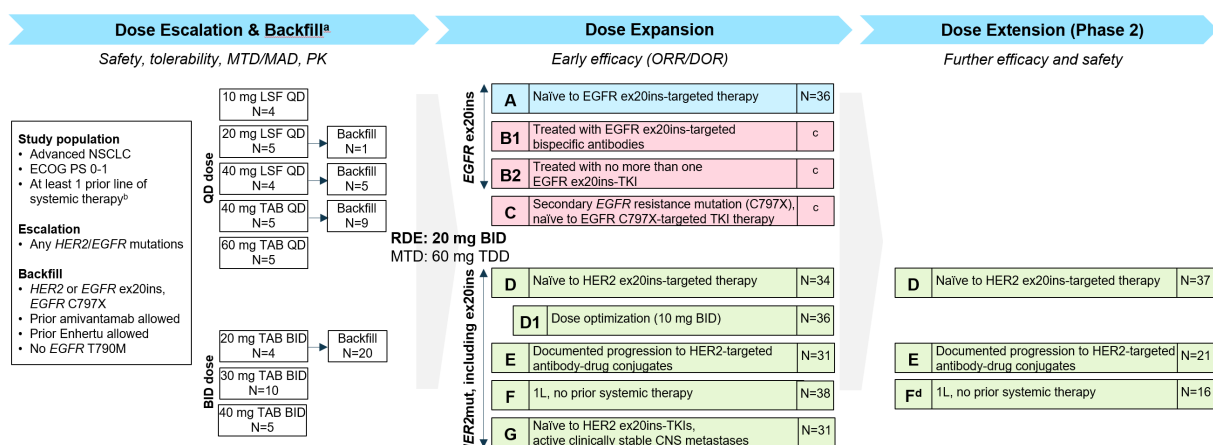
The Applicant’s Description:

Basic study design

The study design is shown in **Figure 5**. The primary objectives of the Escalation, Backfill and Expansion parts of the study were to determine the safety, tolerability, and the MTD or MAD, and to characterize the PK of sevabertinib. The primary objective of the Extension part was to determine the efficacy of sevabertinib at the RP2D based on confirmed ORR per RECIST v1.1, as assessed by BICR, as the primary endpoint.

The study started enrolling participants on 25 OCT 2021 and is being conducted in 14 countries/regions, including the US. At the time of the database cut-off date of 14 OCT 2024, enrollment in the DE/BF and Expansion parts was complete, while enrollment in the Dose Extension part (Group F only) was still ongoing. The Extension Group F was not opened for enrollment in the US.

Figure 5. Study 21607 Design and Status at the Time of the Database Cut-Off Date 14 OCT 2024



1L=First line; BID=Twice daily; CNS=Central nervous system; DLT=Dose-limiting toxicity; DOR=Duration of response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EGFR=Epidermal growth factor receptor; ex20ins=Exon 20 insertion; HER2=Human epidermal growth factor receptor 2; LSF=Liquid service formulation; MAD=Maximum administered dose; MTD=Maximum tolerated dose; NSCLC=Non-small cell lung cancer; ORR=Objective response rate; PK=Pharmacokinetics; PS=performance status; QD=Quaque die (once daily); RDE=Recommended dose(s) for Expansion; Tab=Tablets; TDD=Total daily dose; TKI=Tyrosine kinase inhibitor; US=United States

'N' represents the number of participants actually treated as of the database cut-off date.

a: Dose Escalation: Starting dose 10 mg QD with minimum of 3 DLT evaluable participants/dose level; Backfill: maximum 24 participants/cohort.

b: Except for Group F.

c: Development of Groups B1, B2 and C was deprioritized.

d: Dose Extension Group F was not opened for enrollment in the US

Trial location

This study was conducted at 23 study centers during the DE/BF part and at 75 study centers during the Expansion and Extension parts in Asia, North America, South America, and Europe

Study treatments

Sevabertinib was administered as a liquid formulation or as coated tablets in 21-days cycles of continuous dosing. The liquid formulation was used in 3 cohorts in the DE/BF part of the study (**Figure 5**).

Dose selection

The sevabertinib doses administered across 8 dosing regimens (QD and BID schedules) in the DE/BF cohorts are shown in **Figure 5**. Based on the totality of the available data at the time of PK/PD analysis from the ongoing Study 21607, 20 mg BID was considered the recommended dose of sevabertinib for the Expansion part, with an optimal balance of highest predicted benefit to patients while maintaining an acceptable safety profile. Further details are provided in Section 6.3.

Assignment to treatment

Randomization was not applicable in this open-label, single-arm study. At the time this study was initiated, there was no approved targeted therapy for patients with metastatic NSCLC with *HER2* (*ERBB2*) mutations who have received a prior systemic therapy.

Dose modification, discontinuation

Specific rules for dose modifications and discontinuation are outlined in the study protocol (Section 6.2). If a participant experienced a CTCAE Grade 3 or 4 and/or unacceptable toxicity including a DLT, not attributable to the disease or disease-related processes under investigation, dosing was interrupted until the toxicity resolved or recovered to $\leq$ Grade 2 within 21 days of onset and could be then resumed at the same dose or at a lower dose according to the rules for dose modifications.

If toxicity did not resolve to $\leq$ Grade 2 after 21 days, then the participant could be withdrawn from treatment and observed until resolution of the toxicity. If a toxicity required dose reduction and the participant was already on the starting dose of Dose Escalation (10 mg), study treatment was discontinued. A maximum of 2 dose level reductions was allowed, and re-escalation was not allowed.

Administrative structure

An independent SMC was established to ensure the ongoing safety of the study participants. The SMC closely monitored the safety and tolerability throughout the Expansion and Extension parts of the study and made recommendations.

As of 14 OCT 2024, there were 3 SMC meetings for safety, all with the recommendation to continue the study without modification.

Procedures and schedule

Screening period: Screening tests were performed up to 28 days prior to receiving the first dose of the study drug.

Treatment period: Participants received study treatment until disease progression per RECIST v1.1 by investigator assessment, unacceptable toxicity or until any other withdrawal were met. Participants were evaluated for efficacy (tumor assessments by CT/MRI) every 6 weeks (± 7 days) for the first 36 weeks and then every 9 weeks (± 7 days) thereafter. The treatment period ended with the EoT visit or, if the EoT visit was not performed, at the time of last intake of study medication.

Active follow-up period: Following the completion of the EoT visit, this period comprised a Safety follow-up visit and Imaging follow-up visits (for participants who discontinue study treatment without disease progression). Participants who discontinued study treatment due to disease progression, per RECIST v1.1 as by Investigator assessment, were to terminate the Active follow-up period after the Safety follow-up visit. During the Imaging follow-up visits, tumor assessments by CT/MRI, brain MRI/CT and/or bone scans (when applicable) were acquired.

Long-term (survival) follow-up period: A Long-term follow-up period started after the Safety follow-up visit/contact or after the last Imaging follow-up visit (whichever was last). Participants were contacted every 3 months (± 14 days) to determine survival.

The full schedule of evaluations is provided in Section 1.2 of the study protocol.

Concurrent medications

Prohibited and permitted medications are described in Section 6.7 of the study protocol.

Treatment compliance

Study drug administration was to be documented in the source documents and in the CRF. When participants self-administered study treatments at home, compliance with study treatment was to be assessed at each visit. Deviation(s) from the prescribed dosage regimen were to be recorded in the CRF.

Rescue medication

Throughout the course of the study, participants were to receive appropriate supportive care measures as deemed necessary by the treating Investigator for management of symptoms and underlying medical conditions, which may develop during the study.

Patient completion, discontinuation, or withdrawal

Participants received study treatment until disease progression per RECIST v1.1 by Investigator assessment, unacceptable toxicity or until any other withdrawal criteria was met. After treatment discontinuation, participants entered the follow-up periods as aforementioned.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the trial design. While the Applicant refers to Group D as the primary efficacy population and Group E as the supportive efficacy population, FDA is evaluating data from Groups D and E as the primary evidence of efficacy in support of the indication. Due to limited data and insufficient evidence of effectiveness in patients with non-TKD mutations and squamous histology, FDA revised the primary efficacy population to include only patients with TKD mutations and non-squamous histology. Please refer to the later section - Efficacy Results for Primary Endpoint for details.

Eligibility Criteria

The Applicant's Description:

Key eligibility criteria included:

- Females or males aged ≥ 18 years, with documented histologically or cytologically confirmed locally advanced NSCLC, not suitable for definitive therapy, or recurrent or metastatic NSCLC. Documented activating *EGFR* and/or *HER2* mutation and documented disease progression after treatment with at least 1 prior systemic therapy for advanced disease (except for participants eligible for Group F [Expansion or Extension] who should have received no prior systemic treatment for locally advanced or metastatic disease).
- Measurable disease by RECIST v1.1.
- *Group D*: NSCLC with *HER2* activating mutations (including ex20ins) and naïve to treatment with a *HER2* ex20ins-targeted therapy (e.g. poziotinib, trastuzumab deruxtecan). Participants who had prior treatment with *HER2* ex20ins-targeted therapy for ≤ 2 months and stopped treatment due to reasons other than progressive disease were also eligible.
- *Group E*: NSCLC with *HER2* activating mutations (including ex20ins) and documented progression to *HER2*-targeted ADCs (e.g. trastuzumab deruxtecan). Prior treatment with *HER2* ex20ins-TKIs (i.e. poziotinib) was exclusionary unless treatment lasted for ≤ 2 months and was stopped due to reasons other than progressive disease.
- *Backfill, Expansion, Extension*: Participants with a known history or presence of the *EGFR* T790M mutation were excluded.

- ECOG PS of 0 or 1, and adequate bone marrow, kidney, liver, coagulation, and cardiac functions.

The FDA's Assessment:

FDA agrees with the description of the eligibility criteria. In addition, patients with mixed histology were excluded.

Study Endpoints

The Applicant's Description:

Given the single-arm nature of Study 21607, the evaluation of antitumor activity was performed using the primary endpoint of confirmed **ORR, as assessed by BICR, according to RECIST v1.1**. ORR is defined as the proportion of participants who achieved a BOR of CR or PR, with the requirement that CR and PR must be confirmed at least 4 weeks apart.

There was an agreement with the FDA that the primary endpoint of ORR along with the secondary endpoint of DOR as assessed by BICR could be used for accelerated approval provided the results are provided in the context of a positive benefit-risk profile (*FDA Type B End-of-Phase 1 Meeting [30 JAN 2024]*).

The study used established RECIST v1.1 criteria (Eisenhauer et al. 2009) for response and progression assessments, based on standard imaging (CT or MRI scans), assessed by both the BICR and the investigator. Radiological tumor assessments were performed every 6 weeks (± 7 days) for the first 36 weeks and every 9 weeks (± 7 days) thereafter.

The primary endpoint of confirmed ORR was supported by the following **secondary endpoints**:

- **ORR by investigator assessment**
- **DCR by BICR and investigator assessments**, defined as the proportion of participants whose BOR was either CR, PR or SD of at least 12 weeks following the first administration of study treatment, taking into account the requirement for confirmation of CR and PR at least 4 weeks apart.
- **DOR by BICR and investigator assessments**, defined as the time from the first observed PR or CR to the date of disease progression assessed by the investigator or BICR per RECIST v1.1 or death due to any cause (if death occurs before progression is documented).
- **PFS by BICR and investigator assessment**, defined as the time from the start date of study treatment to the date of first documented disease progression (radiological tumor assessment) or death due to any cause (if death occurs before progression is documented).
- **OS**, defined as the time from the start of study treatment to death, due to any cause.

Other pre-specified efficacy endpoints include TTR, by BICR and investigator assessment:

- TTR is defined as the time from the start of study treatment to the date of first observed PR or CR. Only participants with a confirmed PR or CR were considered for TTR.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of study endpoints and that ORR as assessed by BICR per RECIST v1.1 supported by DOR is appropriate to support accelerated approval in this disease setting. FDA notes that DCR is not considered to be a clinically relevant endpoint for efficacy evaluation given the inability to attribute stable disease to an effect of the study drug. Time-to-event endpoints such as PFS and OS in non-comparative trials are not interpretable and are considered descriptive only.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The statistical analyses were based on the SAP version 2.0, dated 14 OCT 2024, which was finalized before the database lock for the primary completion analysis of Group D. Additionally, a supplemental SAP version 1.0, dated 11 FEB 2025, was prepared. Details regarding the SAP versions are summarized in the Study 21607 CSR (Module 5.3.5.2, CSR B003047, Section 10.1.9.). The end of the study is defined as the date of the LPLV.

This NDA includes efficacy results from the primary and supportive populations of participants with NSCLC harboring *HER2* activating mutations (including ex20ins) treated with sevabertinib monotherapy in Study 21607. The primary efficacy population is Group D, which includes participants who have received prior systemic therapy but were naïve to *HER2* ex20ins-targeted therapy. Supportive efficacy data are provided by Group E, which includes participants who have received prior systemic therapy and had documented progression to *HER2*-targeted ADCs.

The safety analyses in support of the proposed indication are based on the data from Study 21607. The primary safety population is Group D. Safety data from participants who received at least 1 dose of sevabertinib at 20 mg BID (RP2D dose) and participants who received at least 1 dose of sevabertinib at any dose level are also presented (see Section 8.2).

Analysis Populations

Efficacy analyses for Groups D and E were performed using the FAS, which included all participants who received at least 1 dose of study treatment at 20 mg BID. In addition, sensitivity analyses of ORR were performed using the EFS, including all participants who received at least 1 dose of study treatment at 20 mg BID, had a measurable disease at baseline and either at least 1 post-baseline efficacy evaluation or clinical disease progression before the first post-baseline efficacy evaluation (treatment failure). Of note, population characteristics and treatment

exposure are provided for the SAF, which was identical to the FAS.

Data imputation was applied for instances of partial missing dates for AEs or concomitant medication, and missing parts of either the censoring date or the event date for the time-to event endpoints (only if the day was missing), where missing or partial dates were imputed as detailed in the SAP.

Determination of sample size

For Group D, a true ORR of $\geq 50\%$ was hypothesized. An approximate sample size of 70 participants including participants from Dose Expansion and Dose Extension, with a minimum of 30 responders, was estimated to provide 90.6% power to achieve a lower bound of a 2-sided 95% exact binomial CI for the estimated ORR that exceeds 30%. For Group E, a true ORR of $\geq 40\%$ was hypothesized. An approximate sample size of 51 participants, including participants from Dose Expansion and Dose Extension, with a minimum of 17 responders, was estimated to provide 86.8% power to achieve a lower bound of a 2-sided 95% exact binomial CI for the estimated ORR that exceeds 20%.

Analysis of the efficacy endpoints

The ORR was assessed by both BICR (primary efficacy endpoint) and by the investigator (secondary efficacy endpoint). The exact 2-sided 95% CIs for the ORR were calculated based on binomial distribution. Sensitivity analyses of ORR by BICR were performed similarly for the EFS. The secondary efficacy endpoints, DOR and PFS by investigator assessment and BICR, and OS were evaluated using Kaplan-Meier methods, and the median value and corresponding 95% CIs for each were calculated. In addition, analysis of time to response was performed as an additional efficacy endpoint by both BICR and by the investigator using Kaplan-Meier methods. RECIST v1.1 criteria were used for response and progression assessments.

Exploratory subgroup analyses of ORR were performed for the following prespecified subgroups of the FAS: demographics (age, sex, and race), ECOG PS at baseline, geographical region, smoking status, histology (adenocarcinoma yes vs. no; squamous vs. non-squamous), prior surgery (pneumonectomy), number of prior systemic anti-cancer therapy regimens, presence/absence of brain metastases at baseline, prior platinum therapy, prior anti-PD(L)1 treatment, and HER2 TKD mutations status at baseline.

Safety analyses are described in Section 8.2.

Interim Analysis

During the Dose Expansion and Dose Extension parts, no formal interim analyses of the data were planned, and futility was to be assessed independently for each Expansion cohort when approximately 14-17 participants evaluable for efficacy were observed. Based on futility assessments in the Expansion part, Groups D and E were prioritized in the Extension part. 2 primary analyses were planned to be performed when Group D and Group E participants completed the Dose Extension part, respectively.

The FDA’s Assessment:

FDA generally agrees with the Applicant’s description of the statistical analysis plan. The Supplemental SAP version 1.0 is based on protocol version 6.0 (dated 02 FEB 2024) and main SAP version 2.0 (dated 14 OCT 2024). It described additional analyses that were not included in the main SAP but used in the reports (e.g., CSR, Summary of Clinical Efficacy) for marketing application. The additional analyses include concordance and discordance rates of ORR by BICR and investigator, summary of DOR, and ORR subgroup analysis.

Although the supplemental SAP was created after the initial data cutoff date, it only documented additional exploratory analyses and did not modify any prespecified primary analyses. These analyses were descriptive in nature and did not influence regulatory decisions or labeling claims.

Protocol Amendments

The Applicant’s Description:

There were 4 global protocol amendments to the original Study 21607 protocol, dated 19 AUG 2021. A description of the key modifications in the 4 global amendments is presented in **Table 28**. In addition, there were 8 local amendments to the protocol. In the local protocol amendment 5 for the US, dated 12 DEC 2023, the Extension part of the study was removed. However, based on Health Authority feedback, the Extension part is applicable to the US and, therefore, this change was reversed in global protocol Amendment 6.

The changes made to the protocol amendments did not impact the integrity of the study or the interpretation of the results.

Table 28. Study 21607 Global Protocol Amendments, Including Key Modifications

Protocol amendment number and date	Key modifications
Global amendment 1, dated 12 MAY 2022	• Population in both Backfill and Expansion cohorts was refined to allow for faster recruitment and data collected in both <i>EGFR</i> exon20ins naïve and pre-treated populations. • Number of maximum participants to be treated in Backfill increased. • Expansion groups B1 and B2 were included. • Participants with brain metastases, that are clinically stable and asymptomatic, were allowed in the study • Withdrawal from Active Follow-Up edited. • Exploratory PK/ PD assessment description was added.

Table 28. Study 21607 Global Protocol Amendments, Including Key Modifications

Protocol amendment number and date	Key modifications
Global amendment 2, dated 24 NOV 2022	- Stopping criteria for the Backfill and Dose Expansion part of the study was included 1 or more dose levels were allowed to be tested in dose expansion groups. - All <i>HER2</i> activating mutations were allowed. 10 mg tablets were added to the unit dose strengths for tablets. - Guidance for the management of additional toxicities was added. - Text on central collection of imaging files was added. - Radiomics analysis was added (exploratory endpoint).
Global amendment 3, dated 17 OCT 2023	- Extension part was added; new objectives and endpoints specific to the Extension part were included. - Expansion Group F was added: NSCLC with a <i>HER2</i> activating mutation (including ex20ins) who have not received prior systemic anticancer treatment for locally advanced or metastatic disease. 100 mg BAY 2927088 tablets and high dose bioavailability cohort (example for bridging to the 100 mg tablet formulation) removed as not applicable. - The definition of the end of the study was clarified. - Details added on PK sampling for metabolite M1 and for the Dose Extension part. M1 exploratory analysis added. Details on PK population analysis added. - Details on baseline biomarker assessments were added, text on biomarker test was clarified.
Global amendment 6, dated 02 FEB 2024	- Dose Expansion Group G for participants with <i>HER2</i> mutant NSCLC and active brain metastases was added. - Extension will not include participants with <i>EGFR</i> mutations only. - Statistical considerations for Dose Extension Groups D, E, and F were updated to limit the number of participants treated in a single arm, FiH study. - Futility analysis in the Extension part was removed. - Possibility for randomization if more than one dose level/regimen is tested concurrently for the same group was added. - Country-specific changes valid for the US only were removed based on health authority feedback as the Extension part of the study is applicable for the US.

Source: Section 10.12 of the Study 21607 Protocol, Section 10.1.1

The FDA’s Assessment:

FDA agrees with the Applicant’s description of the protocol amendments.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

The study was conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines, applicable ICH GCP Guidelines, and applicable laws and regulations. The protocol, and protocol amendments were reviewed and approved by the IRBs/IECs.

The Applicant's Position:

This study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) to GCP.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Financial Disclosure

Data:

Financial disclosure information was collected from the 904 investigators across the sites participating in Study 21607. 1 of the 904 total investigators had financial interests to disclose. The details of the financial disclosure are provided in Section 19.2.

The Applicant's Position:

The Applicant has adequately assessed any financial interest/arrangements with the clinical investigators and found that 1 investigator had financial interests to disclose.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to Section 19.2 for additional details.

Patient Disposition

Data:

Sevabertinib (BAY 2927088) – Version 2.0

In this NDA submission, the primary efficacy population of interest is **Group D**, with 81 treated participants. Supportive efficacy data are provided by **Group E**, which included 55 treated participants.

Participant disposition is presented for two database cut-off dates to facilitate the understanding of the updated ORR and DOR results for Groups D and E presented in Section **8.1.2**.

- *Updated data as of 28 MAR 2025*: A total of 376 participants had started treatment in Study 21607, including participants from the DE/BF part, as well as participants from the Expansion and Extension parts.

A summary of participant disposition of Groups D and E is provided in **Table 29**.

- *As of 14 OCT 2024*: A total of 357 participants had started treatment in Study 21607, including participants from the DE/BF part, as well as participants from the Expansion and Extension parts (see **Figure 5**).

Enrolment of participants in Groups D and E was complete as of this database cut-off date. A summary of participant disposition of Groups D and E is provided in **Table 30**.

Table 29. Disposition in Study 21607, Updated Data as of 28 MAR 2025

	Group D N=81 (100%)	Group E (supportive) N=55 (100%)
Started study drug (included in SAF)	81 (100.0%)	55 (100.0%)
Discontinued study drug	51 (63.0%)	40 (72.7%)
Primary reason:		
Progressive disease: radiological assessment	41 (50.6%)	27 (49.1%)
Adverse event	4 (4.9%)	2 (3.6%)
Progressive disease: non-radiological assessment	2 (2.5%)	3 (5.5%)
Subject decision	2 (2.5%)	2 (3.6%)
Death	1 (1.2%)	3 (5.5%)
Physician decision	1 (1.2%)	1 (1.8%)
Other	0	2 (3.6%)
Ongoing with study drug (as of the cut-off date)	30 (37.0%)	15 (27.3%)
Active Follow-up phase		
Started Active Follow-up	36 (44.4%)	27 (49.1%)
Discontinued Active Follow-up	35 (43.2%)	25 (45.5%)
Ongoing with Active Follow-up (as of the cut-off date)	1 (1.2%)	2 (3.6%)
Long-term Follow-up		
Started Active Long-term Follow-up	44 (54.3%)	34 (61.8%)
Discontinued Long-term Follow-up	23 (28.4%)	21 (38.2%)
Ongoing with Long-term Follow-up (as of the cut-off date)	21 (25.9%)	13 (23.6%)

N=Total number of participants; SAF=Safety analysis set

Source: Module 5.3.5.2, Report B004166, t_14_1_1_adds_overview.sas (Datasets ADDS, ADSV, and ADSL)

Table 30. Disposition in Study 21607 as of 14 OCT 2024

	Group D N=81 (100%)	Group E (supportive) N=55 (100%)
Started study drug (included in SAF)	81 (100.0%)	55 (100.0%)
Discontinued study drug	40 (49.4%)	30 (54.5%)
Primary reason:		
Progressive disease: radiological assessment	30 (37.0%)	18 (32.7%)
Adverse event	4 (4.9%)	1 (1.8%)
Progressive disease: non-radiological assessment	2 (2.5%)	3 (5.5%)
Subject decision	2 (2.5%)	2 (3.6%)
Death	1 (1.2%)	3 (5.5%)
Physician decision	1 (1.2%)	1 (1.8%)
Other	0	2 (3.6%)
Ongoing with study drug (as of the cut-off date)	41 (50.6%)	25 (45.5%)
Active Follow-up phase		
Started Active Follow-up	27 (33.3%)	19 (34.5%)
Discontinued Active Follow-up	26 (32.1%)	17 (30.9%)
Ongoing with Active Follow-up (as of the cut-off date)	1 (1.2%)	2 (3.6%)
Long-term Follow-up		
Started Active Long-term Follow-up	33 (40.7%)	24 (43.6%)
Discontinued Long-term Follow-up	15 (18.5%)	11 (20.0%)
Ongoing with Long-term Follow-up (as of the cut-off date)	18 (22.2%)	13 (23.6%)

N=Total number of participants; SAF=Safety analysis set

Source: Module 5.3.5.2, Report B003047, t_14_1_1_adds_overview.sas (Datasets ADDS, ADSL, and ADSV)

The Applicant's Position:

Updated data as of 28 MAR 2025: 37.0% of the participants in Group D were on sevabertinib treatment. Progressive disease (assessed radiologically) was the primary reason (50.6%) for discontinuing study treatment. In the supportive efficacy population Group E, 27.3% of the participants were ongoing with treatment, with progressive disease (assessed radiologically) as the primary reason (49.1%) for treatment discontinuation. AE was the primary reason for discontinuation of 4 participants (4.9%) in Group D and in 2 participants (3.6%) in Group E.

As of 14 OCT 2024: Approximately half of the participants in Group D (50.6%) were on sevabertinib treatment at the time of the database cut-off date. Progressive disease (assessed radiologically) was the primary reason (37.0%) for discontinuing study treatment. In the supportive efficacy population, Group E, 45.5% of the participants were ongoing with treatment at the time of the cut-off with progressive disease (assessed radiologically) as the primary reason (32.7%) for treatment discontinuation. AE was the primary reason of discontinuation for 4 participants (4.9%) in Group D and in 1 participant (1.8%) in Group E.

The FDA's Assessment:

FDA acknowledges the Applicant's position; however, FDA focused on data from the updated DCO (March 28, 2025) in the revised population, which is presented in (Table 31) and which were generally consistent with those in the original population. The observed median duration of study follow-up as of the updated data cutoff date was 12.2 months (range: 1, 30) in Group D and 10.9 months (range: 2, 20) in Group E.

Table 31. FDA Analysis of Disposition in the Revised Population

	Group D N=70	Group E N=52
Started study drug (included in SAF)	70 (100%)	52 (100%)
Discontinued study drug	43 (61%)	38 (73%)
Progressive disease	36 (51%)	29 (56%)
Adverse event	4 (6%)	2 (3.8%)
Subject decision	2 (2.9%)	2 (3.8%)
Death	1 (1.4%)	2 (3.8%)
Physician decision	0	1 (1.9%)
Other	0	2 (3.8%)
Ongoing with study drug (as of the DCO)	27 (39%)	14 (27%)

DCO date: March 28, 2025

Source: FDA reviewer's analyses

Protocol Violations/Deviations as of 14 OCT 2024Data:

The number of participants with important protocol deviations is presented in Table 32.

Table 32. Number of Participants With Important Protocol Deviations in Study 21607 (SAF)

Protocol Deviation Category	Group D N=81 (100%)	Group E (supportive) N=55 (100%)
Participants with any important deviation^a	24 (29.6%)	20 (36.4%)
Procedure deviations	22 (27.2%)	14 (25.5%)
Excluded concomitant medication treatment	2 (2.5%)	0
Inclusion/exclusion criteria not met but subject entered treatment	2 (2.5%)	5 (9.1%)
Other protocol deviations	2 (2.5%)	3 (5.5%)
Time schedule deviations	1 (1.2%)	0

N=Total number of participants (100%); SAF=Safety analysis set

a: Participants may have had more than one protocol deviation but are only counted once within each deviation category.

Source: Module 5.3.5.2, Report B003047, t_14_1_2_adv_gcat_1_5.sas (Datasets ADDV and ADSL)

The Applicant's Position:

In Group D, 24 participants (29.6%) had at least 1 important protocol deviation. The most commonly reported important protocol deviations were related to the study procedures (27.2%). There were 20 participants (36.4%) in Group E with any important protocol deviation; procedure deviations were the most common of those (25.5%).

None of these protocol deviations were considered to have effect on the overall interpretation of the efficacy and safety results of the study.

The FDA's Assessment:

FDA agrees with the Applicant's position that the described protocol deviations do not appear likely to have a significant impact on the interpretation of safety or effectiveness.

Table of Demographic Characteristics as of 14 OCT 2024

Data:

A table summarizing the demographic characteristics for the primary and supportive efficacy populations is provided in **Table 33**. In addition, the demographic characteristics for populations relevant for safety analysis are also presented and discussed in Section **8.2.1**.

Table 33. Demographics in Study 21607 (SAF)

	Group D 20 mg BID N=81 (100%)	Group E 20 mg BID N=55 (100%)	Whole Study 20 mg BID N=268 (100%)	Whole Study SAF N=357 (100%)
Population analyzed for:	Efficacy/Safety	Efficacy	Safety	Safety
Sex, n (%)				
Female	50 (61.7%)	36 (65.5%)	174 (64.9%)	230 (64.4%)
Male	31 (38.3%)	19 (34.5%)	94 (35.1%)	127 (35.6%)
Race, n (%)				
Asian	57 (70.4%)	32 (58.2%)	179 (66.8%)	230 (64.4%)
White	18 (22.2%)	15 (27.3%)	65 (24.3%)	98 (27.5%)
Black or African American	1 (1.2%)	4 (7.3%)	6 (2.2%)	9 (2.5%)

Table 33. Demographics in Study 21607 (SAF)

	Group D 20 mg BID N=81 (100%)	Group E 20 mg BID N=55 (100%)	Whole Study 20 mg BID N=268 (100%)	Whole Study SAF N=357 (100%)
American Indian or Alaska native	0	0	0	1 (0.3%)
Not reported	5 (6.2%)	4 (7.3%)	18 (6.7%)	19 (5.3%)
Ethnicity, n (%)				
Not Hispanic or Latino	72 (88.9%)	50 (90.9%)	238 (88.8%)	325 (91.0%)
Hispanic or Latino	2 (2.5%)	1 (1.8%)	4 (1.5%)	5 (1.4%)
Not reported	7 (8.6%)	4 (7.3%)	26 (9.7%)	27 (7.6%)
Region, n (%)^a				
Asia	57 (70.4%)	32 (58.2%)	177 (66.0%)	227 (63.6%)
Western Europe and Israel	23 (28.4%)	13 (23.6%)	78 (29.1%)	99 (27.7%)
North America (US)	1 (1.2%)	10 (18.2%)	13 (4.9%)	30 (8.4%)
South America	0	0	0	1 (0.3%)
Age (years)				
Mean (SD)	58.8 (11.2)	63.3 (11.5)	61.2 (11.7)	61.3 (11.3)
Median (min, max)	60.0 (29, 82)	65.0 (35, 91)	62.0 (18, 91)	62.0 (18, 91)
Age group, n (%)				
18 to 64	55 (67.9%)	27 (49.1%)	153 (57.1%)	207 (58.0%)
65 to 84	26 (32.1%)	26 (47.3%)	112 (41.8%)	147 (41.2%)
≥85	0	2 (3.6%)	3 (1.1%)	3 (0.8%)
<65	55 (67.9%)	27 (49.1%)	153 (57.1%)	207 (58.0%)
≥65	26 (32.1%)	28 (50.9%)	115 (42.9%)	150 (42.0%)

BID=Twice daily; max=Maximum; min=Minimum; n=Number of participants within the category; N=Total number of participants; SAF=Safety analysis set; SD=Standard deviation; US=United States.

a: Participants by country/region (Whole Study SAF): Asia: China (88), Hong Kong (12), Japan (37), South Korea (38), Singapore (34), Taiwan (18); Western Europe and Israel: Belgium (8), Spain (15), France (20), Israel (4), Italy (42), Netherlands (10); North America: US (30); South America: Brazil (1).

Source: Module 5.3.5.2, Report B003047, t_14_1_3_adsl_dm.sas (Dataset ADSL)

The Applicant's Position:

Study 21607 was conducted in 14 countries/regions globally, with most participants enrolled from Asia and Western Europe.

The 81 participants in the primary efficacy population, Group D, had a median age of 60.0 years and the participants were predominantly female (61.7%) and Asian (70.4%). In Group E, the median age was 65.0 years, and the majority of participants were female (65.5%) and 58.2% were Asian.

As of the database cut-off date, 30 participants (8.4%) out of the 357 treated participants were from the US. The primary efficacy population, Group D, included 1 participant (1.2%) from the US. Despite the limited representation of US participants in Study 21607, the inclusion of diverse populations from Asia and Western Europe may provide valuable insights into the efficacy and safety of the treatment, which could be relevant for the multiethnic US population with the disease, especially considering the global nature of disease presentation and treatment response.

The FDA's Assessment:

FDA agrees with the Applicant's description of the demographic and baseline characteristics; the revised population characteristics (**Table 34**) were generally consistent. FDA considered the demographics and baseline characteristics generally representative of the US population, with the exception of underrepresentation of Black/African-American patients. Refer to Section **8.2.1** and Section **13** for additional information.

Table 34. Demographics in Revised Population, Efficacy Analysis Set

	D - 20mg BID N=70 (100%)	E - 20mg BID N=52 (100%)	Total N=122 (100%)
Sex			
Male	23 (32.9%)	17 (32.7%)	40 (32.8%)
Female	47 (67.1%)	35 (67.3%)	82 (67.2%)
Race			
WHITE	16 (22.9%)	14 (26.9%)	30 (24.6%)
BLACK OR AFRICAN AMERICAN	1 (1.4%)	3 (5.8%)	4 (3.3%)
ASIAN	49 (70.0%)	32 (61.5%)	81 (66.4%)
NOT REPORTED	4 (5.7%)	3 (5.8%)	7 (5.7%)
Ethnicity			
NOT HISPANIC OR LATINO	62 (88.6%)	48 (92.3%)	110 (90.2%)
HISPANIC OR LATINO	2 (2.9%)	1 (1.9%)	3 (2.5%)
NOT REPORTED	6 (8.6%)	3 (5.8%)	9 (7.4%)
Age (years)			
n	70	52	122
Mean (SD)	58.0 (10.8)	63.7 (11.5)	60.4 (11.4)
Median	59.0	65.0	61.0
Min, Max	29, 77	35, 91	29, 91
Age group (years)			
<18	0	0	0
18-64	49 (70.0%)	25 (48.1%)	74 (60.7%)
65-84	21 (30.0%)	25 (48.1%)	46 (37.7%)
>=85	0	2 (3.8%)	2 (1.6%)
Age group 2 (years)			
<65	49 (70.0%)	25 (48.1%)	74 (60.7%)
>=65	21 (30.0%)	27 (51.9%)	48 (39.3%)
Baseline Body Mass Index (kg/m²)			
n	69	52	121
Mean (SD)	23.50 (3.79)	23.80 (3.33)	23.63 (3.59)
Median	22.90	23.45	23.30
Min, Max	13.9, 34.3	18.4, 34.4	13.9, 34.4
nmiss	1	0	1
Country/Region			
BELGIUM	3 (4.3%)	0	3 (2.5%)
CHINA	19 (27.1%)	13 (25.0%)	32 (26.2%)

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SPAIN	5 (7.1%)	0	5 (4.1%)
FRANCE	4 (5.7%)	3 (5.8%)	7 (5.7%)
HONG KONG	6 (8.6%)	0	6 (4.9%)
ISRAEL	1 (1.4%)	1 (1.9%)	2 (1.6%)
ITALY	4 (5.7%)	8 (15.4%)	12 (9.8%)
JAPAN	8 (11.4%)	6 (11.5%)	14 (11.5%)
SOUTH KOREA	13 (18.6%)	4 (7.7%)	17 (13.9%)
NETHERLANDS	3 (4.3%)	0	3 (2.5%)
SINGAPORE	1 (1.4%)	4 (7.7%)	5 (4.1%)
TAIWAN	2 (2.9%)	5 (9.6%)	7 (5.7%)
UNITED STATES	1 (1.4%)	8 (15.4%)	9 (7.4%)
Region Group			
Asia	49 (70.0%)	32 (61.5%)	81 (66.4%)
North America	1 (1.4%)	8 (15.4%)	9 (7.4%)
Western Europe and Israel	20 (28.6%)	12 (23.1%)	32 (26.2%)
Number of participants initially treated by part			
Escalation	1 (1.4%)	0	1 (0.8%)
Backfill	9 (12.9%)	3 (5.8%)	12 (9.8%)
Expansion	31 (44.3%)	30 (57.7%)	61 (50.0%)
Extension	29 (41.4%)	19 (36.5%)	48 (39.3%)

Note: Body mass index is based on the values collected at screening visit.
Source: Updated Tables by Applicant for FDA IR on 5Sep2025 (SN0040), Table 8.1.3

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

Data:

A table summarizing the baseline cancer characteristics for the primary and supportive efficacy populations is provided in **Table 35**. In addition, the cancer characteristics for populations relevant for safety analysis are also presented and discussed in Section **8.2.1**.

Table 35. Baseline Cancer Characteristics (SAF)

	Group D 20 mg BID N=81 (100%)	Group E 20 mg BID N=55 (100%)	Whole Study 20 mg BID N=268 (100%)	Whole Study SAF N=357 (100%)
Smoking habits at informed consent, n (%)				
Never	50 (61.7%)	35 (63.6%)	179 (66.8%)	239 (66.9%)
Former	27 (33.3%)	19 (34.5%)	81 (30.2%)	110 (30.8%)
Current	4 (4.9%)	1 (1.8%)	8 (3.0%)	8 (2.2%)
Baseline value of ECOG Performance Status, n (%)				

Table 35. Baseline Cancer Characteristics (SAF)

	Group D 20 mg BID N=81 (100%)	Group E 20 mg BID N=55 (100%)	Whole Study 20 mg BID N=268 (100%)	Whole Study SAF N=357 (100%)
0 – fully active	31 (38.3%)	15 (27.3%)	89 (33.2%)	119 (33.3%)
1 – restricted active	50 (61.7%)	40 (72.7%)	179 (66.8%)	238 (66.7%)
Prior brain metastases at baseline, n (%)^a				
No	63 (77.8%)	40 (72.7%)	192 (71.6%)	260 (72.8%)
Yes	18 (22.2%)	15 (27.3%)	76 (28.4%)	97 (27.2%)
Prior systemic anti-cancer therapy regimens, n (%)				
0	0	0	60 (22.4%)	62 (17.4%)
1	46 (56.8%)	13 (23.6%)	93 (34.7%)	125 (35.0%)
2	16 (19.8%)	16 (29.1%)	46 (17.2%)	72 (20.2%)
≥3	19 (23.5%)	26 (47.3%)	69 (25.7%)	98 (27.5%)
Prior platinum and/or anti-PD(L)1 treatment				
Any prior platinum	76 (93.8%)	43 (78.2%)	183 (68.3%)	251 (70.3%)
Any prior platinum and anti-PD(L)1 treatment	56 (69.1%)	31 (56.4%)	130 (48.5%)	178 (49.9%)
Any prior platinum and no prior anti- PD(L)1 treatment	20 (24.7%)	12 (21.8%)	53 (19.8%)	73 (20.4%)
NSCLC histology, n (%)^b				
Adenocarcinoma, NOS	72 (88.9%)	49 (89.1%)	247 (92.2%)	329 (92.2%)
Adenocarcinoma With Mixed Subtypes	3 (3.7%)	1 (1.8%)	6 (2.2%)	7 (2.0%)
Squamous Cell Carcinoma, NOS	3 (3.7%)	0	4 (1.5%)	5 (1.4%)
Bronchiolar Adenocarcinoma	2 (2.5%)	0	2 (0.7%)	2 (0.6%)
Squamous Cell Carcinoma, Small Cell, Nonkeratinizing	1 (1.2%)	0	1 (0.4%)	2 (0.6%)
Papillary Adenocarcinoma, NOS	0	1 (1.8%)	2 (0.7%)	3 (0.8%)
Acinar Cell Carcinoma	0	2 (3.6%)	3 (1.1%)	4 (1.1%)
Acinar Adenocarcinoma	0	1 (1.8%)	1 (0.4%)	2 (0.6%)
Missing	0	1 (1.8%)	1 (0.4%)	1 (0.3%)
Stage at study entry, n (%)				
Stage II B	0	0	1 (0.4%)	1 (0.3%)
Stage III A	0	1 (1.8%)	3 (1.1%)	6 (1.7%)
Stage III B	0	1 (1.8%)	5 (1.9%)	5 (1.4%)
Stage IV A	22 (27.2%)	16 (29.1%)	90 (33.6%)	117 (32.8%)
Stage IV B	52 (64.2%)	31 (56.4%)	145 (54.1%)	201 (56.3%)
Missing	7 (8.6%)	6 (10.9%)	24 (9.0%)	27 (7.6%)
Gene with activating mutations (local testing)				
EGFR	0	0	43 (16.0%)	87 (24.4%)
ERBB2	81 (100.0%)	55 (100.0%)	223 (83.2%)	268 (75.1%)
Incomplete	0	0	2 (0.7%)	2 (0.6%)
HER2 genetic alterations, n (%)				
HER2 Y772_A775dup (YVMA)	48 (59.3%)	40 (72.7%)	153 (57.1%)	176 (49.3%)
HER2 point mutations	13 (16.0%)	5 (9.1%)	22 (8.2%)	27 (7.6%)
Other HER2 ex20ins	19 (23.5%)	9 (16.4%)	44 (16.4%)	61 (17.1%)
Not Applicable ^c	1 (1.2%)	1 (1.8%)	49 (18.3%)	93 (26.1%)
Time since initial diagnosis, months^d				
n	81	55	268	357
Mean (SD)	20.2 (19.6)	26.6 (19.3)	21.3 (27.4)	24.2 (28.4)
Median	13.2	21.8	12.5	15.2
Min, Max	2, 110	2, 103	0, 248	0, 248

Table 35. Baseline Cancer Characteristics (SAF)

	Group D 20 mg BID N=81 (100%)	Group E 20 mg BID N=55 (100%)	Whole Study 20 mg BID N=268 (100%)	Whole Study SAF N=357 (100%)
Time since most recent progression/relapse to first administration of study treatment, months				
n	70	49	197	272
Mean (SD)	1.9 (2.3)	1.6 (2.2)	2.0 (3.1)	2.0 (3.2)
Median	1.2	0.9	1.1	1.2
Min, Max	0, 14	0, 14	0, 27	0, 30
Missing	11	6	71	85

BID=Twice daily; ECOG= Eastern Cooperative Oncology Group; EGFR= Epidermal growth factor receptor; ERBB2=Erb-b2 receptor tyrosine kinase 2; ex20ins=Exon 20 insertion; HER2=Human epidermal growth factor receptor 2; Max=Maximum; Min=Minimum; n=Number of participants within the category; N=Total number of participants; NOS= Not otherwise specified; NSCLC=Non-small cell lung cancer; SAF=Safety analysis set; SD=Standard deviation

Note: Percentages are calculated, including missing values.

a: Participants with brain metastases at baseline are participants with any target and/or non-target lesions having anatomical location being brain according to investigator assessment. Group D updated based on results from 28 MAR 2025, see Figure 7.
b: Histology - adenocarcinoma is defined as Acinar adenocarcinoma; Adenocarcinoma with mixed subtypes; Adenocarcinoma, NOS; Bronchiolar adenocarcinoma; Papillary adenocarcinoma, NOS, Solid adenocarcinoma with mucin formation per medical review.

c: Not applicable includes all patients that cannot be classified as HER2 Y772_A775dup, HER2 point mutations or Other HER2 ex20ins.

d: Missing day and/or month of initial diagnosis date is imputed as 1 and/or JAN.

Source: Module 5.3.5.2, Report B003047, t_14_1_4_adsl_baseline_cancer.sas and t_14_1_6_1_adcm_plat_pdl1.sas (Datasets ADSL and ADCM)

The Applicant's Position:

At baseline, the majority of participants in Groups D and E never had any smoking habits and had an ECOG PS of 1. Most participants had no history of brain metastases, were classified with NSCLC adenocarcinoma, NOS, had Stage IV disease at baseline, and a *HER2* Y772_A775dup (YVMA) ex20ins mutation. All participants in Groups D and E received prior systemic anti-cancer therapy as required by the protocol, with 23.5% and 47.3% of participants receiving 3 or more prior lines of systemic therapy, respectively.

Overall, the primary efficacy population treated in Study 21607 is representative of the intended patient population, and the baseline cancer characteristics are consistent with those described for US patients with advanced NSCLC harboring *HER2* mutations (40, 41). The majority of participants (93.8% in Group D and 78.2% in Group E) had received platinum-based chemotherapy with or without anti-PD(L)1 treatment, reflecting the US standard practice (18).

The FDA's Assessment:

FDA agrees with the Applicant's results of other baseline characteristics. The results in the revised population (Table 36) were generally consistent. FDA's analyses reflect a revised efficacy population excluding patients with squamous NSCLC or and those with *HER2* non-TKD mutations given the extremely limited sample sizes and insufficient evidence of activity in these subsets (refer to subgroup analyses described below). FDA notes that per the Applicant, the patient (ID: (b) (6)) who had received prior Enhertu (trastuzumab deruxtecan;

categorized as HER2 ex20ins-targeted therapy in Table 36) had received Enhertu for <2 months and stopped due to other reasons than disease progression, and therefore met the eligibility criteria for Group D.

Table 36. Baseline Cancer Characteristics in Revised Population, Efficacy Analysis Set

	D - 20mg BID N=70 (100%)	E - 20mg BID N=52 (100%)	Total N=122 (100%)
Number (%) of subjects			
Smoking habits at informed consent			
NEVER	48 (68.6%)	34 (65.4%)	82 (67.2%)
FORMER	20 (28.6%)	18 (34.6%)	38 (31.1%)
CURRENT	2 (2.9%)	0	2 (1.6%)
Gene with activating mutations (local testing)			
ERBB2	70 (100.0%)	52 (100.0%)	122 (100.0%)
Specific activating EGFR/HER2 mutations (local testing)			
ERBB2 exon 20 insertions	66 (94.3%)	49 (94.2%)	115 (94.3%)
ERBB2 point mutation	4 (5.7%)	3 (5.8%)	7 (5.7%)
Baseline value of ECOG Performance Status			
0 - FULLY ACTIVE	27 (38.6%)	15 (28.8%)	42 (34.4%)
1 - RESTRICTED ACTIVE	43 (61.4%)	37 (71.2%)	80 (65.6%)
Prior brain metastases at baseline			
Yes	14 (20.0%)	15 (28.8%)	29 (23.8%)
No	56 (80.0%)	37 (71.2%)	93 (76.2%)
Number of prior systemic anti-cancer therapy regimens			
1	40 (57.1%)	12 (23.1%)	52 (42.6%)
2	14 (20.0%)	16 (30.8%)	30 (24.6%)
>=3	16 (22.9%)	24 (46.2%)	40 (32.8%)

	D - 20mg BID N=70 (100%)	E - 20mg BID N=52 (100%)	Total N=122 (100%)
Use of prior EGFR ex20ins-targeted therapy			
Yes	2 (2.9%)	2 (3.8%)	4 (3.3%)
No	68 (97.1%)	50 (96.2%)	118 (96.7%)
Use of prior HER2 ex20ins-targeted therapy			
Yes	1 (1.4%)	52 (100.0%)	53 (43.4%)
No	69 (98.6%)	0	69 (56.6%)
Use of prior HER2 ex20ins-targeted TKI			
Yes	0	2 (3.8%)	2 (1.6%)
No	70 (100.0%)	50 (96.2%)	120 (98.4%)
HER2 genetic alterations			
HER2 Y772_A775dup (YVMA)	49 (70.0%)	40 (76.9%)	89 (73.0%)
HER2 point mutations	4 (5.7%)	3 (5.8%)	7 (5.7%)
Other HER2 exon20ins	16 (22.9%)	9 (17.3%)	25 (20.5%)
Not Applicable	1 (1.4%)	0	1 (0.8%)
HER2 TKD mutation			
Yes	70 (100.0%)	52 (100.0%)	122 (100.0%)
Use of prior chemotherapy			
Yes	68 (97.1%)	41 (78.8%)	109 (89.3%)
No	2 (2.9%)	11 (21.2%)	13 (10.7%)
Use of prior Enhertu			
Yes	1 (1.4%)	39 (75.0%)	40 (32.8%)
No	69 (98.6%)	13 (25.0%)	82 (67.2%)
Best response to the most recent prior systemic anti-cancer therapy			
PARTIAL RESPONSE	19 (27.1%)	13 (25.0%)	32 (26.2%)
STABLE DISEASE	27 (38.6%)	15 (28.8%)	42 (34.4%)
PROGRESSIVE DISEASE MEASUREMENT PROVEN	10 (14.3%)	4 (7.7%)	14 (11.5%)
PROGRESSIVE DISEASE BY CLINICAL JUDGEMENT	0	2 (3.8%)	2 (1.6%)
PARTIAL REMISSION	2 (2.9%)	4 (7.7%)	6 (4.9%)
NO RESPONSE / TREATMENT FAILURE	2 (2.9%)	0	2 (1.6%)
PROGRESSIVE DISEASE BY RESPONSE ASSESSMENT CRITERIA	2 (2.9%)	1 (1.9%)	3 (2.5%)
NA	3 (4.3%)	4 (7.7%)	7 (5.7%)

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UNKNOWN	4 (5.7%)	9 (17.3%)	13 (10.7%)
NOT ASSESSED	1 (1.4%)	0	1 (0.8%)
NSCLC histology			
ADENOCARCINOMA, NOS	66 (94.3%)	48 (92.3%)	114 (93.4%)
BRONCHIOLAR ADENOCARCINOMA	2 (2.9%)	0	2 (1.6%)
ADENOCARCINOMA WITH MIXED SUBTYPES	2 (2.9%)	1 (1.9%)	3 (2.5%)
PAPILLARY ADENOCARCINOMA, NOS	0	1 (1.9%)	1 (0.8%)
ACINAR CELL CARCINOMA	0	2 (3.8%)	2 (1.6%)
NSCLC histology - adenocarcinoma			
Yes	70 (100.0%)	52 (100.0%)	122 (100.0%)
Grading (AJCC) at initial diagnosis			
G1, WELL DIFFERENTIATED	1 (1.4%)	1 (1.9%)	2 (1.6%)
G2, MODERATELY DIFFERENTIATED	2 (2.9%)	3 (5.8%)	5 (4.1%)
G3, POORLY DIFFERENTIATED	6 (8.6%)	5 (9.6%)	11 (9.0%)
G4, UNDIFFERENTIATED	1 (1.4%)	0	1 (0.8%)
GX, GRADE CANNOT BE ASSESSED	58 (82.9%)	39 (75.0%)	97 (79.5%)
missing	2 (2.9%)	4 (7.7%)	6 (4.9%)
Stage at study entry			
STAGE III A	0	1 (1.9%)	1 (0.8%)
STAGE III B	0	2 (3.8%)	2 (1.6%)
STAGE IV A	19 (27.1%)	14 (26.9%)	33 (27.0%)
STAGE IV B	45 (64.3%)	30 (57.7%)	75 (61.5%)
missing	6 (8.6%)	5 (9.6%)	11 (9.0%)
Time since initial diagnosis (months)			
n	70	52	122
Mean (SD)	20.3 (20.3)	25.7 (16.3)	22.6 (18.8)
Median	13.2	21.8	16.4
Min, Max	2, 110	2, 72	2, 110
Time since most recent progression/relapse to first administration of study treatment (months)			
n	61	46	107
Mean (SD)	1.9 (2.2)	1.5 (2.2)	1.7 (2.2)
Median	1.2	0.8	1.1
Min, Max	0, 14	0, 14	0, 14
nmiss	9	6	15

Prior Surgery Pneumonectomy

156

Version date: March 1, 2024 (ALL NDA/BLA reviews)

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

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Yes	1 (1.4%)	0	1 (0.8%)
No	69 (98.6%)	52 (100.0%)	121 (99.2%)

Note: Percentages are calculated including missing values.
 Participants with brain metastases at baseline are participants with any target and/or non-target lesions having anatomical location being brain according to Investigator assessment.
 Missing day and/or month of initial diagnosis date is imputed as 1 and/or JAN.
 Note: Enhertu (standard drug name: TRASTUZUMAB DERUXTECAN) is categorized as HER2 ex20ins-targeted therapy in this table.
 Note: In Group E, 13 participants, who never received prior Enhertu, actually received other prior ADCs.
 Histology - adenocarcinoma is defined as Acinar adenocarcinoma; Acinar cell carcinoma; Adenocarcinoma with mixed subtypes; Adenocarcinoma, NOS; Bronchiolar adenocarcinoma; Papillary adenocarcinoma, NOS; Solid adenocarcinoma with mucin formation per medical review.
 Source: Updated Tables by Applicant for FDA IR on 5Sep2025 (SN0040), Table 8.1.4

Treatment Compliance, Concomitant Medications, and Rescue Medication Use – as of 14 OCT 2024

Data and the Applicant’s Position:

Treatment compliance

Treatment compliance was high. The median percentage of the actual administered dose of sevabertinib was 98.51% of the planned dose in the primary efficacy population (Group D) and 95.22% in Group E (*Module 5.3.5.2, B003047, Table 8.1.8/4 [Datasets ADSL and ADEXSUM]*).

Concomitant medications

In Group D, 98.8% of participants received at least 1 concomitant medication. In Group E, all participants received at least 1 concomitant medication. The most commonly used concomitant medications, by ATC subclass, taken by >50% of participants in either Group D or Group E, included: (*Module 5.3.5.2, B003047, Table 8.1.7/8 [Datasets ADSL and ADCM]*).

- Ophthalmologicals (82.7% in Group D and 78.2% in Group E)
- Antidiarrheals, intestinal anti-inflammatory/anti-infective agents (81.5% and 85.5%)
- Stomatological preparations (67.9% and 61.8%)
- Corticosteroids, dermatological preparations (65.4% and 54.5%)
- Antibacterials for systemic use (65.4% and 65.5%)
- Drugs for acid related disorders (64.2% and 54.5%)
- Analgesics (61.7% and 63.6%)
- Nasal preparations (56.8% and 50.9%)
- Vasoprotectives (53.1% and 43.6%)
- Antibiotics and chemotherapeutics for dermatological use (51.9% and 43.6%)
- Mineral supplements (44.4% and 58.2%)
- Blood substitutes and perfusion solutions (44.4% and 52.7%)

- Psycholeptics (35.8% and 50.9%)

Concomitant medications were predominantly used for the management of comorbidities and toxicity. Overall, the concomitant treatments administered were representative of those commonly prescribed for patients with locally advanced or metastatic NSCLC harboring *EGFR* and/or *HER2* mutations, and/or for other illnesses commonly encountered in populations of a similar age.

Rescue medication

Not applicable.

The FDA’s Assessment:

FDA agrees with the Applicant’s position. As above the most common concomitant medication was an anti-diarrheal. There are no concomitant medications that are known to affect the efficacy results. FDA notes that the category listed above for antibiotics and chemotherapeutics for dermatologic use refers to ATC subclass D06B containing compounds such as sulfonamides, anti-viral, and metronidazole for rosacea.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

An analysis of ORR in Groups D and E was performed using data from a database cut-off date of 28 MAR 2025. This database cutoff was determined as the date all ongoing responders in Groups D and E had reached at least six months of follow-up on DOR. The results are summarized below, using an extra section to present the updated best overall responses by BICR for Groups D and E for the FAS. Results as of the original cut-off date of 14 OCT 2024 are available in the section below the updated data.

Updated results as of 28 MAR 2025:

Primary analysis of ORR – as of 28 MAR 2025:

In the primary efficacy population, Group D, the confirmed ORR per RECIST v1.1 by BICR was 64.2% (95% CI: [52.8%, 74.6%]) among the 81 participants in the FAS, with the lower limit of the 95% CI exceeding the predefined 30% limit (SAP version 2.0, Module 5.3.5.2, Report B003047, Section 10.1.9). A total of 52 participants achieved a response, including 2 participants (2.5%) with CR and 50 (61.7%) with PR as the best response (37).

Table 37. ORR and DCR by BICR – Group D, as of 28 MAR 2025 (FAS)

Best overall response (RECIST 1.1)	Updated results as of 28 MAR 2025 N=81
ORR, n (%)^a	52 (64.2%)
[95% CI]	[52.8%, 74.6%]
DCR, n (%)^b	66 (81.5%)
[95% CI]	[71.3%, 89.2%]
CR	2 (2.5%)
PR	50 (61.7%)
SD	20 (24.7%)
PD	6 (7.4%)
NE	3 (3.7%)
NA	0

BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; FAS=Full analysis set; MRI=Magnetic resonance imaging; n=Number of participants within the category; NA=Not available; NE=Not evaluable; ORR=Objective response rate; PD=Progressive disease; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease

CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

NE: Requirement of CR/PR/SD/PD not met.

NA: Participants who have no post-baseline tumor assessment, but who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated and were therefore considered evaluable (considered as non-responder).

a: Participants with confirmed CR or PR.

b: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

Source: Module 5.3.5.2, Report B004166, t_14_2_1_adrs_recist.sas [Datasets ADRS and ADSL]

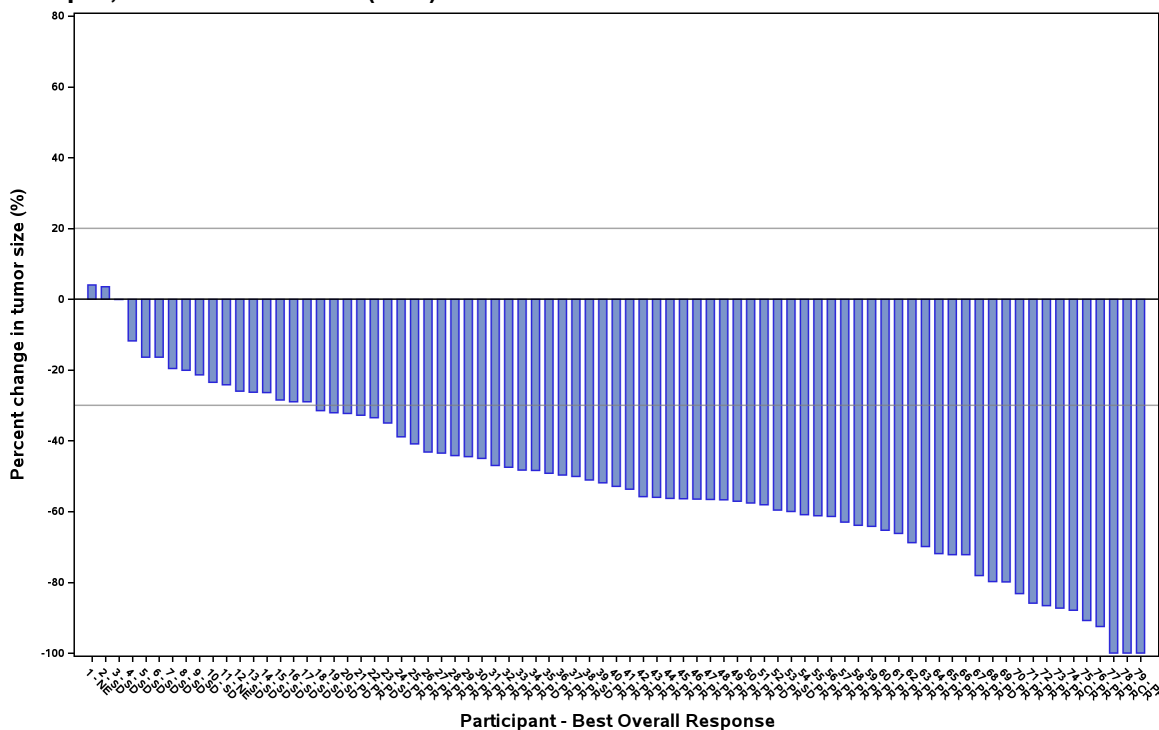
Sensitivity analysis of ORR by BICR – as of 28 MAR 2025

A total of 80 participants were evaluable, as per EFS, and were included in the sensitivity analysis. The ORR was 65.0% (95% CI: [53.5%, 75.3%]) by BICR and 63.8% (95% CI: [52.2%, 74.2%]) by the investigator assessment, which were consistent with the results of the main ORR analysis in the FAS (Module 5.3.5.2, B004166, Tables 8.2.1/1 and 8.2.1/2 [Datasets ADRS and ADSL]).

Best percent change from baseline in the size of the target lesions – as of 28 MAR 2025

The best percent change from baseline in the size of the target lesions based on assessment by BICR is presented for Group D in **Figure 6**. Of the 81 participants in Group D (FAS), the best change could be determined for 79 participants. A reduction in the target lesions from baseline was observed for 77 participants (95.1%), with 16 (19.8%) having a $\geq 70\%$ reduction. 2 participants did not have a complete post-baseline assessment and are not displayed in the waterfall plot (Module 5.3.5.2, B004166, Table 8.2.1/8 [Datasets ADTR and ADSL]).

Figure 6. Best Percent Change in the Size of Target Lesions From Baseline by BICR – Group D, as of 28 MAR 2025 (FAS)

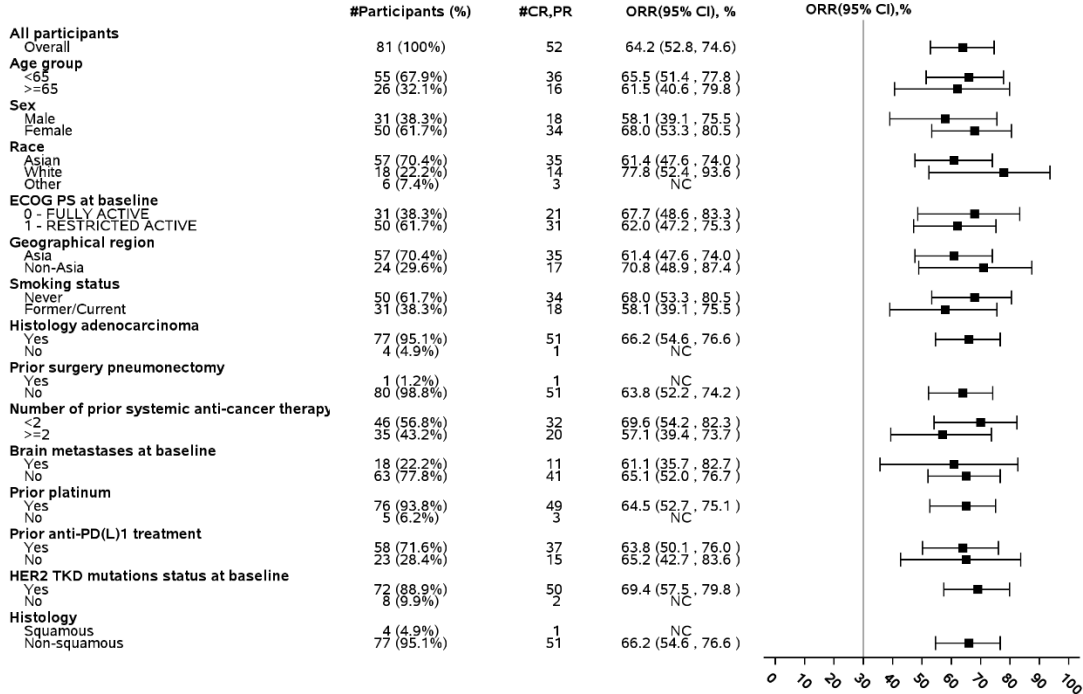


BICR=Blinded independent central review; CR=Complete response, FAS=Full analysis set; NE=Not evaluable; PD=Progressive disease, PR=Partial response, RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease
 RECIST version 1.1
 The best percent change from baseline in size of target lesions occurred after initiation of new anti-cancer therapy are excluded in this figure.
 Participants without target lesion measurement of “Percent Change from Baseline” are not displayed in this figure.
 Not evaluable: requirement of CR/PR/SD/PD not met.
 Source: Module 5.3.5.2, Report B004166, f_14_2_1_adtr_pchgb_l_trt.sas (Datasets ADRS, ADTR, and ADST)

Subgroup analyses of ORR – as of 28 MAR 2025

The ORR results in Group D were consistent and >57% across the pre-specified subgroups, based on demographics, baseline cancer characteristics, and prior treatments (**Figure 7**). The exact binomial 95% CI lower limits about the estimated ORR exceeded 30% for all subgroups.

Figure 7. Subgroup Analysis of ORR by BICR – Group D, as of 28 MAR 2025 (FAS)



BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; FAS=Full analysis set; HER2=Human epidermal growth factor receptor 2; NC=Not calculable; ORR=Objective response rate; PD(L)1=Programmed cell death ligand 1; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; TKD=Tyrosine kinase domain
 95% CI by exact binomial calculation.
 RECIST version 1.1

NC: not calculable due to the number of participants in subgroup <10% of total number of participants in respective treatment group.
 Source: Module 5.3.5.2, Report B004166, f_s1_14_2_2_adrs_recist_forest.sas (Datasets ADRS and ADSL)

No clinically meaningful differences are anticipated in the efficacy of sevabertinib in the US vs. non-US NSCLC patients with *HER2* activating mutations.

Supportive efficacy results in Group E – as of 28 MAR 2025

In the supportive efficacy population, Group E, the confirmed ORR by BICR was 38.2% (95% CI: [25.4%, 52.3%]) among the 55 participants in the FAS. A total of 21 participants achieved a response, including 3 participants (5.5%) with a CR and 18 participants (32.7%) who had a PR as their best response (Table 38).

The sensitivity analysis of ORR by BICR, analyzed in 54 evaluable participants in the EFS, was 38.9% (95% CI: [25.9%, 53.1%]), which was consistent with the results from the primary ORR analysis by BICR in the FAS (38.2%) (Module 5.3.5.2, B004166, Table 8.2.1/2 [Datasets ADRS and ADSL]).

Table 38. ORR and DCR by BICR – Group E, as of 28 MAR 2025 (FAS)

Best overall response (RECIST 1.1)	Updated results as of 28 MAR 2025 N=55
ORR, n (%) ^a [95% CI]	21 (38.2%) [25.4%, 52.3%]
DCR, n (%) ^b [95% CI]	39 (70.9%) [57.1%, 82.4%]
CR	3 (5.5%)
PR	18 (32.7%)
SD	23 (41.8%)
PD	7 (12.7%)
NE	4 (7.3%)
NA	0

BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; FAS=Full analysis set; MRI=Magnetic resonance imaging; n=Number of participants within the category; NA=Not available; NE=Not evaluable; ORR=Objective response rate; PD=Progressive disease; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease

CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

NE: Requirement of CR/PR/SD/PD not met.

NA: Participants who have no post-baseline tumor assessment, but who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated and were therefore considered evaluable (considered as non-responder).

a: Participants with confirmed CR or PR.

b: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

Source: Module 5.3.5.2, Report B004166, t_14_2_1_adrs_recist.sas (Datasets ADRS and ADSL)

Results as of 14 OCT 2024:

Primary analysis of ORR – as of 14 OCT 2024:

In the primary efficacy population, Group D, the confirmed ORR per RECIST v1.1 by BICR was 60.5% (95% CI: [49.0, 71.2]) among the 81 participants in the FAS, with the lower limit of the 95% CI exceeding the predefined 30% limit (SAP version 2.0, Module 5.3.5.2, Report B003047, Section 10.1.9). A total of 49 participants achieved a response, including 1 participant (1.2%) with a CR and 48 participants (59.3%) with a PR as the best response (**Table 39**).

As follow-up was longer and the data are more mature in the DE/BF and Dose Expansion parts when compared to the Dose Extension part, the ORR is also presented by study part:

- In DE/BF/Expansion (N=44), the ORR by BICR was 56.8% (95% CI: [41.0, 71.7]).
- In Extension (N=37), the ORR by BICR was 64.9% (95% CI: [47.5, 79.8]).

Table 39. ORR and DCR by BICR – Group D, as of 14 OCT 2024 (FAS)

Best overall response (RECIST 1.1)	DE/BF/Expansion N=44	Extension N=37	Total DE/BF/Expansion + Extension N=81
ORR, n (%) ^a	25 (56.8%)	24 (64.9%)	49 (60.5%)
[95% CI]	[41.0%, 71.7%]	[47.5%, 79.8%]	[49.0%, 71.2%]
DCR, n (%) ^b	34 (77.3%)	32 (86.5%)	66 (81.5%)
[95% CI]	[62.2%, 88.5%]	[71.2%, 95.5%]	[71.3%, 89.2%]
CR	1 (2.3%)	0	1 (1.2%)
PR	24 (54.5%)	24 (64.9%)	48 (59.3%)
SD	11 (25.0%)	11 (29.7%)	22 (27.2%)
PD	5 (11.4%)	2 (5.4%)	7 (8.6%)
NE	3 (6.8%)	0	3 (3.7%)
NA	0	0	0
NA (ongoing)	0	0	0

BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; DE/BF=Dose Escalation/Backfill; FAS=Full analysis set; MRI=Magnetic resonance imaging; NA=Not available; NE=Not evaluable; ORR=Objective response rate; PD=Progressive disease; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease. CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

NE: Requirement of CR/PR/SD/PD not met.

NA: Participants who have no post-baseline tumor assessment, but who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated and were therefore considered evaluable (considered as non-responder).

NA (ongoing): Participants who have no post-baseline tumor assessment and are considered as 'ongoing'.

a: Participants with confirmed CR or PR.

b: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

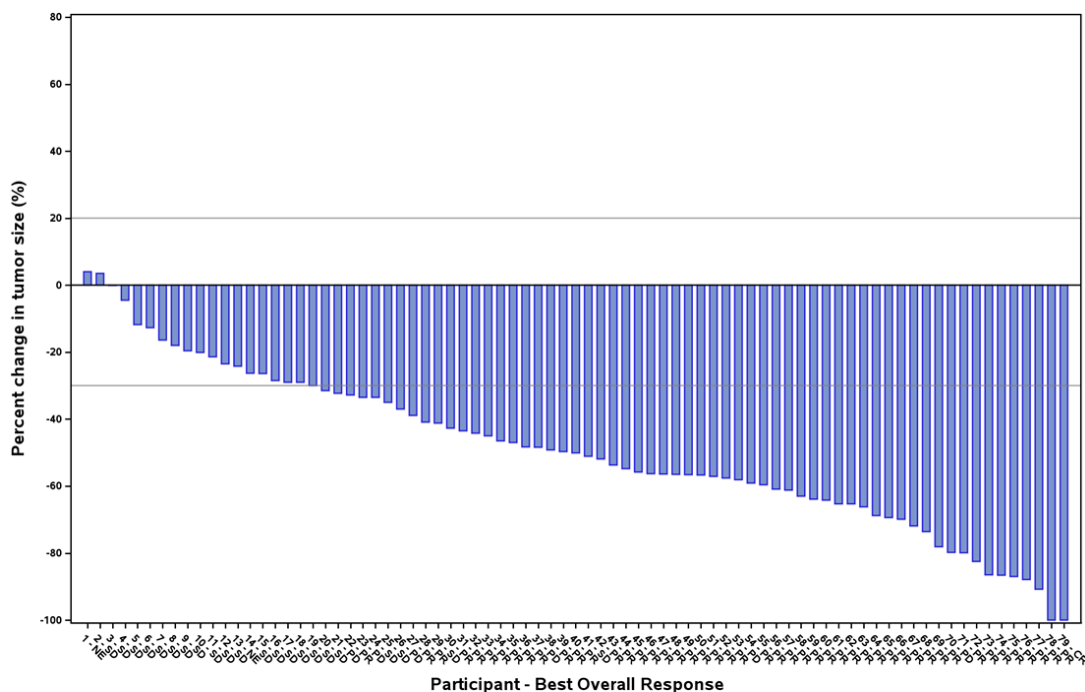
Source: Module 5.3.5.2, Report B003047, t_14_2_1_adrs_recist.sas [Datasets ADRS and ADSL]

Sensitivity analysis of ORR by BICR – as of 14 OCT 2024

A total of 80 participants were evaluable, as per EFS, and were included in the sensitivity analysis. The ORR was 61.3% (95% CI: [49.7, 71.9]) by BICR and 60.0% (95% CI: [48.4, 70.8]) by the investigator assessment, which were consistent with the results of the main ORR analysis in the FAS (Module 5.3.5.2, B003047, Table 8.2.1/3 [Datasets ADSL and ADTR]).

The best percent change from baseline in the size of the target lesions based on response assessment by BICR is presented for Group D in **Figure 8**. Of the 81 participants in Group D (FAS), the best change could be determined for 79 participants (97.5%). A reduction in the target lesions from baseline was observed for 77 participants (95.1%), with 13 participants (16.0%) having a $\geq 70\%$ reduction. 2 participants did not have a complete post-baseline assessment and are not displayed in the waterfall plot (Module 5.3.5.2, B003047, Table 8.2.1/3s1 [Datasets ADSL, ADTR]).

Figure 8. Best Percent Change in the Size of Target Lesions From Baseline by BICR – Group D, as of 14 OCT 2024 (FAS)

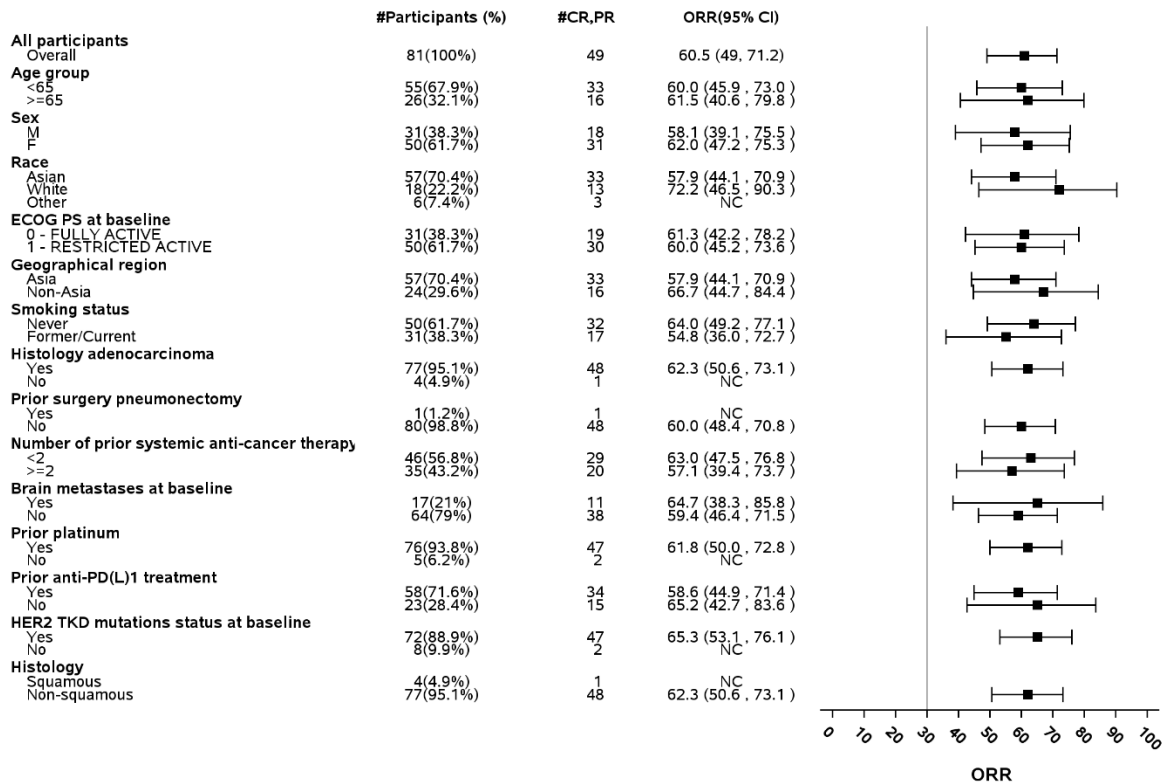


BICR=Blinded independent central review; CR=Complete response, FAS= Full analysis set; NE=Not evaluable; PD=Progressive disease, PR=Partial response, RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1, SD=Stable disease
RECIST version 1.1
The best percent change from baseline in size of target lesions occurred after initiation of new anti-cancer therapy is excluded in this figure.
Participants without target lesion measurement of "Percent Change from Baseline" are not displayed in this figure.
NE: Requirement of CR/PR/SD/PD not met.
Source: Module 5.3.5.2, Report B003047, f_14_2_1_adtr_pchgbl_trt.sas (Datasets ADSL, ADRS, and ADTR)

Subgroup analyses of ORR – as of 14 OCT 2024

The ORR results in Group D were consistent and >57% across the pre-specified subgroups, based on demographics, baseline cancer characteristics, and prior treatments (**Figure 9**).

Figure 9. Subgroup Analysis of ORR by BICR – Group D, as of 14 OCT 2024 (FAS)



BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; FAS=Full analysis set; HER2=Human epidermal growth factor receptor 2; ORR=Objective response rate; PD(L)1 =Programmed death-ligand 1; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; TKD=Tyrosine kinase domain; #=Number

95% CI by exact binomial calculation.

NC: not calculable due to number of participants in subgroup <10% of total number of participants in respective treatment group.

RECIST version 1.1

Source: Module 5.3.5.2, Report B003047, f_s1_14_2_2_adrs_recist_forest.sas (Datasets ADSL, ADRS, and ADFAE)

Results of exposure-response analyses confirm that the efficacy benefit of sevabertinib was highest in the targeted patient population, i.e. patients with advanced NSCLC whose tumors have activating *HER2* mutations (see Section 6.3.2.1), regardless of baseline demographic and clinical characteristics.

Based on data from Study 21607, no clinically meaningful differences are anticipated in the efficacy of sevabertinib in the US vs. non-US NSCLC patients with *HER2* activating mutations.

Supportive efficacy results in Group E – as of 14 OCT 2024

In the supportive efficacy population, Group E, the confirmed ORR by BICR was 34.5% (95% CI: [22.2, 48.6]) among the 55 participants in the FAS. A total of 19 participants achieved a response, including 3 participants (5.5%) with a CR and 16 participants (29.1%) who had a PR as their best response (Table 40).

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In DE/BF/Expansion (N=34) part, the confirmed ORR by BICR was 35.3% (95% CI: [19.7, 53.5]), and in the Extension part (N=21), the ORR by BICR was 33.3% (95% CI: [14.6, 57.0]).

The sensitivity analysis of ORR by BICR, analyzed in 54 evaluable participants in the EFS, was 35.2% (95% CI: [22.7, 49.4]), which was consistent with the results from the primary ORR analysis by BICR in the FAS (34.5%) (*Module 5.3.5.2, B003047, Table 8.2.1/3 [Datasets ADSL and ADTR]*).

Table 40. ORR and DCR by BICR – Group E, as of 14 OCT 2024 (FAS)

Best overall response (RECIST 1.1)	DE/BF/Expansion N=34	Extension N=21	Total DE/BF/Expansion + Extension N=55
ORR, n (%) ^a	12 (35.3%)	7 (33.3%)	19 (34.5%)
[95% CI]	[19.7%, 53.5%]	[14.6%, 57.0%]	[22.2%, 48.6%]
DCR, n (%) ^b	21 (61.8%)	17 (81.0%)	38 (69.1%)
[95% CI]	[43.6%, 77.8%]	[58.1%, 94.6%]	[55.2%, 80.9%]
CR	3 (8.8%)	0	3 (5.5%)
PR	9 (26.5%)	7 (33.3%)	16 (29.1%)
SD	13 (38.2%)	12 (57.1%)	25 (45.5%)
PD	5 (14.7%)	2 (9.5%)	7 (12.7%)
NE	4 (11.8%)	0	4 (7.3%)
NA	0	0	0
NA (ongoing)	0	0	0

BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; DE/BF=Dose Escalation/Backfill; FAS=Full analysis set; MRI=Magnetic resonance imaging; N=Total number of participants; n=Number of participants with an event; NA=Not available; NE=Not evaluable; ORR=Objective response rate; PD=Progressive disease; PR=Partial response, RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease.
CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

NE: Requirement of CR/PR/SD/PD not met.

NA: Participants who have no post-baseline tumor assessment, but who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated and were therefore considered evaluable (considered as non-responder).

NA (ongoing): Participants who have no post-baseline tumor assessment and are considered as 'ongoing'.

a: Participants with confirmed CR or PR.

b: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

Source: *Module 5.3.5.2, Report B003047, t_14_2_1_adrs_recist.sas (Datasets ADRS and ADSL)*

The Applicant's Position:

In terms of efficacy, sevabertinib demonstrated clinically meaningful activity in the treatment of advanced NSCLC patients with *HER2* activating mutations, who have received prior systemic therapy.

Updated results as of 28 MAR 2025:

- In Group D, the updated confirmed ORR by BICR was 64.2% (95% CI: [52.8%, 74.6%]) among the 81 participants in the FAS (including 2 CRs and 50 PRs), exceeding the ORR of 60.5% reported for participants at the 14 OCT 2024 database cut-off date.
- The majority of participants in Group D (FAS) experienced a reduction in tumor size as the best change from baseline, with 19.8% of participants having a $\geq 70\%$ reduction.
- Sensitivity analyses of ORR by BICR, performed in 80 evaluable participants in the EFS, were consistent with the results from the main analysis in the FAS.
- The ORR results were consistent and $>57\%$, and the lower limit of the 95% CI exceeded 30% across the pre-specified subgroups in Group D.
- The data from Group E (N=55) aligns with and further supports the findings from Group D, demonstrating efficacy in a participant population that had received prior systemic therapy and progressed to *HER2*-targeted ADC therapy.

Results as of 14 OCT 2024:

- In Group D, the confirmed ORR by BICR was 60.5% (95% CI: [49.0, 71.2]) among the 81 participants in the FAS, including 1 CR and 48 PRs.
- The majority of participants in Group D (FAS) experienced a reduction in tumor size as the best change from baseline, with 16.0% participants having a $\geq 70\%$ reduction.
- Sensitivity analyses of ORR by BICR, performed in 80 evaluable participants in the EFS, were consistent with the results from the main analysis in the FAS.
- The ORR results were consistent and $>57\%$ across the pre-specified subgroups in Group D, including demographics (age, sex, and race), ECOG PS at baseline, geographical region, smoking status, histology (adenocarcinoma yes vs. no; squamous vs. non-squamous), prior surgery (pneumonectomy), number of prior systemic anti-cancer therapy regimens, presence/absence of brain metastases at baseline, prior platinum therapy, prior anti-PD(L)1 treatment, and *HER2* TKD mutations status at baseline.
- Based on data from Study 21607, no clinically meaningful differences are anticipated in the efficacy of sevabertinib in the US vs. non-US NSCLC patients with *HER2* activating mutations.
- The data from Group E (N=55) aligns with and further supports the findings from Group D, demonstrating efficacy in a participant population that had received prior systemic therapy and progressed to *HER2*-targeted ADC therapy.

The FDA's Assessment:

FDA agrees with the Applicant’s efficacy results for the primary endpoint of confirmed ORR by BICR at both data cutoffs. Following review of the subgroup analyses of ORR at the updated data cutoff, FDA determined that given the limited data, there was insufficient evidence of efficacy in patients with non-TKD mutations or in patients with squamous histology, with extremely limited numbers of patients in both groups. Four patients with squamous histology were included in Group D (with one responding patient); no patients with squamous histology were included in Group E. Two of eight patients with non-TKD mutations in Group D demonstrated an objective response, and one of three patients with non-TKD mutations in Group E demonstrated an objective response. Therefore, the primary efficacy population was limited to include only patients with both TKD mutations and non-squamous histology. The updated results for this revised population are presented in **Table 41** below. Among 70 patients in Group D, the confirmed ORR by BICR was 71% (95% CI: 59, 82). Among 52 patients in Group E, the confirmed ORR by BICR was 38% (95% CI: 25, 53).

Table 41. Updated Primary Analysis of ORR by BICR in the Revised Population

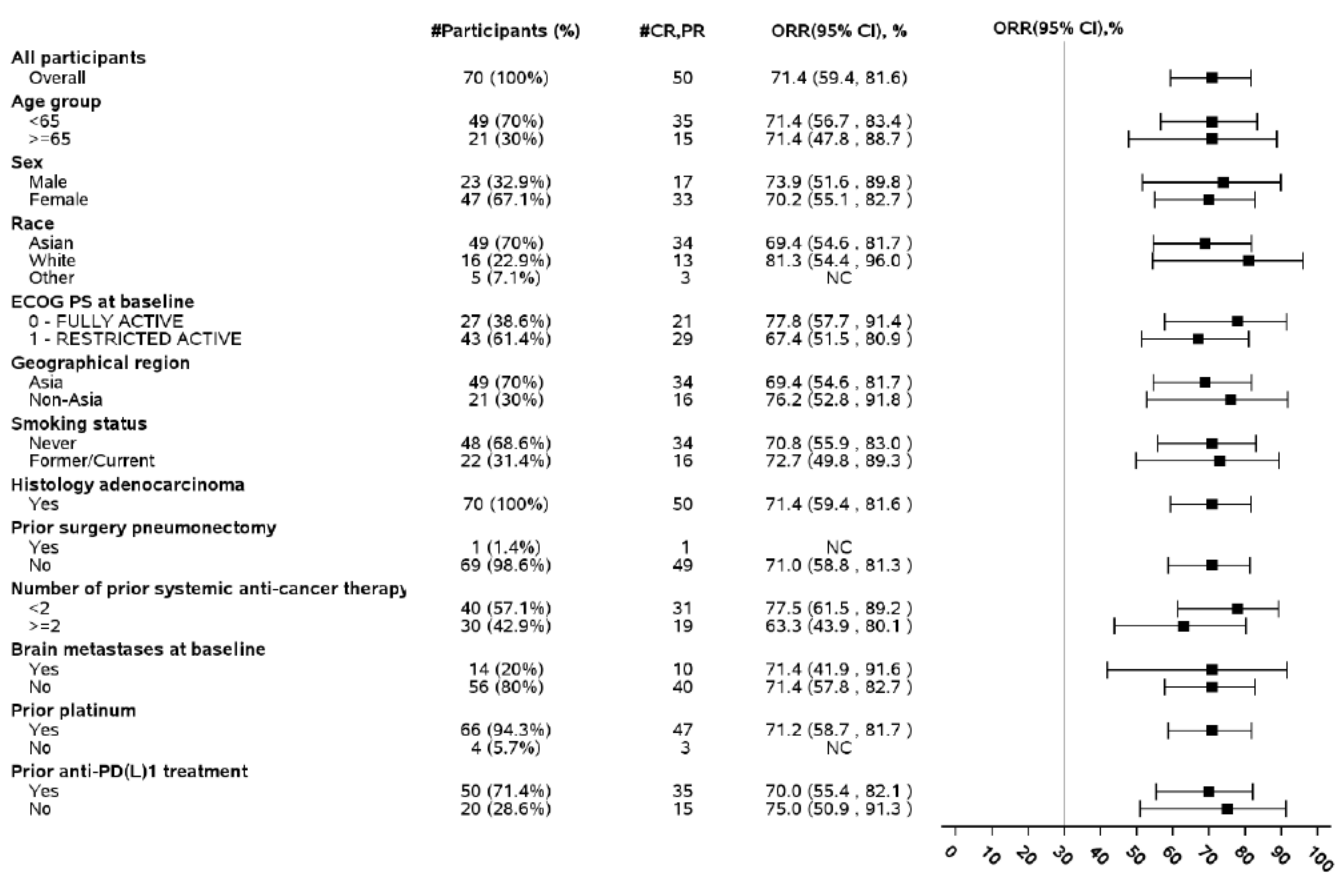
	Group D – HER2 ADC Naïve N=70	Group E – Post HER2 ADC N=52
Best overall response, n (%)		
Complete response (CR)	2 (2.9)	3 (6)
Partial response (PR)	48 (69)	17 (33)
Stable disease (SD)	13 (19)	23 (44)
Progressive disease (PD)	4 (6)	5 (10)
Not evaluable (NE)	3 (4.3)	4 (8)
Confirmed ORR, n (%) [95% CI]	50 (71) [59, 82]	20 (38) [25, 53]

CR = Complete response, ORR = Objective response rate, NE = Not evaluable; requirement of CR/PR/SD/PD not met.

Source: FDA reviewer’s analyses

ORR results in Group D were consistent across prespecified subgroups. ORR results in Group E were generally consistent across subgroups, however, limited number of patients and responses in each subgroup resulted in wide confidence intervals. These subgroup results are considered exploratory and should be interpreted with caution, particularly those with fewer patients or responses.

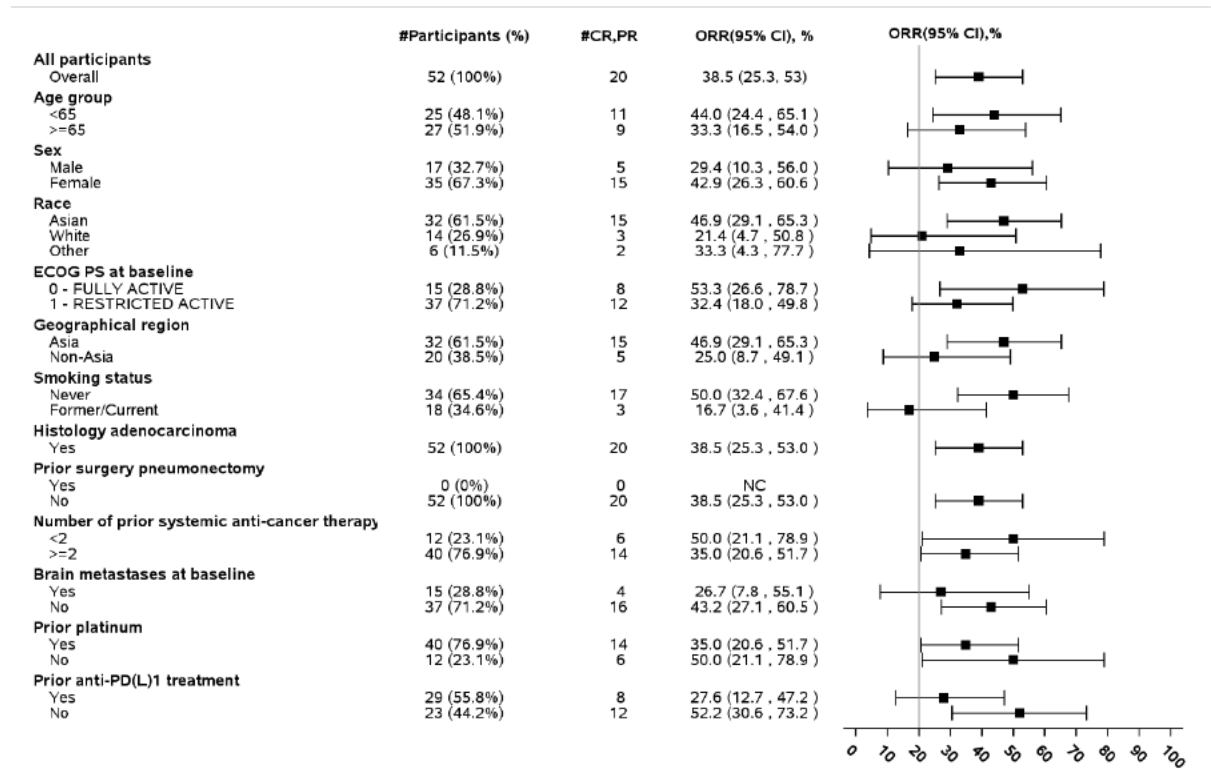
Figure 10. Updated Subgroup Analysis of ORR by BICR, Group D



CR = Complete Response, PR= Partial Response, 95% CI by exact binomial calculation.
 NC: not calculable due to number of participants in subgroup <10% of total number of participants in respective treatment group.

Source: Updated Tables by Applicant for FDA IR on 5Sep2025 (SN0040), Figure 8.2.1.1

Figure 11. Updated Subgroup Analysis of ORR by BICR, Group E



CR = Complete Response, PR= Partial Response, 95% CI by exact binomial calculation.
 NC: not calculable due to number of participants in subgroup <10% of total number of participants in respective treatment group.

Source: Updated Figures by Applicant for FDA IR on 5Sep2025 (SN0040), Figure 8.2.1.1

Data Quality and Integrity

Data:

See the Applicant’s Position below.

The Applicant’s Position:

Dedicated quality assurance and quality control systems were implemented to assure the quality of the data. No issues relating to data integrity or quality were identified for Study 21607.

The FDA’s Assessment:

During the review, the Applicant identified a data discrepancy regarding the TKD mutation status for patient (b) (6). This patient was initially reported by the local site (54001) as having a non-TKD mutation, however, it was incorrectly recorded in the eCRF and consequently

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

misreported in the submitted data. The correction resulted in a change to the revised population in Group D, increasing from 69 to 70 patients. The Applicant documented this issue in a cover letter submitted to the FDA on July 18, 2025 (SN0023) and subsequently formally corrected this discrepancy in the response document and updated USPI, which were submitted on September 10, 2025 (SN0037). FDA notes that the correction of TKD mutation status also applied to the HER2 genetic alteration status for this patient ^{(b) (6)} changing from HER2 point mutations to YVMA.

Efficacy Results – Secondary and other relevant endpoints

Data:

An analysis of all secondary endpoints was performed at the time of the primary endpoint analysis (14 OCT 2024). The secondary endpoints included ORR by investigator assessment, DCR, DOR, and PFS by BICR and investigator assessments, and OS. The other efficacy endpoint, TTR, was also analyzed by BICR and investigator assessments.

An analysis of ORR and DCR by investigator assessment and DOR using a database cut-off date of 28 MAR 2025 was also performed in Groups D and E, when all ongoing responders in Groups D and E had reached at least six months of follow-up on DOR. These results are summarized below, with an extra section added to present the updated data for Groups D and E for the FAS.

DOR by BICR was analyzed for the subset of participants with confirmed CR or PR. A summary is provided for the following participants:

- **“Updated data Confirmed Responders”**: Updated results providing cumulative data up to 28 MAR 2025 for the participants with a confirmed response by 14 OCT 2024 (the database cut-off date for the previous Clinical Study Report B003047):
 - N=49 in Group D
 - N=19 in Group E
- **“All Responders”**: Additional results for all participants with confirmed CR or PR as of the database cut-off date 28 MAR 2025:
 - N=52 in Group D
 - N=21 in Group E

Results as of the original cut-off date of 14 OCT 2024 (including ORR by investigator assessment, DOR, TTR, PFS, and OS) are available in the section below the updated data.

Updated results as of 28 MAR 2025:

ORR – as of 28 MAR 2025

Based on the investigator assessment, 51 of the 81 participants in Group D (FAS) achieved a confirmed response, resulting in an ORR of 63.0% (95% CI: [51.5%, 73.4%]). The responders included 1 participant (1.2%) with a CR and 50 (61.7%) with a PR (**Table 42**).

Considering the responders and the non-responders, the concordance rate between BICR and investigator assessments, with an agreement rate of 69.14% for Group D, suggests reliable data consistency (*Module 5.3.5.2, B004166, Table 8.2.1/10 [Datasets ADRS and ADSL]*).

DCR – as of 28 MAR 2025

The DCR by BICR for Group D was 81.5% (95% CI: [71.3%, 89.2%]) (37). The DCR based on the investigator assessment was 84.0% (95% CI: [74.1%, 91.2%]) (**Table 42**), which was consistent with the result by BICR.

Table 42. ORR and DCR by Investigator Assessment – Group D, as of 28 MAR 2025 (FAS)

Best overall response (RECIST 1.1)	Group D N=81
ORR, n (%) ^a [95% CI]	51 (63.0%) [51.5%, 73.4%]
DCR, n (%) ^b [95% CI]	68 (84.0%) [74.1%, 91.2%]
CR	1 (1.2%)
PR	50 (61.7%)
SD	19 (23.5%)
PD	10 (12.3%)
NE	1 (1.2%)
NA	0

CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; FAS=Full analysis set; MRI=Magnetic resonance imaging; N=Total number of participants; n=Number of participants within the category; NA=Not available; NE=Not evaluable; ORR=Objective response rate; PD=Progressive disease; PR=Partial response; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SD=Stable disease

CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

NE: Requirement of CR/PR/SD/PD not met.

NA: Participants who have no post-baseline tumor assessment, but who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated and were therefore considered evaluable (considered as non-responder).

a: Participants with confirmed CR or PR.

b: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

Source: Module 5.3.5.2, Report B004166, t_14_2_1_adrs_recist.sas (Datasets ADRS and ADSL)

DOR in Group D – 28 MAR 2025**Updated data Confirmed Responders:**

At the database cutoff date of 28 MAR 2025, the median DOR by BICR for participants with confirmed CR or PR in Group D by 14 OCT 2024 (N=49) was 9.2 months (95% CI: [5.8, 15.0]) in the FAS (**Table 43**), with a median follow-up time of 6.8 months from initial radiological response (Module 5.3.5.2, B004166, Table 8.2.2/5 [Datasets ADTTE and ADSL]).

Of the 49 responders, 27 participants (55.1%) had an observed DOR of ≥ 6 months, 12 (24.5%) had an observed DOR of ≥ 9 months, and 9 (18.4%) had an observed DOR of ≥ 12 months (Module 5.3.5.2, B004166, Table 8.2.2/8 [Datasets ADTTE and ADSL]).

Based on the Kaplan-Meier method, 64.1% of responders were estimated to have a DOR of ≥ 6 months after initial radiological response, and 51.0% and 42.5% of the responders were estimated to be still responding at 9 months and 12 months, respectively (**Table 43**).

Of the responders, 21 participants (42.9%) were censored (**Table 43**), with 76.2% of censored participants having no documented radiological PD or death up to the date of last tumor

assessment (*Module 5.3.5.2, B004166, Table 8.2.2/9 [Datasets ADTTE and ADSL]*). Therefore, the median DOR is subject to change with longer follow-up of the responders who showed no evidence of radiological PD or death as of the database cut-off date.

All Responders:

The median DOR for all participants with confirmed CR or PR in Group D (N=52) by BICR as of 28 MAR 2025 based on the Kaplan-Meier estimate was 9.2 months (95% CI: [6.3, 15.0]) (**Table 43**), with a median follow-up time of 6.5 months from initial radiological response (*Module 5.3.5.2, B004166, Table 8.2.3/5 [Datasets ADTTE and ADSL]*).

Of the 52 responders, 28 participants (53.8%) had an observed DOR of ≥ 6 months, 13 (25.0%) had an observed DOR of ≥ 9 months, and 9 participants (17.3%) had an observed DOR of ≥ 12 months as of the database cut-off date (*Module 5.3.5.2, B004166, Table 8.2.3/8 [Datasets ADTTE and ADSL]*).

Based on the Kaplan-Meier method, 65.6% of responders were estimated to have a DOR of ≥ 6 months after initial radiological response, and 52.8% and 44.0% of the responders were estimated to be still responding at 9 months and 12 months, respectively (**Table 43**).

Of the responders, 24 participants (46.2%) were censored (**Table 43**), with 79.2% of censored participants having no documented radiological PD or death up to the date of last tumor assessment (*Module 5.3.5.2, B004166, Table 8.2.3/9 [Datasets ADTTE and ADSL]*).

The median DOR based on investigator assessment was 8.2 months (95% CI: [5.5, 12.2]), which was consistent with the BICR assessment of response (9.2 months (95% CI: [6.3, 15.0]) (**Table 43**).

The Kaplan-Meier curves for DOR by BICR in Group D are shown in **Figure 12** and the Swimmer plots in **Figure 13**.

Table 43. DOR by BICR and Investigator Assessment – Group D, as of 28 MAR 2025 (FAS)

	BICR			Investigator
	As of 14 OCT 2024 (for reference) ^a	Updated data Confirmed Responders ^b	All Responders as of 28 MAR 2025 ^c	All Responders as of 28 MAR 2025 ^c
N	49	49	52	51
Number (%) of participants with event				
Death	20 (40.8%)	28 (57.1%)	28 (53.8%)	35 (68.6%)
First progression	2 (4.1%)	2 (4.1%)	2 (3.8%)	0 (0%)
Number (%) of participants censored	18 (36.7%)	26 (53.1%)	26 (50.0%)	35 (68.6%)
25th percentile [95% CI], months	29 (59.2%)	21 (42.9%)	24 (46.2%)	16 (31.4%)
Median [95% CI], months	4.3 [3.6, 5.5]	5.2 [3.9, 6.3]	5.2 [3.9, 6.8]	4.3 [2.8, 5.5]
75th percentile [95% CI], months	6.8 [5.2, 15.0]	9.2 [5.8, 15.0]	9.2 [6.3, 15.0]	8.2 [5.5, 12.2]
Range (including censored values), months	A [9.2, A]	15.9 [12.6, A]	15.9 [12.6, A]	17.6 [10.9, A]
Range (without censored values), months	(1.3** - 21.5**)	(1.3** - 25.7**)	(1.3** - 25.7**)	(1.4** - 25.7**)
DOR rate at Month 3 [95% CI]	(2.6 - 15.0)	(2.6 - 24.1)	(2.6 - 24.1)	(2.5 - 25.1)
Month 6 [95% CI]	0.934 [0.861, 1.000]	0.936 [0.866, 1.000]	0.940 [0.874, 1.000]	0.839 [0.736, 0.941]
Month 9 [95% CI]	0.558 [0.382, 0.734]	0.641 [0.499, 0.782]	0.656 [0.519, 0.794]	0.569 [0.429, 0.708]
Month 12 [95% CI]	0.472 [0.287, 0.657]	0.510 [0.357, 0.663]	0.528 [0.378, 0.679]	0.457 [0.315, 0.600]
	0.425 [0.237, 0.613]	0.425 [0.258, 0.592]	0.440 [0.272, 0.608]	0.374 [0.230, 0.519]

BICR=Blinded independent central review; CI=Confidence interval; DOR=Duration of response; FAS=Full analysis set; N=Number of participants

** Censored observation

A: Value cannot be estimated due to censored data.

Median, percentile, timepoint DOR rate and 95% CIs were calculated using Kaplan-Meier estimates.

The 95% CIs for the median and percentiles were calculated using a log-log transformation, and the 95% CIs for the timepoint DOR rate were calculated using a linear (identity) transformation.

a: Results from the database cut-off date 14 OCT 2024, provided as a reference (ie, results from the previous clinical study report B003047), see **Table 46**.

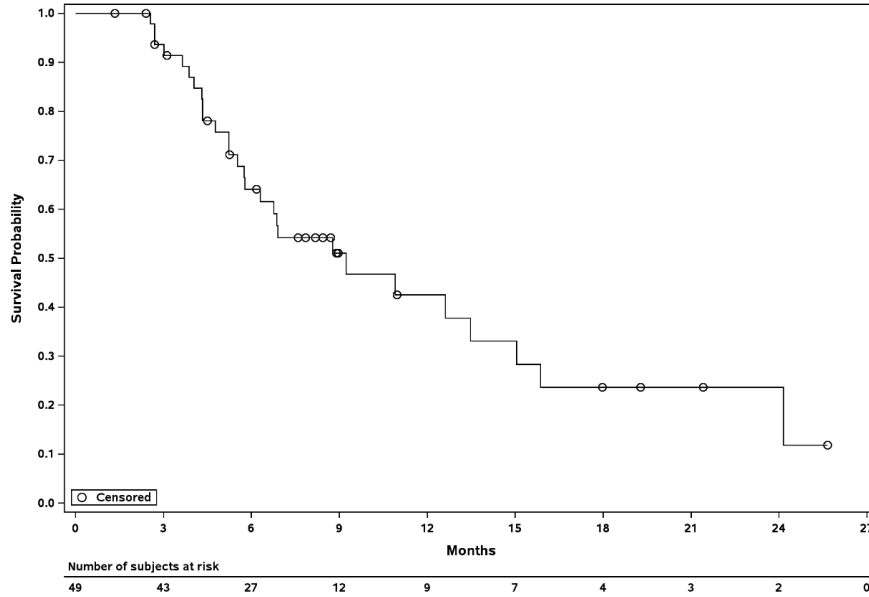
b: Updated results providing cumulative data up to 28 MAR 2025, for those participants with a confirmed response as of 14 OCT 2024.

c: Results for all responders as of the database cut-off date 28 MAR 2025.

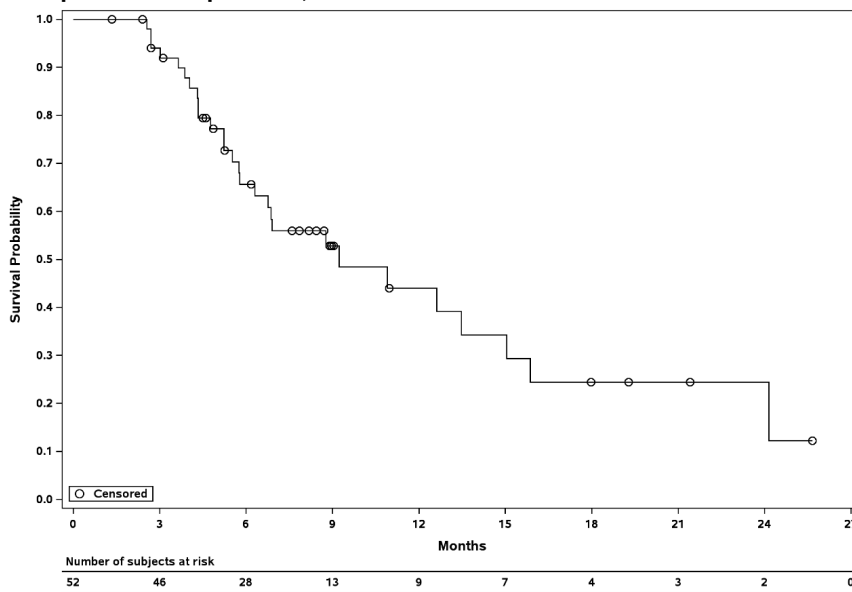
Source: Module 5.3.5.2, Report B004166, t_14_2_2_tte_dorkm14.sas, t_14_2_2_tte_dorkm28.sas (Datasets ADTTE and ADSL)

Figure 12. Kaplan-Meier Curve of DOR by BICR – Group D, as of 28 MAR 2025 (FAS – Subset of Participants With Confirmed PR or CR)

Group D – Updated data Confirmed Responders, N=49^a



Group D – All Responders, N=52^b



BICR=Blinded independent central review; CR=Confirmed response; DOR=Duration of response; FAS=Full analysis set; N=Number of participants; PR=partial response

At-risk participants were calculated as at start of timepoint.

a: Updated results providing cumulative data up to 28 MAR 2025, for those participants with a confirmed response as of 14 OCT 2024.

b: Results for all responders as of the database cut-off date 28 MAR 2025.

Source: Module 5.3.5.2, Report B004166, f_14_2_2_tte_dorkm14.sas, f_14_2_2_tte_dorkm28.sas (Datasets ADTTE and ADSL)

Figure 13. Swimmer Plot for DOR by BICR – Group D, as of 28 MAR 2025 (FAS – Subset of Participants With Confirmed PR or CR)

Group D – Updated data Confirmed Responders, N=49^a

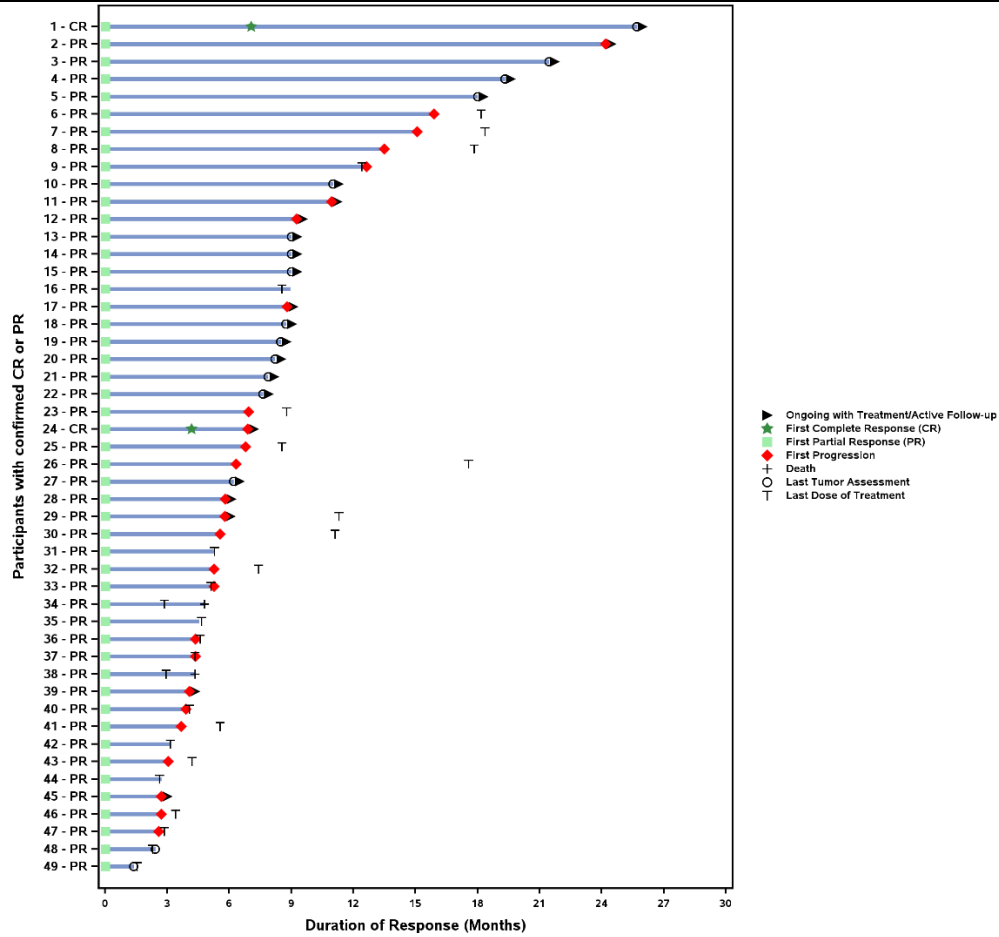
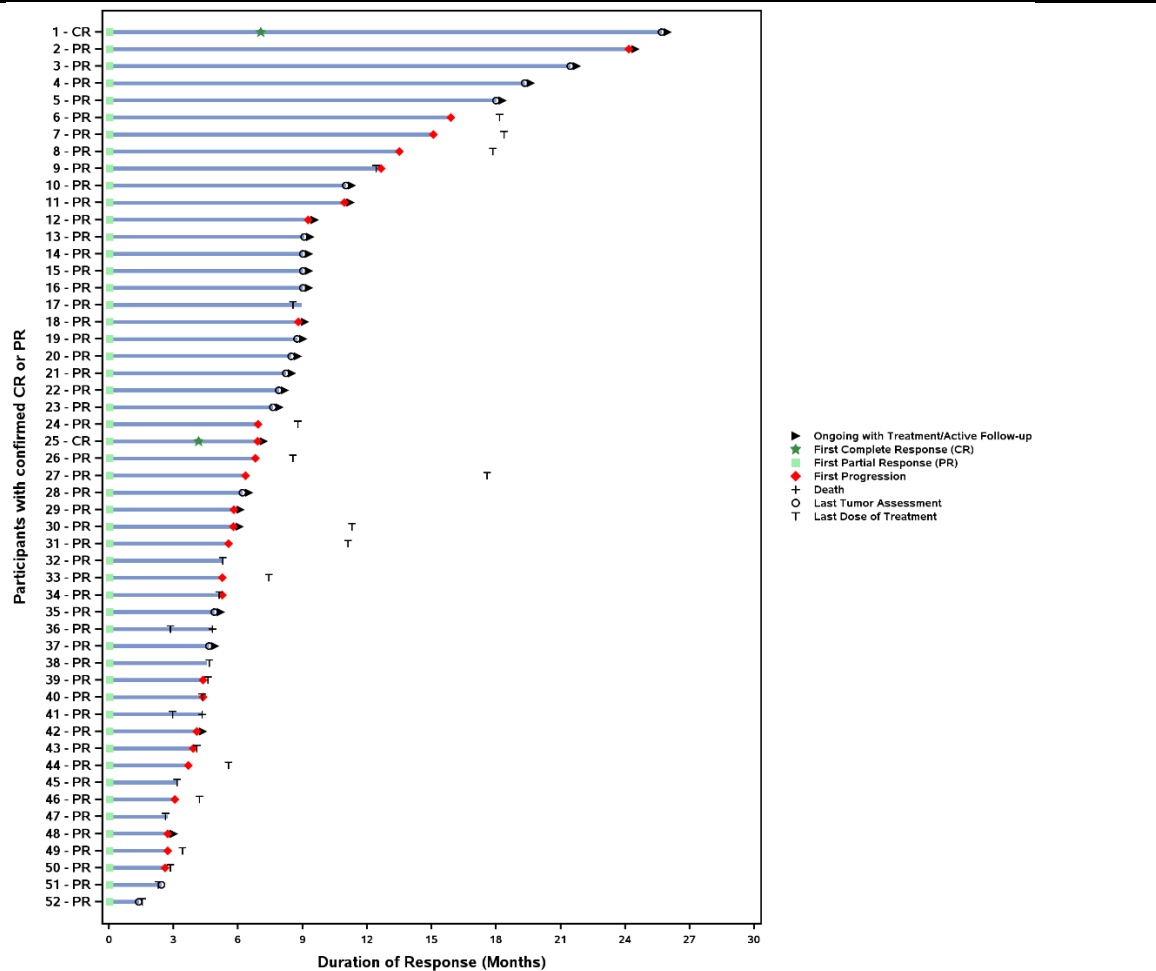


Figure 13. Swimmer Plot for DOR by BICR – Group D, as of 28 MAR 2025 (FAS – Subset of Participants With Confirmed PR or CR)

Group D – All Responders, N=52^b



BICR=Blinded independent central review; CR=Complete response; DOR=Duration of response; FAS=Full analysis set; N=Number of participants; PR=Partial response

X-axis is given as time in months since the first CR or PR.

a: Updated results providing cumulative data up to 28 MAR 2025, for those participants with a confirmed response as of 14 OCT 2024.

b: Results for all responders as of the database cut-off date 28 MAR 2025.

Source: Module 5.3.5.2, Report B004166, f_14_2_2_tte_dorswim14.sas, f_14_2_2_tte_dorswim28.sas (Datasets ADTE, ADDS, ADRS, ADSL)

Supportive efficacy results in Group E – 28 MAR 2025

Updated data Confirmed Responders:

In the supportive efficacy population Group E, for participants with confirmed CR or PR in by 14 OCT 2024 (N=19), the median DOR by BICR was 7.0 months (95% CI: [5.6, not estimable]) in the FAS (Table 44) with a median DOR follow-up time of 6.8 months from initial

radiological response. Of the 19 responders, 12 participants (63.2%) had observed DOR of ≥ 6 months, 6 (31.6%) had an observed DOR of ≥ 9 months, and 2 (10.5%) had an observed DOR of ≥ 12 months (*Module 5.3.5.2, B004166, Tables 8.2.2/5 and 8.2.2/8 [Datasets ADTTE and ADSL]*).

All Responders:

As of 28 MAR 2025, the ORR by investigator assessment was 38.2% (95% CI: [25.4%, 52.3%]), which was the same as the results by BICR (**Table 44**) in the FAS.

For all participants with confirmed CR or PR in Group E (N=21) by BICR as of 28 MAR 2025, the median DOR by BICR was 7.0 months (95% CI: [5.6, not estimable]) with a median DOR follow-up time of 6.8 months from initial radiological response. Of the 21 responders, 12 participants (57.1%) had an observed DOR of ≥ 6 months, 6 (28.6%) had an observed DOR of ≥ 9 months and 2 (9.5%) had an observed DOR of ≥ 12 months (*Module 5.3.5.2, B004166, Table 8.2.3/5 and 8.2.3/8 [Datasets ADTTE and ADSL]*). The median DOR by investigator assessment was 7.1 months (95% CI: [5.4, 16.4]) (**Table 44**).

Table 44. Summary of Efficacy Results in Study 21607 – Group E, as of 28 MAR 2025 (FAS)

	BICR				Investigator	
	As of 14 OCT 2024 (for reference) ^d N=55		Updated DOR Confirmed Responders ^e N=55		All Responders as of 28 MAR 2025 ^f N=55	
Response endpoints	n (%)	[95% CI]			n (%)	[95% CI]
ORR ^a	19 (34.5%)	[22.2, 48.6]			21 (38.2%)	[25.4, 52.3]
DCR ^b	38 (69.1%)	[55.2, 80.9]			36 (65.5%)	[51.4, 77.8]
CR	3 (5.5%)				0	
PR	16 (29.1%)				21 (38.2%)	
SD	25 (45.5%)				22 (40.0%)	
DOR	Months	[95% CI]	Months	[95% CI]	Months	[95% CI]
Median DOR (range) ^c	8.5 (1.0*–13.2*)	[4.1, A]	7.0 (1.0*–17.2*)	[5.6, A]	7.0 (1.0*–17.2*)	[5.6, A]

A=Value cannot be estimated due to censored data; BICR=Blinded independent central review; CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; DOR=Duration of response; FAS=Full analysis set; MRI=Magnetic resonance imaging; N=Total number of participants; n=Number of participants with an event; ORR=Objective response rate; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease

*: Censored observation

a: Participants with confirmed CR or PR.

b: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

c: Including censored values. Calculated for the subset of participants with confirmed CR or PR.

d: Results from the database cut-off date 14 OCT 2024, provided as a reference (ie, results from the previous clinical study report B003047), see Table 48

e: Updated DOR results providing cumulative data up to 28 MAR 2025, for those participants with a confirmed response as of 14 OCT 2024 (ORR, DCR, CR, PR, and SD results are the same as of 14 OCT 2024).

f: Results for all responders as of the database cut-off date 28 MAR 2025.

Notes:

RECIST version 1.1.

CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Response endpoints: Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

Time-to-event-endpoints: Median and 95% CIs were calculated using Kaplan-Meier estimates. The 95% CIs for the median were calculated using a log-log transformation.

Source: Module 5.3.5.2, Report B004166, t_14_2_1_adrs_recist.sas, t_14_2_2_tte_dorkm14.sas, t_14_2_2_tte_dorkm28.sas (Datasets ADRS, ADSL, and ADTTE)

Results as of 14 OCT 2024:

ORR – as of 14 OCT 2024

Based on the investigator assessment, 48 of the 81 participants in Group D (FAS) achieved a confirmed response, resulting in an ORR of 59.3% (95% CI: [47.8, 70.1]). The responders included 1 participant (1.2%) with a CR and 47 (58.0%) with a PR (Table 45).

Considering the responders and the non-responders, the concordance rate between BICR and investigator assessments, with an agreement rate of 71.60% for Group D, suggests reliable data consistency (Module 5.3.5.2, B003047, Table 8.2.1/12 [Datasets ADSL and ADRS]).

DCR – as of 14 OCT 2024

The DCR by BICR for Group D was 81.5% (95% CI: [71.3, 89.2]) (Table 39). The DCR based on the investigator assessment was 84.0% (95% CI: [74.1, 91.2%]), which was consistent with the result by BICR (Table 45).

Table 45. ORR and DCR by Investigator Assessment – Group D, as of 14 OCT 2024 (FAS)

Best overall response (RECIST 1.1)	Investigator assessment N=81 (100%)
ORR, n (%) ^a [95% CI]	48 (59.3%) [47.8%, 70.1%]
DCR, n (%) ^b [95% CI]	68 (84.0%) [74.1%, 91.2%]
CR	1 (1.2%)
PR	47 (58.0%)
SD	22 (27.2%)
PD	10 (12.3%)
NE	1 (1.2%)
NA	0
NA (ongoing)	0

CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; FAS=Full analysis set; MRI=Magnetic resonance imaging; n=Number of participants within the category; NA=Not available; NE=Not evaluable; ORR=Objective response rate; PD=Progressive disease; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease.

CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

NE: Requirement of CR/PR/SD/PD not met.

NA: Participants who have no post-baseline tumor assessment, but who discontinued due to a drug-related toxicity, death or progression by clinical judgment before disease was re-evaluated and were therefore considered evaluable (considered as non-responder).

NA (ongoing): Participants who have no post-baseline tumor assessment and are considered as 'ongoing'.

a: ORR: Participants with confirmed CR or PR.

b: DCR: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

Source: Module 5.3.5.2, Report B003047, t_14_2_1_adrs_recist.sas (Datasets ADRS and ADSL)

Time-to-event endpoints – as of 14 OCT 2024

DOR – as of 14 OCT 2024

The median DOR by BICR in Group D, based on Kaplan-Meier estimate from the subset of participants with confirmed CR or PR (N=49), was 6.8 months (95% CI: [5.2, 15.0]) in the FAS,

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with a median DOR follow-up time of 4.3 months from initial radiological response (Table 46). Of the 49 responders, 13 participants (26.5%) had an observed DOR of ≥ 6 months, 10 participants (20.4%) had an observed DOR of ≥ 9 months, and 8 participants (16.3%) had an observed DOR of ≥ 12 months, as of the database cut-off date (*Module 5.3.5.2, B003047, Tables 8.2.2/3 and 8.2.2/2s1 [Datasets ADSL and ADTTE]*).

Based on the Kaplan-Meier method, 55.8% of responders were estimated to have a DOR of ≥ 6 months after initial radiological response, and 47.2% and 42.5% of the responders were estimated to be still responding at 9 months and 12 months, respectively.

Of the responders, 29 participants (59.2%) were censored, with 86.2% of censored participants having no documented radiological PD or death up to the date of last tumor assessment (Table 46). Therefore, the median DOR is subject to change with longer follow-up of the responders who showed no evidence of radiological PD or death as of the database cut-off date of 14 OCT 2024. When analyzed by study part, the median DOR was 9.2 months for the DE/BF/Expansion part, at a median follow-up time of 6.3 months from initial radiological response compared to the median DOR of 5.2 months for the Extension part, with a median follow-up time of 4.1 months (*Module 5.3.5.2, B003047, Tables 8.2.2/3, 8.2.2/3s1, 8.2.2/6 and 8.2.2/7 [Datasets ADSL and ADTTE]*).

The Kaplan-Meier curve for DOR by BICR in Group D is shown in Figure 14 and the Swimmer plot in Figure 15. The median DOR, based on investigator assessment, was 6.8 months (95% CI: [5.2, not estimable]), which was consistent with the BICR assessment of response (6.8 months (95% CI: [5.2, 15.0])) (Table 46).

TTR, PFS, and OS – as of 14 OCT 2024

Responses were achieved in a relatively short time in Group D; the median **TTR** of participants with confirmed CR or PR by BICR was 1.4 months (95% CI: [1.3, 1.4]), with a range of 1.1 months to 4.2 months. These results were consistent with the TTR assessed by the investigator (Table 47).

The median **PFS** in Group D was 7.1 months (95% CI: [6.5, 14.7]) by BICR and 7.5 months (95% CI: [6.6, 12.4]) by investigator assessment. As of the database cut-off date for the efficacy analyses, follow-up of participants was still limited for a mature **OS** analysis. The median OS was not reached in Group D, with 62 participants (76.5%) censored. The range in OS (including censored values) was 0.9 months to 24.3 months.

Table 46. DOR by BICR and Investigator Assessment – Group D, as of 14 OCT 2024 (FAS)

	BICR			Investigator
	DE/BF/Expansion	Extension	Total	Total
N	25	24	49	48
Number (%) of participants with event	13 (52.0%)	7 (29.2%)	20 (40.8%)	23 (47.9%)
Death	1 (4.0%)	1 (4.2%)	2 (4.1%)	0 (0.0%)
First progression	12 (48.0%)	6 (25.0%)	18 (36.7%)	23 (47.9%)
Number (%) of participants censored	12 (48.0%)	17 (70.8%)	29 (59.2%)	25 (52.1%)
25th percentile [95% CI], months	4.8 [2.6, 6.8]	4.3 [2.7, A]	4.3 [3.6, 5.5]	4.2 [2.8, 5.3]
Median [95% CI], months	9.2 [5.2, A]	5.2 [4.3, A]	6.8 [5.2, 15.0]	6.8 [5.2, A]
75th percentile [95% CI], months	A [13.5, A]	5.7 [5.2, A]	A [9.2, A]	A [9.7, A]
Range (including censored values), months	(2.6 - 21.5**)	(1.3** - 5.7)	(1.3** - 21.5**)	(1.4** - 21.5**)
Range (without censored values), months	(2.6 - 15.0)	(2.7 - 5.7)	(2.6 - 15.0)	(2.7 - 12.2)
DOR rate at Month 3 [95% CI]	0.920 [0.814, 1.000]	0.950 [0.854, 1.000]	0.934 [0.861, 1.000]	0.869 [0.772, 0.967]
Month 6 [95% CI]	0.648 [0.449, 0.846]	0.000 [A, A]	0.558 [0.382, 0.734]	0.508 [0.345, 0.672]
Month 9 [95% CI]	0.548 [0.337, 0.759]	0.000 [A, A]	0.472 [0.287, 0.657]	0.441 [0.274, 0.607]
Month 12 [95% CI]	0.493 [0.278, 0.708]	0.000 [A, A]	0.425 [0.237, 0.613]	0.407 [0.240, 0.573]

BICR=Blinded independent central review; CI=Confidence interval; DOR=Duration of response; DE/BF=Dose Escalation/Backfill; FAS=Full analysis set; N=Total number of participants

** censored observation

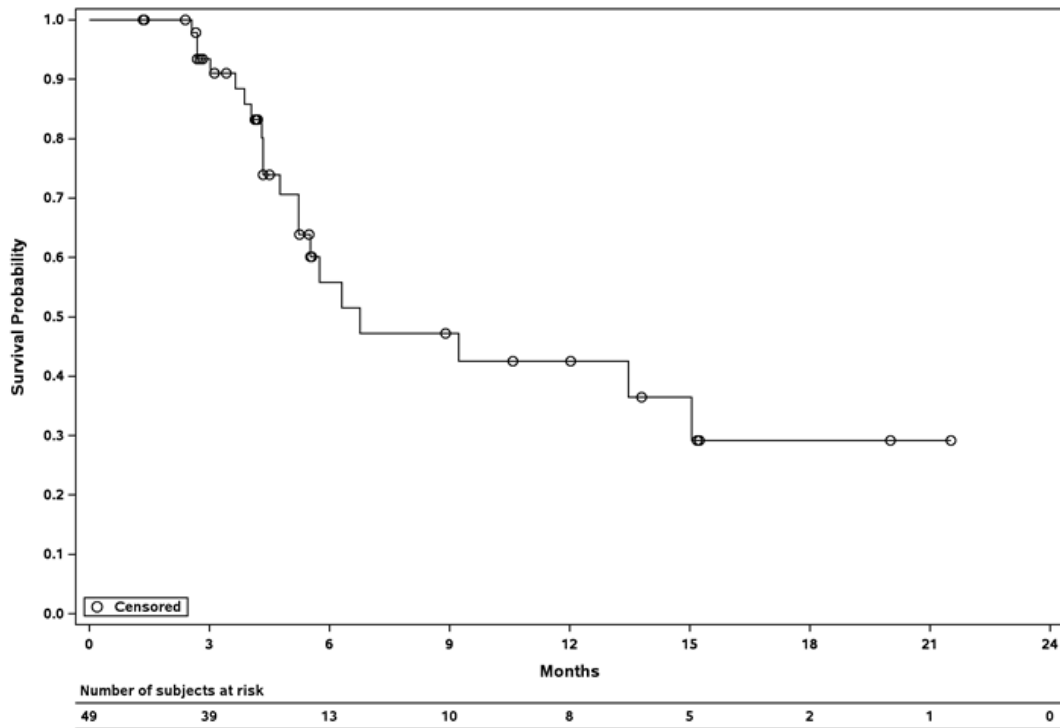
A: Value cannot be estimated due to censored data.

Median, percentile, timepoint DOR rate and 95% CIs were calculated using Kaplan-Meier estimates.

The 95% CIs for the median and percentiles were calculated using a log-log transformation, and the 95% CIs for the timepoint DOR rate were calculated using a linear (identity) transformation.

Source: Module 5.3.5.2, Report B003047, t_14_2_2_adtte_dor_km.sas (Datasets ADTTE and ADSL)

Figure 14. Kaplan-Meier Curve of DOR by BICR – Group D, as of 14 OCT 2024 (FAS – Subset of Participants With Confirmed PR or CR)

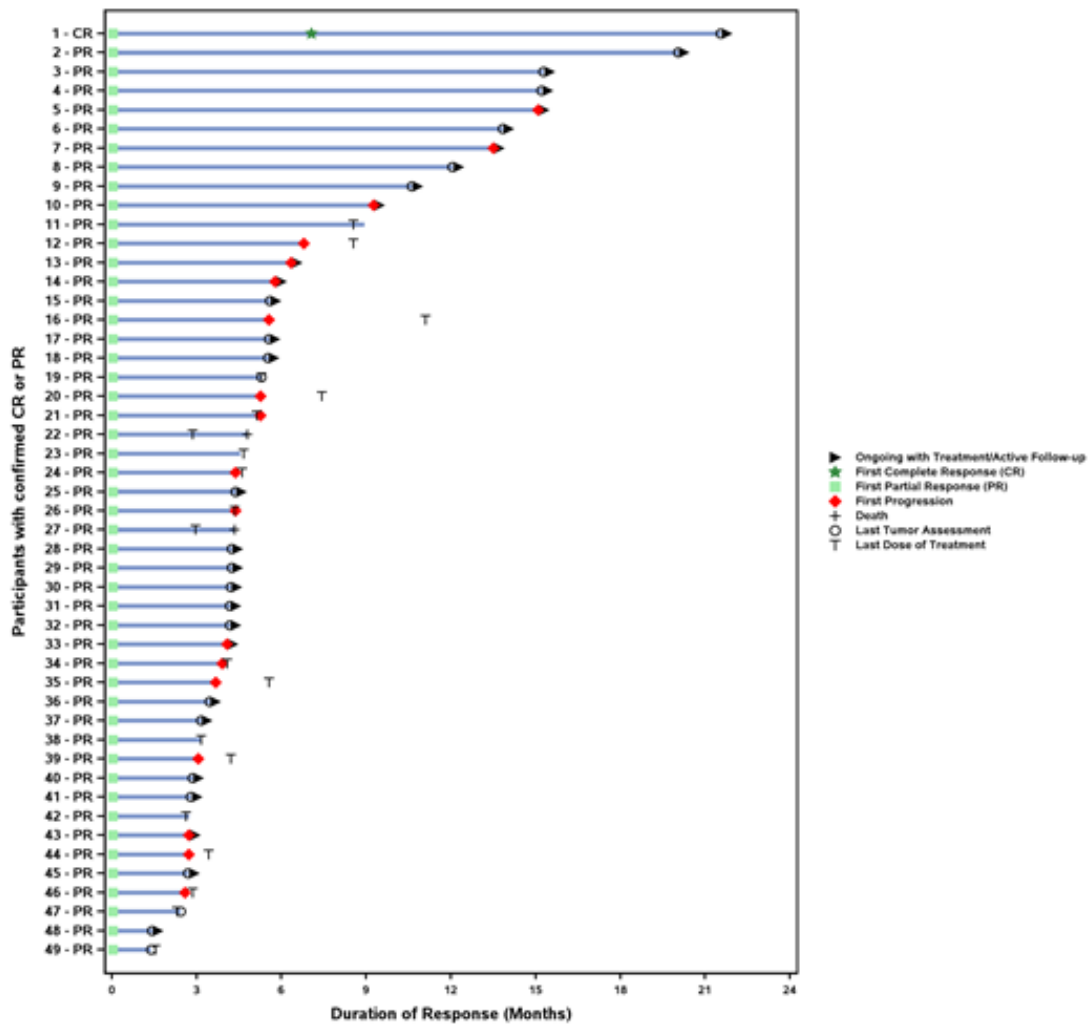


BICR=Blinded independent central review; CR=Complete response; DOR=Duration of response; FAS=Full analysis set; PR=Partial response

At-risk participants were calculated as at start of timepoint.

Source: Module 5.3.5.2, Report B003047, f_14_2_2_adtte_dor_km.sas (Datasets ADTTE and ADSL)

Figure 15. Swimmer Plot for DOR by BICR – Group D, as of 14 OCT 2024 (FAS – Subset of Participants With Confirmed PR or CR)



BICR=Blinded independent central review; CR=Complete response; DOR=Duration of response; FAS=Full analysis set; PR=Partial response

X-axis is given as time in months since the first CR or PR.

Source: Module 5.3.5.2, Report B003047, f_14_2_2_adtte_dor_swimmer.sas (Datasets ADTTE, ADDS, ADRS, and ADSL)

Table 47. Summary of TTR, PFS and OS by BICR and Investigator – Group D, as of 14 OCT 2024 (FAS)

	BICR			Investigator
	DE/BF/Expansion N=44	Extension N=37	Total N=81	Total N=81
Time-to-event endpoints (months)				
Median PFS (range) [95% CI]	8.1 (0.0*–22.8*) [6.5, 16.4]	6.6 (2.5–7.1) [5.5, A]	7.1 (0.0*–22.8*) [6.5, 14.7]	7.5 (0.0*–22.8*) [6.6, 12.4]
Median TTR (range) ^a [95% CI]	NA	NA	1.4 (1.1–4.2) [1.3, 1.4]	1.3 (1.1–10.2) [1.2, 1.4]
Median OS (range) [95% CI]	NA	NA	A (0.9*–24.3*) [15.4, A]	A (0.9*–24.3*) [15.4, A]

A=Value cannot be estimated due to censored data; BICR=Blinded independent central review; CI=Confidence interval; DE/BF=Dose Escalation/Backfill; FAS=Full analysis set; N=Total number of participants; NA=Not applicable; OS=Overall survival; PFS=Progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors; TTR=Time to response.

*: Censored observation

a: Calculated for the subset of participants with confirmed CR or PR.

Time to event-endpoints: Median and 95% CIs were calculated using Kaplan-Meier estimates. The 95% CIs for the median were calculated using a log-log transformation.

RECIST version 1.1.

Source: Module 5.3.5.2, Report B003047, t_14_2_2_adtte_ttr_km.sas (TTR), t_14_2_2_adtte_pfs_km.sas (PFS), t_14_2_2_adtte_os_km.sas (OS) (Datasets ADSL and ADTTE)

Supportive efficacy results in Group E – as of 14 OCT 2024

In the supportive efficacy population, Group E, the ORR by the investigator assessment was 38.2% (95% CI: [25.4, 52.3]), which was consistent with the results by BICR (34.5%; 95% CI: [22.2, 48.6]) (Table 48).

The median DOR by BICR was 8.5 months (95% CI: [4.1, not estimable]) in the FAS with a median DOR follow-up time of 4.1 months from initial radiological response. Of the 19 responders, 5 participants (26.3%) had observed DOR of ≥ 6 months, 3 participants (15.8%) had an observed DOR of ≥ 9 months, and 1 participant (5.3%) had an observed DOR of ≥ 12 months, as of the database cut-off. The median DOR by the investigator assessment was 9.5 months (95% CI: [4.1, A]) (Module 5.3.5.2, B003047, Tables 8.2.2/2, 8.2.2/1s1 and 8.2.2/3 [Datasets ADTTE, ADSL and ADFACE]).

The median PFS was 5.4 months (95% CI: [4.1, 9.7]) by BICR and 6.5 months (95% CI: [4.2, 10.7]) by the investigator assessment. The median OS was 12.9 months (95% CI: [11.1, not estimable]), with 41 participants (74.5%) censored. The range in OS (including censored values) was 1.9 months to 14.9 months.

Table 48. Summary of Efficacy Results in Study 21607 – Group E, as of 14 OCT 2024 (FAS)

	Blinded Independent Central Review						Investigator	
	DE/BF/Expansion N=34		Extension N=21		Total N=55		Total N=55	
Response endpoints	n (%)	[95% CI]	n (%)	[95% CI]	n (%)	[95% CI]	n (%)	[95% CI]
ORR ^a	12 (35.3%)	[19.7, 53.5]	7 (33.3%)	[14.6, 57.0]	19 (34.5%)	[22.2, 48.6]	21 (38.2%)	[25.4, 52.3]
DCR ^b	21 (61.8%)	[43.6, 77.8]	17 (81.0%)	[58.1, 94.6]	38 (69.1%)	[55.2, 80.9]	35 (63.6%)	[49.6, 76.2]
CR	3 (8.8%)		0		3 (5.5%)		0	
PR	9 (26.5%)		7 (33.3%)		16 (29.1%)		21 (38.2%)	
SD	13 (38.2%)		12 (57.1%)		25 (45.5%)		22 (40.0%)	
Time-to-event endpoints	Months	[95% CI]	Months	[95% CI]	Months	[95% CI]	Months	[95% CI]
Median DOR (range) ^c	A (1.0*–13.2*)	[4.1, A]	A (1.1*–4.2*)	[2.7, A]	8.5 (1.0*–13.2*)	[4.1, A]	9.5 (1.2*–13.2*)	[4.1, A]
Median PFS (range)	5.3 (0.0*–14.5*)	[3.9, 8.1]	A (1.1–5.5*)	[4.1, A]	5.4 (0.0*–14.5*)	[4.1, 9.7]	6.5 (0.0*–14.5*)	[4.2, 10.7]
Median TTR (range) ^c	NA		NA		1.3 (1.1–2.7)	[1.2, 1.3]	1.3 (1.1–5.5)	[1.3, 1.4]
Median OS (range)	NA		NA		12.9 (1.9*–14.9*)	[11.1, A]	12.9 (1.9*–14.9*)	[11.1, A]

A=Value cannot be estimated due to censored data; CI=Confidence interval; CR=Complete response; CT=Computed tomography; DCR=Disease control rate; DE/BF=Dose Escalation/Backfill; DOR=Duration of response; FAS=Full analysis set; MRI=Magnetic resonance imaging; N=Total number of participants; n=Number of participants with an event; NA=Not available; ORR=Objective response rate; OS=Overall survival; PFS=Progression-free survival; PR=Partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=Stable disease; TTR=Time to response.

*: Censored observation

a: Participants with confirmed CR or PR.

b: Participants with confirmed CR or confirmed PR or SD for at least 12 weeks.

c: Calculated for the subset of participants with confirmed CR or PR.

Notes:

CT/MRI scans for confirmation of PR or CR were performed no sooner than 4 weeks after the initial scan demonstrating PR or CR.

Response endpoints: Number (percentages) and 95% CI for percentages of participants. 95% CI by exact binomial calculation.

Time-to-event-endpoints: Median and 95% CIs were calculated using Kaplan-Meier estimates. The 95% CIs for the median were calculated using a log-log transformation.

RECIST version 1.1.

Source: Module 5.3.5.2, Report B003047, t_14_2_1_adrs_recist.sas, t_14_2_2_adtte_dor_km.sas, t_14_2_2_adtte_tr_km.sas, t_14_2_2_adtte_pfs_km.sas, and t_14_2_2_adtte_os_km.sas (Datasets ADRS, ADSL, and ADTTE)

The Applicant's Position:

Treatment with sevabertinib at a dose of 20 mg BID resulted in rapid, deep, and durable responses in advanced NSCLC patients with *HER2* activating mutations, who had received prior systemic therapy but were naïve to *HER2* ex20ins-targeted therapy.

Updated results as of 28 MAR 2025:

At the data cut-off date of 28 MAR 2025, the updated ORR and DOR results from Group D indicate that treatment with sevabertinib at 20 mg BID led to rapid, deep, and durable response in participants with advanced NSCLC harboring *HER2* activating mutations, who had received prior systemic therapy but were naïve to *HER2* ex20ins-targeted therapy. In addition, the results from Group E, consisting of participants who had received prior systemic therapy and had documented progression to *HER2*-targeted ADC, further support the efficacy observed in Group D.

The increased ORR and median DOR in the updated analysis highlights the potential clinical benefit of sevabertinib for participants with *HER2*-mutant NSCLC who have received a prior systemic therapy.

Group D, N=81 (FAS)

- For the subset of 49 participants with a confirmed response by 14 OCT 2024, the median DOR by BICR was 9.2 months (95% CI: [5.8, 15.0]), indicating the durable and mature follow-up data in Group D.
- For all 52 responders as of 28 MAR 2025, the confirmed ORR by BICR was 64.2% (95% CI: [52.8%, 74.6%]), exceeding the ORR of 60.5% reported for participants at the 14 OCT 2024 database cut-off date.

The median DOR by BICR of 9.2 months (95% CI: [6.3, 15.0]) of all responders was consistent with the results for the previous responders.

Group E, N=55 (FAS)

- For all 21 responders as of 28 MAR 2025, the confirmed ORR by BICR was 38.2% (95% CI: [25.4%, 52.3%]).
- The updated median DOR by BICR was 7.0 months (95% CI: [5.6, not estimable]) for both the 19 responders as of 14 OCT 2024 and all 21 responders.
- The observed ORR and the preliminary durability of response further support the findings from Group D.

Results as of 14 OCT 2024:

The median DOR by BICR was 6.8 months (range: 1.3 months to 21.5 months), with 55.8% of responders estimated to have a DOR of ≥ 6 months after initial radiological response. The

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censoring rate was 59.2%, with the majority of the censored participants having no documented radiological PD or death up to the date of last tumor assessment. The median DOR by investigator assessment was 6.8 months (range: 1.4 months to 21.5 months), which was consistent with the BICR assessment.

The durability of the treatment effect was supported by the longer median DOR in participants with a longer follow-up; in the DE/BF/Expansion part, the median DOR was 9.2 months (range: 2.6 months to 21.5 months) and 5.2 months (range: 1.3 to 5.7 months) in the Extension part.

Responses to sevabertinib treatment were achieved in a relatively short time in Group D with a median TTR of 1.4 months by BICR. The results for the other secondary endpoint analyses, including DCR (69.1% by BICR; 84.0% by investigator) and PFS (median of 7.1 months by BICR; 7.5 months by investigator) provide additional support for the primary analysis, with OS data pending maturity at the time of the database cut-off date. Furthermore, the supportive efficacy data from Group E, which showed a median DOR by BICR of 8.5 months (with a range of 1.0–13.2 months), aligns with and further supports findings from Group D in a participant population that had received prior systemic therapy and progressed to HER2-targeted ADCs.

The FDA's Assessment:

The updated results for DOR in the revised population are presented below. Among 50 responders in Group D, median DOR by BICR was 9.2 months (95% CI: 6.3, 15.0), with a slightly shorter median DOR follow-up of 9.0 months (95% CI: 8.2, 19.3). Among 20 responders in Group E, median DOR by BICR was 7.0 months (95% CI: 5.6, NR), with a median DOR follow-up of 9.7 months (95% CI: 6.8, NR).

Table 49. Updated Analysis of DOR by BICR in the Revised Population

	Group D – HER2 ADC Naïve N=70	Group E – Post HER2 ADC N=52
Responders, n	50	20
Events, n (%)	27 (54)	10 (50)
Death	1 (2.0)	1 (5)
First Progression	26 (52)	9 (45)
Censored, n (%)	23 (46)	10 (50)
Median [95% CI], months	9.2 [6.3, 15.0]	7.0 [5.6, NR]
Range, months	1.3+, 25.7+	1.0+, 17.2+
DOR ≥ 6 months, %	27 (54)	12 (60)
DOR ≥ 9 months, %	13 (26)	6 (30)
DOR ≥ 12 months, %	9 (18)	2 (10)

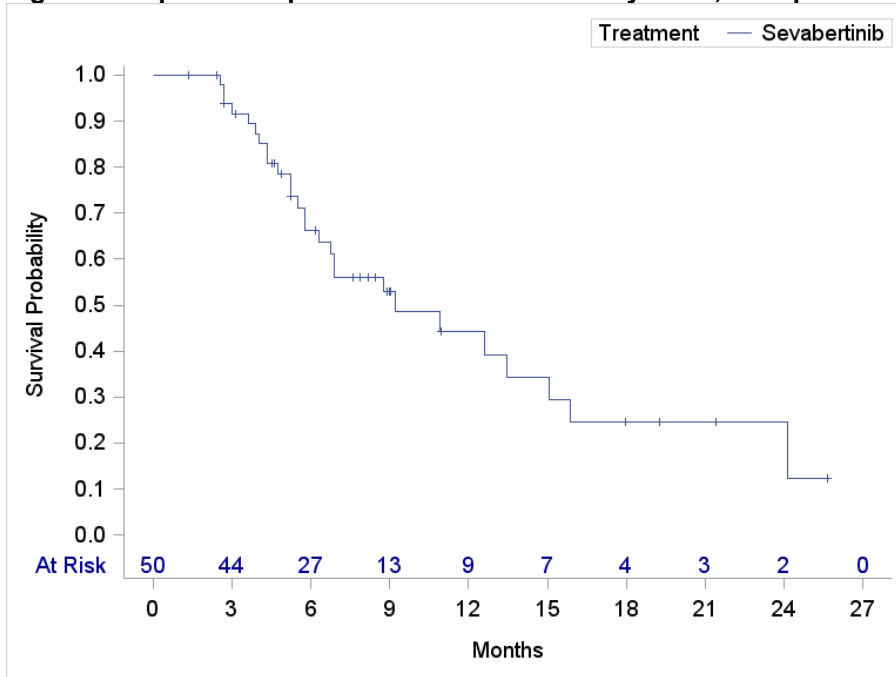
+ = ongoing response, NR = not reached

¹ Based on observed proportion of responders with DOR beyond landmark time.

DCO date: March 28, 2025

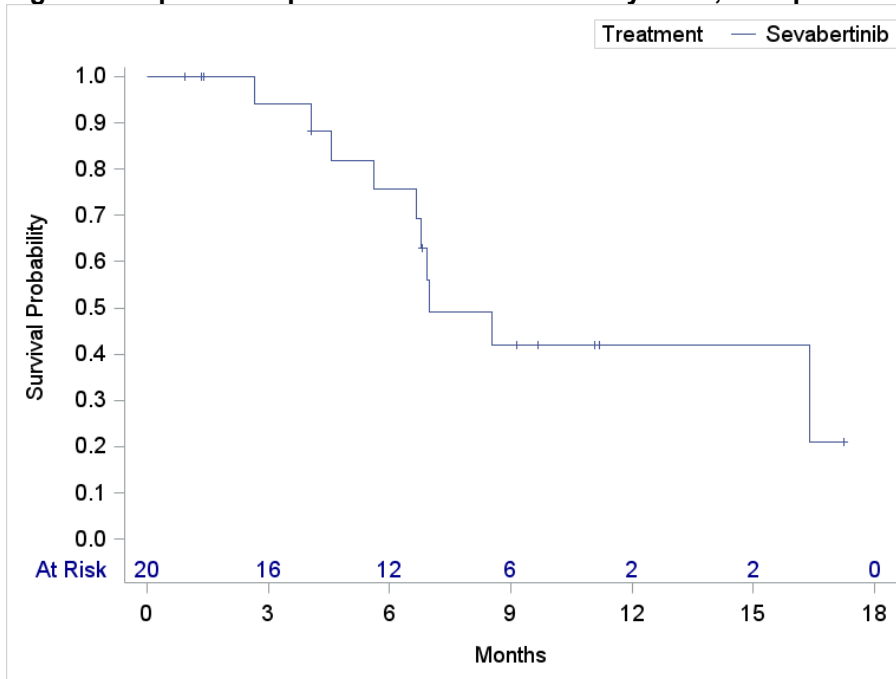
Source: FDA reviewer's analyses

Figure 16. Updated Kaplan-Meier Curve of DOR by BICR, Group D



Source: FDA reviewer's analyses

Figure 17. Updated Kaplan-Meier Curve of DOR by BICR, Group E



Only 13 patients remained at risk near the median, with 17 patients censored before reaching this point, some likely representing informative censoring. To assess the robustness of DOR estimates in Group D, FDA conducted three sensitivity analyses. In Sensitivity Analysis 1, patients censored by BICR due to new anticancer therapy (ACT) were treated as having an event at ACT initiation (n=4), resulting in a median DOR of 8.8 months (95% CI: 5.8, 12.6). In Sensitivity Analysis 2, patients censored by BICR for ongoing response after investigator-assessed progression were treated as having an event (n=6), resulting in a median DOR of 8.2 months (95% CI: 5.7, 11.0). In Sensitivity Analysis 3, all patients censored by BICR for ACT, ongoing response, and progression after more than one missing assessment were treated as having an event (n=11), resulting in a median DOR of 6.8 months (95% CI: 5.2, 9.2).

Although these sensitivity analyses may represent conservative scenarios, the results suggest that the DOR estimate is sensitive to additional events or censoring and should be interpreted with caution. Additional follow-up data would help confirm the durability of response and provide a more stable estimate of median DOR.

While the Applicant presents PFS results as supportive, given the single arm nature of the trial, the results of time-to-event endpoints in the absence of a comparator arm are challenging to interpret and are considered descriptive.

Dose/Dose Response

Data and the Applicant's Position:

Data collected in Study 21607 were used for population PK and exposure-response analyses. The results of these analyses are summarized in Section 6.3.2.

The FDA's Assessment:

Refer to Section 6.3.2.

Durability of Response

Data and the Applicant's Position:

See discussion of DOR as aforementioned under Secondary and other relevant endpoints.

The FDA's Assessment:

FDA agrees with the Applicant's position. See the preceding section for the updated DOR results.

Persistence of Effect

Data and The Applicant’s Position:

Participants in Study 21607 received sevabertinib until disease progression according to RECIST v1.1, unacceptable toxicity, or any other withdrawal criteria were met. The persistence of effect is reflected in the durability of response. See discussion of DOR as aforementioned under Secondary and other relevant endpoints.

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 COA (PRO) endpoints

Data and the Applicant’s Position:

Not applicable.

The FDA’s Assessment:

Not applicable.

Additional Analyses Conducted on the Individual Trial

Data and the Applicant’s Position:

Not applicable. Exploratory analysis of TTR is described in Section “Efficacy Results – Secondary and other relevant endpoints”.

The FDA’s Assessment:

Not applicable.

8.1.3. Integrated Review of Effectiveness

Data and the Applicant’s Position:

Not applicable. There is 1 clinical study assessing effectiveness and the results are presented in

Section 8.1.2.

The FDA's Assessment:

Refer to Section 8.1.5.

8.1.4. **Assessment of Efficacy Across Trials**

Data and Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.1.5. **Integrated Assessment of Effectiveness**

Data:

Results from the pivotal Study 21607, supporting the efficacy of sevabertinib in the treatment of patients with advanced NSCLC, whose tumors harbor *HER2* activating mutations, are provided in Section 8.1.2.

Applicant's Position:

The primary efficacy data supporting this application are from 81 participants treated with 20 mg BID sevabertinib who qualified for Group D in the Phase 1/2 Study 21607. This includes participants with advanced NSCLC whose tumors harbor *HER2* activating mutation and who received at least 1 prior line of systemic therapy but are naïve to *HER2* ex20ins-targeted therapy.

Treatment with sevabertinib 20 mg BID resulted in rapid, deep, and durable responses in this primary efficacy population, as assessed by ORR, DOR and TTR by BICR. The confirmed ORR assessed by BICR in Group D was 60.5% (FAS) as of 14 OCT 2024, with a median DOR of 6.8 months and a median TTR of 1.4 months. Updated data as of 28 MAR 2025 for Group D show a confirmed ORR of 64.2% and median DOR of 9.2 months, assessed by BICR. The increased ORR and median DOR in the updated analysis highlights the potential clinical benefit of sevabertinib for participants with *HER2*-mutant NSCLC who have received a prior systemic therapy.

The results for the other secondary endpoint analyses performed for Group D (including ORR and DOR by investigator assessment, DCR, and PFS) were consistent and provide additional

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support for the primary analysis. OS data are pending maturity at the time of the database cut-off dates.

The efficacy results in Group E from participants who had received prior systemic therapy and progressed to HER2-targeted ADC therapy further support the efficacy results observed in the primary efficacy population.

The FDA’s Assessment:

The primary efficacy data for this application are based on a revised population of 70 patients with non-squamous NSCLC with activating HER2 TKD mutations who were naïve to HER2-targeted therapy (Group D), and 52 patients who had received a prior HER2 ADC (Group E). The efficacy results demonstrated clinically meaningful and durable antitumor activity in this population, with a confirmed ORR of 71% (95% CI: 59, 82) as assessed by BICR in Group D. Among the 50 responders in Group D, the median DOR was 9.2 months (95% CI: 6.3, 15.0) with a median follow-up of 9.0 months. At least 54% of the responders in Group D had a confirmed response maintained for 6 months or longer. Although the DOR estimate was sensitive to different censoring scenarios, the overall durability of response demonstrated that sevabertinib provides a potential clinical benefit in this patient population with limited therapeutic options.

Among patients in Group E (n=52), the confirmed ORR was 38% (95% CI: 25, 53) with median DOR of 7.0 months (95% CI: 5.6, NR) and at least 60% of the responders in Group E had a confirmed response maintained for 6 months or longer. The evidence of efficacy was consistent across prespecified subgroups.

8.2. Review of Safety

Data:

The main safety analyses to support the proposed indication are based on the data from **Study 21607** (SOHO-01), a non-randomized, open-label, single-arm, multicenter, Phase 1/2 study in participants with advanced NSCLC harboring activating mutations in *HER2* and/or *EGFR*. The key safety findings from Study 21607 are presented in the following sections. An integrated analysis of safety was not performed, since no data from other clinical studies in cancer patients are available for this submission. All safety analyses were performed using the SAF, which included all participants who received at least 1 dose of sevabertinib. As of the database cut-off date, a total of 357 participants had started treatment and were included in the safety analyses.

For completeness, supportive safety data from 5 clinical pharmacology studies (Studies 22249, 22250, 22251, 22252, and 2253), conducted in 89 healthy participants to evaluate sevabertinib for DDI potential, mass balance, and the effect of food, is provided in the NDA Module 2.7.4.

The primary safety analysis population is Group D (N=81), which includes participants with

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advanced NSCLC harboring *HER2* activating mutations, who have received prior systemic therapy but were naïve to *HER2* ex20ins-targeted therapy and were treated with sevabertinib at 20 mg BID (RP2D). The **Whole Study 20 mg BID** (N=268) safety population includes all participants who received at least 1 dose of sevabertinib at 20 mg BID and the **Whole Study SAF** (N=357) safety population includes all participants who received at least 1 dose of sevabertinib at any dose level in Study 21607. These safety analysis populations include participants who received sevabertinib in the DE/BF cohorts and/or in the Dose Expansion/Dose Extension part of the study.

The proposed 3 safety populations (Group D, Whole Study 20 mg BID, and Whole Study SAF), including the planned number of participants in each safety population, were described in the briefing document provided in advance of the BTM meeting on 31 MAY 2024 (**Table 2**). The FDA indicated that the proposed 3 safety populations appear generally reasonable to be included in the NDA submission. Clinical efficacy and safety data of sevabertinib, as of 14 OCT 2024 (the database cutoff date of the anticipated initial NDA filing), were included in a briefing package for a Type B meeting dated 08 NOV 2024. The Agency’s feedback on the briefing package was received on 02 JAN 2025 and the Agency found the clinical efficacy and safety data reasonable to support an NDA filing.

The safety results in the following sections focus mostly on Group D and the Whole Study 20 mg BID population, receiving the RP2D throughout the study.

The Applicant’s Position:

The safety profile of sevabertinib was established by the pivotal Study 21607. Overall, the data from the Phase 1/2 study show that sevabertinib was generally well tolerated at the 20 mg BID dose, and the most common drug-related TEAEs were of low grade, reversible, monitorable, and manageable.

The FDA’s Assessment:

FDA generally agrees that the safety data provided allowed for a comprehensive review and adequate assessment of the safety profile. All FDA independent safety analyses were performed using the datasets submitted with the original application (with data cut-off [DCO] date of October 14, 2024).

FDA’s review of safety data to inform Section 6 labeling relied upon analyses of 136 patients with unresectable or metastatic NSCLC with *HER2* mutations who have received prior systemic therapy and who were naïve to prior *HER2* ADC (Group D) or had received prior anti-*HER2* therapy (Group E), who received the recommended dose of 20 mg PO BID (n=136). The pooled safety population, used to inform Section 5 of labeling, includes all patients in SOHO-01 with NSCLC treated at a dose of 20 mg BID (n=268).

Safety Review Approach

Data:

The safety profile of sevabertinib was assessed by standard approaches and measures: monitoring of AEs, laboratory evaluations (hematology, general chemistry, and urinalysis), measurement of vital signs, and recording of 12-lead ECGs. In addition, this safety summary includes subgroup analyses by age (<65 years vs. ≥65 years), sex (male vs. female), race (Asian vs. White vs. Other), and geographical region (Asia vs. non-Asia).

The primary safety population comprises of 81 participants who qualified for Group D in Study 21607 and were treated with sevabertinib at 20 mg BID (RP2D). In addition, safety data are provided from 268 participants receiving the 20 mg BID dose (Whole Study 20 mg BID population) and from 357 participants who received at least 1 dose of sevabertinib at any dose level in Study 21607 (Whole Study SAF) (Section 8.2).

The Applicant’s Position:

The safety data from 81 participants in the target indication population, together with data from 268 participants treated with the RP2D and 357 participants treated with any dose of sevabertinib, are sufficient to establish the safety profile for the proposed indication of sevabertinib as a treatment for patients with advanced NSCLC whose tumors have activating *HER2 (ERBB2)* mutations and who have received a prior systemic therapy. As agreed with the FDA, the Applicant will use the primary safety population to inform the Adverse Drug Reactions section of the USPI and the pooled safety population (20 mg BID) to inform the Warnings and Precautions section of the USPI.

The FDA’s Assessment:

FDA agrees that the safety analyses presented were comprehensive and allowed sufficient review of the safety data; however, FDA reviews all AEs regardless of attribution given the challenges assessing relatedness in the context of a single-arm trial. Therefore, FDA’s analyses report AEs regardless of attribution.

8.2.1. **Review of the Safety Database**

Overall Exposure

Data:

The extent of exposure to sevabertinib is summarized in **Table 50**. As of the database cut-off date for the submission (14 OCT 2024), a total of 357 participants with advanced NSCLC harboring activating mutations in *HER2* and/or *EGFR* have been exposed to sevabertinib in Study 21607.

Table 50. Study Drug Exposure in Study 21607 (SAF)

	Group D 20 mg BID N=81 (100%)	Whole Study 20 mg BID N=268 (100%)	Whole Study SAF N=357 (100%)
Overall time on treatment (including interruptions/ delays while excluding the washout)			
Time on treatment, months			
Mean (SD)	7.9 (5.4)	5.7 (4.4)	5.9 (4.5)
Median (min, max)	6.2 (0, 24)	4.8 (0, 24)	5.0 (0, 24)
Categories n (%)			
≤1 month	2 (2.5%)	17 (6.3%)	22 (6.2%)
>1 to 3 months	8 (9.9%)	58 (21.6%)	85 (23.8%)
>3 to 6 months	22 (27.2%)	99 (36.9%)	115 (32.2%)
>6 to 9 months	30 (37.0%)	54 (20.1%)	65 (18.2%)
>9 to 12 months	3 (3.7%)	9 (3.4%)	30 (8.4%)
>12 to 15 months	1 (1.2%)	11 (4.1%)	17 (4.8%)
>15 months	15 (18.5%)	20 (7.5%)	23 (6.4%)
Dose			
Actual dose per day, mg			
Mean (SD)	34.69 (8.16)	34.16 (8.23)	32.98 (10.26)
Median (min, max)	39.52 (7.4, 40.0)	39.23 (7.4, 40.0)	38.40 (7.4, 80.0)
Percent of the planned dose			
Mean (min, max)	86.71 (20.38)	85.40 (20.59)	86.44 (19.75)
Median (min, max)	98.51 (18.5, 100.0)	98.06 (18.5, 100.5)	99.09 (18.5, 101.8)
Total amount of dose, mg			
Mean (SD)	8368.64 (5967.26)	5842.28 (4730.83)	5749.94 (4746.80)
Median (min, max)	7400.00 (200.0, 28420.0)	4990.00 (120.0, 28420.0)	4920.00 (120.0, 28420.0)
BID=Twice daily; max=Maximum; min=Minimum; n=Number of participants within the category; N=Total number of participants SAF=Safety analysis set; SD=Standard deviation Source: Module 5.3.5.2, Report B003047, t_14_1_8_adexsum_trt_dur.sas and t_14_1_8_adexsum_dosage.sas (Datasets ADSL and ADEXSUM)			

The Applicant's Position:

As of the database cut-off date, the maximum time on sevabertinib treatment was 24 months across the 3 safety populations. The median treatment duration was 6.2 months in the primary safety population, Group D, and 4.8 months in the Whole Study 20 mg BID population. In the Whole Study SAF, including all treated participants from the start of the study (encompassing the DE/BF), the median treatment duration was 5.0 months.

The median daily dose was >39 mg in both Group D and the Whole Study 20 mg BID population, and the median percentage of the actual administered dose was >98% of the planned dose across the safety populations, indicating a high level of compliance with the study treatment.

The FDA's Assessment:

FDA conducted an independent analysis of treatment exposure, **Table 51**. Among Groups D + E,

the median duration of treatment was 5.7 months (range: 0.2-24.4 months), with 32% of patients treated for > 6 months and 15% of patients treated for > 12 months. In the pooled population, the median duration of treatment was 4.8 months (range 0.1-24.4 months), with 24% of patients treated for > 6 months and 12% of patients treated for > 12 months.

Table 51. Summary of Treatment Exposure

	Cohort Groups D + E	Pooled 20mg patients
	N = 136	N = 268
Duration of treatment (months)		
Median	5.7	4.8
Range	0.2 - 24	0.1-24
Duration of treatment (%)		
> 6 months	32	24
> 12 months	15	12

Source: FDA analysis of adae.xpt

Relevant characteristics of the safety population:

Data:

Demographics and the baseline cancer characteristics of the groups used for the safety analyses are presented in **Table 33** and **Table 35**, respectively.

The Applicant's Position:

Overall, more female than male participants received sevabertinib in Study 21607, and the majority of the participants were Asian across the safety populations (**Table 33**). The median age ranged from 60.0 years in Group D to 62.0 years in the Whole Study 20 mg BID and the Whole Study SAF populations.

Overall, the baseline cancer characteristics in Study 21607 were representative of the patient population with locally advanced or metastatic NSCLC and were consistent across the safety populations (**Table 35**). At baseline, the majority of the participants in all safety populations never had any smoking habits, had an ECOG performance status of 1, had Stage IV disease, and had no brain metastases. All participants in Group D had a *HER2* activating mutation and had received at least 1 prior line of systemic anti-cancer therapy, as per protocol.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. FDA's independent analysis of the

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demographics of the primary and pooled safety populations is presented in **Table 52**. The key demographics of the primary safety population are largely representative of the target patient population with two notable exceptions. First, only 8% of patients in the combined Group D + E and 4.9% of patients in the pooled safety population were enrolled from North American sites (all United States). Second, the Black or African American population of patients was underrepresented in this study. Review of the SEER database for patients with NSCLC from 2007 to 2018 identified that 12.1% of the population was Black (Primm 2022). Among 559 patients with NSCLC with HER2 mutations identified in a review of US Flatiron database, 7.2% were African-American (Le 2024). Among 144 patients from the same review with NSCLC with HER2 mutations in the TKD domain receiving first-line treatment, 7.6% were African American. There were 3.7% Black or African American patients in the combined Group D + E and only 2.2% in the pooled safety population in SOHO-01. Please refer to Section 13 for a discussion on the need for post-marketing characterization of safety and effectiveness in a population representative of the United States.

Table 52. Demographic Characteristics of the Safety Population

	Group D + E N = 136 n (%)	Pooled 20mg BID N = 268 n (%)
Age		
<65	82 (60)	153 (57)
>=65	54 (40)	115 (43)
<75	121 (89)	233 (87)
>=75	15 (11)	35 (13)
Mean (SD)	60.6 (11.5)	61.2 (11.7)
Median (Range)	62 (29–91)	62 (18–91)
Race		
Asian	89 (65)	179 (67)
White	33 (24)	65 (24)
Not Reported	9 (7)	18 (7)
Black Or African American	5 (3.7)	6 (2.2)
Ethnicity		
Not Hispanic oOr Latino	122 (90)	238 (89)

	Group D + E N = 136 n (%)	Pooled 20mg BID N = 268 n (%)
Not Reported	11 (8)	26 (10)
Hispanic oOr Latino	3 (2.2)	4 (1.5)
Country/Region		
Chn	36 (26)	75 (28)
Kor	19 (14)	34 (13)
Jpn	15 (11)	32 (12)
Esp	7 (5)	11 (4.1)
Hkg	6 (4.4)	9 (3.4)
Fra	8 (6)	19 (7)
Ita	12 (9)	30 (11)
Nld	4 (2.9)	7 (2.6)
Twn	8 (6)	15 (6)
Bel	3 (2.2)	7 (2.6)
Usa	11 (8)	13 (4.9)
Sgp	5 (3.7)	12 (4.5)
Isr	2 (1.5)	4 (1.5)
Geographic Region 1		
Asia	89 (65)	177 (66)
Western Europe And Israel	36 (26)	78 (29)
North America	11 (8)	13 (4.9)
Sex		
F	86 (63)	174 (65)
M	50 (37)	94 (35)
Pooled Age Group 1		

	Group D + E N = 136 n (%)	Pooled 20mg BID N = 268 n (%)
18-64	82 (60)	153 (57)
65-84	52 (38)	112 (42)
>=85	2 (1.5)	3 (1.1)
ECOG Performance Status at Baseline		
1	90 (66)	179 (67)
0	46 (34)	89 (33)

Source: FDA analysis of adsl.xpt

Adequacy of the safety database:

The Applicant's Position:

The safety database comprising of all participants who received at least 1 dose of sevabertinib in Study 21607 (N=357), as of the database cutoff date of 14 OCT 2024, including the target population for the proposed indication, i.e. participants with pre-treated *HER2*-mutated NSCLC naïve to *HER2* ex20ins-targeted therapy, who were treated with sevabertinib at the RP2D (N=81), and participants treated with the RP2D dose (Whole Study 20 mg BID, N=268), is considered by the Applicant to be adequate to assess the safety and benefit-risk profile of sevabertinib. In addition, the Whole Study SAF safety population (N=357) allows for the characterization of less common toxicities associated with *HER2*-targeted therapy.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the adequacy of the available safety database; however, the FDA's assessment is based on a primary safety population including 136 patients with non-squamous NSCLC treated with sevabertinib at 20 mg BID from the combined Groups D + E who received prior systemic chemotherapy but were either naïve to or had progression on anti-*HER2* therapy respectively, in the unresectable or metastatic setting. The pooled safety population used to inform Section 5 of labeling includes 268 total patients. The number of patients in the primary and pooled safety populations is adequate to perform a comprehensive safety review.

8.2.2. Adequacy of Applicant’s Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Please see The Applicant’s Position below.

The Applicant’s Position:

Dedicated quality assurance and quality control systems were implemented to assure the quality of the data. No issues were identified regarding data integrity or submission quality that had an effect on the safety review.

The FDA’s Assessment:

The FDA agrees with the Applicant’s position. The data submitted was organized and adequate to perform a complete review of the safety of sevabertinib.

Categorization of Adverse Event

Data and the Applicant’s Position:

Safety evaluations: Generally, the safety evaluations were performed at Screening, during the Treatment period, at the EoT visit within 7 days after the last administration of sevabertinib, and at the Safety Follow-Up visit, 30 to 35 days after the last treatment with sevabertinib. During the Active follow-up (imaging FU visits) period, only (S)AEs related to the study procedures were to be collected.

TEAE definition: AEs were considered to be treatment-emergent if they had started or worsened after the first administration of study treatment, up to 30 days after the last administration of study treatment. (S)AEs were to be collected from the start of study treatment until 30 days after the last dose of study drug administration. Only TEAEs are reported in this Assessment Aid, and all tables (descriptive summaries) and discussions relate to the number of patients with TEAEs, unless explicitly stated otherwise.

MedDRA coding: AEs were coded and are presented using the MedDRA, version 27.1.

Severity grading: The severity of TEAEs was graded using CTCAE v. 5.0, as reported by the investigators, and is presented by the worst grade observed. Hematological and general chemistry laboratory abnormalities were graded according to CTCAE v. 5.0 but using laboratory measurements only, and no signs and symptoms or therapies were considered. Laboratory parameter hyperglycemia has no numeric values in CTCAE v. 5.0 and was therefore graded according to CTCAE v. 4.03.

Special topic AEs: Special safety topics were selected based on AEs reported within the sevabertinib program and the class toxicities of TKIs targeting EGFR and/or HER2, and included gastrointestinal toxicities, skin-related toxicities, ILD/pneumonitis, ocular toxicity, and cardiac toxicities. The Sponsor defined each of the queries for these special topics using SMQs, SOCs, HLTs, PTs or Sponsor-generated MLGs, as shown in **Table 53**. Relevant findings are presented in Section 8.2.4.

Table 53. Special Topic TEAE Definitions

Grouped term	MedDRA search criteria for special topics
Gastrointestinal toxicities	PT: Diarrhea PT: Nausea PT: Vomiting
Stomatitis	HLT: Stomatitis and ulceration
Rash	MLG: Rash + MLG: Skin erythema + PT: Dermatitis +PT: Dermatitis acneiform + PT: Acne
Paronychia	PT: Paronychia + PT: Nail infection + PT: Nail bed infection + HLT: Nail and nail bed conditions (excluded: infections and infestations)
Interstitial lung disease/pneumonitis	SMQ: Interstitial lung disease (narrow search)
Ocular toxicity	SOC: Eye disorders
Cardiac toxicities	SOC: Cardiac disorders

HLT=High-level term; MedDRA=Medical dictionary for regulatory activities; MLG=MedDRA labeling grouping; PT=Preferred term; SAP=Statistical analysis plan; SMQ=Standardized MedDRA query; SOC=System organ class; TEAE=Treatment-emergent adverse event

MLGs are pre-defined, customized MedDRA queries created and centrally maintained by Bayer internal coding experts. The specific terms used for searches for MLG Rash included PTs butterfly rash, drug eruption, fixed eruption, heliotrope rash, mucocutaneous rash, nodular rash, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash maculo-vesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash rubelliform, rash scarlatiniform, rash vesicular, symmetrical drug-related intertriginous and flexural exanthema, and MLG skin erythema included PT erythema.

Source: SAP v. 2.0, Module 5.3.5.2, Report B003047, Table 6–2 in Section 10.1.9

The FDA’s Assessment:

The FDA agrees with the Applicant’s categorization of AEs. The safety assessment focused on the frequency and severity of all treatment-emergent AEs (TEAEs). A TEAE was defined as any AE occurring between the start of treatment and within 30 days after completion of treatment). AEs that start before first drug intake and worsen under treatment are also considered as ‘treatment-emergent’. Additional analyses included assessment of TEAEs leading to death, SAEs, and TEAEs leading to dose reduction, interruption, or permanent discontinuation of sevabertinib. FDA’s independent analyses of these outcomes are presented in Section 8.2.4. The FDA review was completed using MedDRA preferred terms (PTs) and CTCAE version 5.0 grading criteria.

Routine Clinical Tests

Data:

Details on the safety assessments, including routine clinical laboratory tests (hematology, general chemistry, and urinalysis), vital signs (temperature, heart rate, respiratory rate, body weight, BMI, and blood pressure), 12-lead ECGs, cardiac function testing, and physical examinations are provided in the Study 21607 protocol.

In Study 21607, hematological and general chemistry laboratory abnormalities were graded according to CTCAE v. 5.0 but using laboratory measurements only, and no signs and symptoms or therapies were considered. Laboratory parameter hyperglycemia has no numeric values in CTCAE v. 5.0 and was therefore graded according to CTCAE v. 4.03 (which does incorporate numeric values). Shift tables “Laboratory abnormalities worsening from baseline” were created. In addition, for hypokalemia, hyponatremia, lipase increased, and serum amylase increased, worsening from baseline was summarized using categories obtained from the grade definitions in CTCAE v. 5.0 but based on laboratory measurements only. Laboratory abnormalities reported as TEAEs that include clinical assessments are presented in TEAE tables.

The Applicant’s Position:

The methods and time points for collection and analysis of safety assessments including routine clinical laboratory tests, were appropriate to monitor and assess the safety of sevabertinib in Study 21607.

The FDA’s Assessment:

FDA agrees with the Applicant’s position.

8.2.3. Safety Results

Deaths

Data:

A summary of all deaths occurring during Study 21607, as of the database cut-off date, is provided in **Table 54**. The incidence of participants with Grade 5 TEAEs and a listing of participants who died during treatment or within 30 days of the last dose of the study drug (excluding deaths due to progressive disease) are presented in **Table 55** and **Table 56**, respectively.

Table 54. Overview of Deaths in Study 21607 (SAF)

Primary cause of death	Group D	Whole Study	Whole Study
	20 mg BID N=81 (100%) n (%)	20 mg BID N=268 (100%) n (%)	SAF N=357 (100%) n (%)
Total number of deaths	19 (23.5%)	58 (21.6%)	90 (25.2%)
Adverse event	0	4 (1.5%)	10 (2.8%)
Progressive disease	18 (22.2%)	49 (18.3%)	69 (19.3%)
Other ^a	1 (1.2%)	3 (1.1%)	6 (1.7%)
Unknown	0	2 (0.7%)	5 (1.4%)
Death from start of treatment up to 30 days of last treatment	6 (7.4%)	15 (5.6%)	25 (7.0%)
Adverse event	0	3 (1.1%)	9 (2.5%)
Progressive disease	6 (7.4%)	12 (4.5%)	15 (4.2%)
Unknown	0	0	1 (0.3%)
Death after 30 days of last treatment	13 (16.0%)	43 (16.0%)	65 (18.2%)
Adverse event	0	1 (0.4%)	1 (0.3%)
Progressive disease	12 (14.8%)	37 (13.8%)	54 (15.1%)
Other ^a	1 (1.2%)	3 (1.1%)	6 (1.7%)
Unknown	0	2 (0.7%)	4 (1.1%)

BID=Twice daily; COVID-19=coronavirus disease 2019; N=Total number of participants; n=Number of participants with an event; SAF=Safety analysis set

a: Other includes: COVID-19 (1 participant), acute myocardial infarction (1), interstitial pneumonia (1), pneumonia (1), and respiratory failure (2),

Source: Module 5.3.5.2, Report B003047, t_14_3_2_1_deaths_overall_summary.sas (Datasets: ADSL and ADAE);
l_16_2_7_death_list.sas (Datasets ADAE, ADSL, ADEX, ADEXSUM, ADCE, and ADDS)

Table 55. Grade 5 TEAEs in Study 21607 (SAF)

Preferred term	Group D	Whole Study	Whole Study
	20 mg BID N=81 (100%) n (%)	20 mg BID N=268 (100%) n (%)	SAF N=357 (100%) n (%)
Any fatal TEAE	6 (7.4%)	16 (6.0%)	26 (7.3%) ^a
Disease progression	5 (6.2%)	9 (3.4%)	13 (3.6%)
General physical health deterioration	1 (1.2%)	1 (0.4%)	1 (0.3%)
Dyspnoea	0	2 (0.7%)	3 (0.8%)
Respiratory failure	0	1 (0.4%)	3 (0.8%)
Cardio-respiratory arrest	0	1 (0.4%)	1 (0.3%)
Pulmonary embolism	0	1 (0.4%)	1 (0.3%)
Multiple organ dysfunction syndrome	0	1 (0.4%)	1 (0.3%)
Pneumonia	0	0	1 (0.3%)
Brain herniation	0	0	1 (0.3%)
Death	0	0	1 (0.3%)

BID=Twice daily; MedDRA=Medical dictionary for regulatory activities; N=Total number of participants; n=Number of participants with an event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

a: For 1 participant, the start date of the Grade 5 TEAE (occurring within 30 days from the last dose) was partial and it was included in the analysis of TEAEs. However, the death date was 1 day after the database cutoff date, and therefore, this death is not included in the overview of deaths (Table 54).

Sorted by preferred term incidences in Group D. MedDRA v. 27.1, CTCAE v. 5.0

Source: Module 5.3.5.2, Report B003047, t_14_3_1_adae_teae_wst0.sas (Datasets ADSL, ADAE and ADDS)

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Table 56. Grade 5 TEAEs From Start of Treatment up to 30 Days of Last Treatment (Excluding PT Disease Progression) (Whole Study SAF)

Participant ID	Age/ Treatment group	Primary Cause of Death	SAE with fatal outcome	Study Day of Death	Day from Last Dose	Related to Study Drug (Y/N)
(b) (6)	69/M/ F – 20 mg BID	AE	Cardio-respiratory arrest	45	3	Y
	66/M/40 mg QD LSF	AE	Respiratory failure	109	26	N
	69/F/40 mg QD LSF	AE	Pneumonia	186	22	N
	48/F/20 mg BID TAB	AE	Respiratory failure	327	5	N
	46/F/30 mg BID TAB	AE	Brain herniation	47	2	N
	67/F/40 mg BID TAB	AE	Respiratory failure	181	1	N
	66/F/A - 20 mg BID	Progressive disease	Dyspnoea	30	5	N
	43/M/A - 20 mg BID	AE	Pulmonary embolism	39	5	N
	77/F/D1 – 10 mg BID	AE	Dyspnoea	221	10	N
	54/F/D1 – 10 mg BID	Unknown	Death	53	20	N
	54/M/D – 20 mg BID	Progressive disease	General physical health deterioration	99	17	N
	61/M/ E – 20 mg BID	Progressive disease	Dyspnoea	63	2	N

AE=Adverse event; BID=Twice daily; CTCAE=Common Terminology Criteria for Adverse Events; LSF=Liquid service formulation; MedDRA=Medical dictionary for regulatory activities; PT=Preferred term; QD=Once daily; SAE=Serious adverse event; TAB=Tablets

MedDRA v. 27.1, CTCAE v. 5.0

Source: Module 5.3.5.2, Report B003047, I_16_2_7_death_list.sas (Datasets ADAE, ADSL, ADEX, ADEXSUM, ADCE and ADDS)

The Applicant's Position:

Overall, 90 participants (25.2%) of the 357 in the Whole Study SAF had died, as of the database cut-off; there were 19 deaths (23.5%) in Group D and 58 deaths (21.6%) in the Whole Study 20 mg BID population (**Table 54**). The majority of the deaths in the study (65 participants; 18.2%) occurred >30 days after the last sevabertinib dose. Death (including Grade 5 disease progression) from the start of treatment up to 30 days after the last dose was reported in 6 participants (7.4%) in Group D and in 15 participants (5.6%) in the Whole Study 20 mg BID population, with progressive disease being the most common primary cause of death.

The incidence of participants with fatal TEAEs was consistent across the 3 safety populations (**Table 55**). In the Whole Study SAF, 26 participants (7.3%) had a Grade 5 TEAE, with disease progression being the most common event (13 participants, 3.6%), followed by respiratory events, of which dyspnea and respiratory failure occurred in >1 participant (0.8% of participants each).

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1 Grade 5 TEAE (cardio-respiratory arrest in participant (b) (6)) in the Whole Study 20 mg BID population was assessed as related to the study drug by the investigator (**Table 56**). This 69-year-old male, with a low body mass index (18.4 kg/m²), and a history of inappetence since approximately 5 months before starting the study drug, ongoing hypotension and supraventricular tachycardia (which recovered 7 days after initiation of sevabertinib treatment), was reported with the following TEAEs starting from Day 38: Grade 2 vomiting, ileus, and hypokalemia, as well as Grade 1 pneumonia, hypertriglyceridemia, hyperglycemia, blood bilirubin increased, supraventricular tachycardia, and diarrhea. On Day 42, Grade 3 renal failure developed, leading to sevabertinib discontinuation; the participant was found to have diffuse bilateral renal lesions, abnormal, on an ultrasound scan. The participant was hospitalized on Day 44, received medical treatments and incomplete hemodialysis; however, his general condition worsened. The participant passed away at home on Day 45 due to cardio-respiratory arrest. The participant's risk of cardio-respiratory arrest was heightened by underlying advanced lung cancer, emphysema, coronary artery calcification, sinus tachycardia, and left anterior fascicular block. The participant's condition was further complicated by renal failure, pneumonia exacerbation, and concomitant medications (e.g. moxifloxacin, benzylpenicillin, insulin). Importantly, the participant was found to have diffused bilateral renal lesions; therefore, the role of the study treatment and renal failure remains unclear.

Narratives of all participants with fatal TEAEs are provided with the NDA, Module 5.3.5.2, Report B003047, Section 9.

The FDA's Assessment:

Although FDA agrees with the listing of deaths provided by the Applicant above in **Table 56**, FDA's review could not exclude a potential contribution of sevabertinib to all fatal adverse reactions described above. An overall summary of the FDA's analysis of TEAEs is presented in FDA **Table 57**. A summary of deaths amongst the safety populations is presented in FDA **Table 58**. Comprehensive narrative review and FDA assessment for all cases of death in the primary safety population is presented in FDA **Table 59**.

Table 57. TEAE Overall Summary

	Cohorts Group D + E	Pooled 20mg patients
	N = 136	N=268
	%	%
All-Grade TEAEs	100	99
Grade 3-4 TEAEs	44	39
Serious TEAEs	31	27
Fatal TEAEs	7	6

	Cohorts Group D + E	Pooled 20mg patients
	N = 136	N=268
	%	%
TEAEs leading to dose reduction	28	27
TEAEs leading to dose interruption	46	42
TEAEs leading to drug discontinuation	3.7	2.2

Source: FDA analysis of adae.xpt

Table 58. Summary of Deaths

	Cohorts Group D + E	Pooled 20mg patients
	N = 136	N=268
	%	%
Total Deaths	25	22
Disease Progression	22	18
Adverse Event	0.7	1.9
Unknown	0.7	0.7
Within 30 days after last dose	7	6
Disease Progression	5	4.5
Adverse Event	1.4	1.9
TEAEs with outcome of death	7	6
Respiratory failure	1.5	0.4
Multiple organ dysfunction syndrome	0.7	0.4
Dyspnea	0.7	0.7
General physical health deterioration	0.7	0.4
Pulmonary embolism	0	0.4
Beyond 30 days after last dose	18	16

Disease Progression	17	14
Other	0.7	1.1
Unknown	0.7	0.7

Source: FDA analysis of adae.xpt

Table 59. Death Narrative Review

Patient ID	Brief Narrative (bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality
(b) (6)	This is a 61-year-old female who on study Day 6 was hospitalized for Grade 4 dyspnea. This hospitalization was prolonged requiring supplemental oxygen. Disease progression was noted on day 15 The Grade 5 TEAE of dyspnea occurred 26 days after the last dose of study drug. The Sponsor considered this unrelated to sevabertinib and attributed to disease progression.	Based on imaging evidence of disease progression, FDA considers the cause of death likely due to disease progression. Though the differential based on data from the narrative includes PJP Pneumonia, malignant disease progression, pulmonary embolism, and pneumonitis/ILD from study drug, disease progression is the likely cause given imaging evidence.
(b) (6)	This is a 69-year-old male who experienced a number of TEAEs (colitis, transaminitis, and pancreatic enzyme elevation) over the course of treatment. The patient suffered a Grade 4 PE on study Day 301 attributed as unrelated to study drug by the investigator. Progressive disease was noted on Study Day 305, 19 days after last dose of sevabertinib. The Sponsor considered this unrelated to sevabertinib.	Disease progression complicated by a pulmonary embolism FDA agrees that the Grade 5 TEAE in this case could be due to disease progression. Disease progression may have contributed to the formation of a pulmonary embolism.

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(b) (6)	This is a 59-year-old male who experienced a pleural effusion that was drained on study Day 83. No other therapy was noted and it was not noted if the fluid contained malignant cells. Disease progression was noted on study Day 89, 4 days after the last dose. The Sponsor considered this unrelated.	Disease progression complicated by pleural effusion. Although no details were provided concerning the etiology of the pleural effusion, FDA agrees that this Grade 5 TEAE was most likely due to disease progression.
(b) (6)	This is a 71-year-old female who rapidly experienced Grade 3 decreased appetite. On Day 12, Grade 3 hypokalemia was noted. Grade 1 diarrhea was also noted but without definitive linkage to the hypokalemia. Disease progression and death was noted on study Day 84, with last dose of sevabertinib 14 days prior (discontinued per patient choice). Per the Sponsor this was unrelated to study drug.	Disease progression. The FDA agrees that this Grade 5 TEAE could be attributed to disease progression. It remains possible that diarrhea led to the Grade 3 hypokalemia. There is no clear description in the narrative of a temporal relationship with this and any arrhythmia.
(b) (6)	This is a 60-year-old male who initially had Grade 2 fatigue and then in (b) (6) (~2 months after initiating treatment) had a fall with head injury reportedly due to lower extremity weakness. The etiology of this is unclear. Disease progression was noted on Study Day 77 with the last dose of study drug 14 days prior.	Disease progression FDA agrees that this Grade 5 TEAE could be attributed to disease progression. No imaging data was provided in the narrative describing any CNS metastases so this and a mechanical fall remain on the differential.
(b) (6)	This is a 54 year old female who experienced Grade 3 elevation of liver transferases alongside a 1.5x elevation in blood bilirubin and slight	Physical health deterioration Given imaging evidence of progressive disease, and

	increase in ALP (<1.5xULN) on study Day 29. Both the Investigator and Sponsor attributed this to study drug. The official cause of death was listed as general physical health deterioration. General physical health deterioration was noted on study Day 58 days from the start of treatment with the last dose of sevabertinib on this date. On Day 63, progressive disease was noted with multiple new brain lesions, and death occurred on Day 98. Neither the Investigator nor the Sponsor attributed this to study drug.	timing of cessation of sevabertinib disease progression is the likely cause of death.
(b) (6)	This is a 61-year-old male who experienced Grade 2 diarrhea and nausea. Dyspnea was noted on study Day 61, as well as Grade 3 & 4 asthenia, Grade 3 & 4 pneumonia, and Grade 3 & 4 hypoxia leading to a Grade 5 event on Day 63. The narrative is unclear but ultimately attributed to disease progression.	Respiratory Failure FDA agrees that it is possible that this Grade 5 event was related to disease progression. Given the lack of ancillary data regarding the workup of the dyspnea in this case the etiology is unclear but the time course would be most consistent with progressive disease. No other clear etiologies were described in the narrative.
(b) (6)	This is a 48-year-old male who experienced a Grade 5 event listed as Noninfectious multiple organ dysfunction syndrome after an unspecified length of treatment. The patient had a Grade 2 upper respiratory infection reported on study Day 43 alongside Grade 1	Multiple organ dysfunction of uncertain etiology The Grade 5 event can likely be attributed to disease progression given the prior imaging evidence of progression and timing of cessation of sevabertinib.

	sinus arrhythmia and Grade 1 hoarseness/dysphonia. Multiple organ dysfunction syndrome was noted in (b) (6) resulting in a Grade 5 event (date of AE not reported, death reported as Day 113). The cause of this Grade 5 event was attributed to disease progression, which had been reported on Day 85, with the last dose of sevabertinib on that date.	
(b) (6)	This is 48-year-old female who was on therapy for approximately 326 days who presented at an emergency department of an outside hospital with acute deterioration and hypoxia resulting in a Grade 5 event of respiratory failure on Day 327. The last dose of sevabertinib was received five days prior to death. Tumor assessment on Day 323 was partial response per investigator; subsequent BICR read indicated progressive disease with recurrent liver metastases, increased pleural effusion and suspected peritoneal carcinomatosis.	Respiratory Failure The FDA agrees that given available details and BICR-assessed disease progression, disease progression is the likely cause of this Grade 5 event.
(b) (6)	This is a 69-year-old male who was on therapy for 45 days before experiencing Grade 5 cardio-respiratory arrest. This patient was included in Group F (included in the pooled but not Group D +E safety population). This patient also experienced Grade 3 renal failure 42 days	Cardio-respiratory event While the FDA recognizes that this was a complex event, given the arrhythmia, renal failure, and evidence that tumor was responding to treatment, that a contribution from study drug cannot be excluded.

after start of treatment. A CT of the chest performed the day before this Grade 5 event noted a shrinking mass in the left upper lobe next to the mediastinum, increased mediastinal lymph nodes and bilateral exudative lesions. ECG demonstrated sinus tachycardia and left anterior fascicular block with U wave changes. The Investigator considered the event as related to study drug; the applicant assessed it as not related.

Note: Fatal adverse reactions described in Section 6 of the product label include only patients in Group D and E; therefore, this fatal event is not described in the label.

Serious Adverse Events

Data:

A summary of treatment-emergent SAEs (TESAEs), that occurred in ≥ 2 of participants is provided in Table 60.

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Table 60. Treatment-Emergent Serious Adverse Events (Any Grade) Occurring in ≥2 Participants^a in Study 21607 (SAF)

Preferred term	Group D 20 mg BID N=81 (100%) n (%)		Whole Study 20 mg BID N=268 (100%) n (%)		Whole Study SAF N=357 (100%) n (%)	
	Any	Related	Any	Related	Any	Related
TESAE	26 (32.1%)	11 (13.6%)	72 (26.9%)	28 (10.4%)	110 (30.8%)	33 (9.2%)
Diarrhoea	5 (6.2%)	5 (6.2%)	10 (3.7%)	10 (3.7%)	13 (3.6%)	12 (3.4%)
Disease progression	5 (6.2%)	0	9 (3.4%)	0	13 (3.6%)	0
Pneumonia	2 (2.5%)	1 (1.2%)	8 (3.0%)	2 (0.7%)	14 (3.9%)	2 (0.6%)
Vomiting	2 (2.5%)	1 (1.2%)	7 (2.6%)	5 (1.9%)	10 (2.8%)	6 (1.7%)
Pleural effusion	2 (2.5%)	0	4 (1.5%)	0	9 (2.5%)	0
Hepatic function abnormal	2 (2.5%)	2 (2.5%)	3 (1.1%)	3 (1.1%)	3 (0.8%)	3 (0.8%)
Nausea	2 (2.5%)	2 (2.5%)	3 (1.1%)	3 (1.1%)	4 (1.1%)	4 (1.1%)
Malaise	2 (2.5%)	0	2 (0.7%)	0	2 (0.6%)	0
Pericardial effusion	2 (2.5%)	0	2 (0.7%)	0	4 (1.1%)	0
Dyspnoea	1 (1.2%)	1 (1.2%)	5 (1.9%)	1 (0.4%)	10 (2.8%)	1 (0.3%)
Pericarditis	1 (1.2%)	0	2 (0.7%)	0	2 (0.6%)	0
Pulmonary embolism	1 (1.2%)	0	2 (0.7%)	0	3 (0.8%)	0
Tumour pain	1 (1.2%)	0	2 (0.7%)	0	2 (0.6%)	0
Acute kidney injury	0	0	3 (1.1%)	0	3 (0.8%)	0
Decreased appetite	0	0	2 (0.7%)	2 (0.7%)	3 (0.8%)	3 (0.8%)
Hypokalaemia	0	0	2 (0.7%)	0	2 (0.6%)	0

BID=Twice daily; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical dictionary for regulatory activities; N=Total number of participants; n=Number of participants with an event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

This table contains counts of participants. If a participant experienced more than one episode of a TEAE, the participant is counted only once within a preferred term. Participants may have more than one entry.

Sorted by preferred term incidences in Group D.

a: Cut-off ≥2 participants applies to the Whole Study 20 mg BID population.

MedDRA v. 27.1, CTCAE v. 5.0

Source: Module 5.3.5.2, Report B003047, t_14_3_2_2_adae_tesae_wst0.sas and t_14_3_2_2_adae_tesae_wst.sas [Datasets ADSL, ADAE and ADDS]

The Applicant's Position:

Overall, the most commonly reported TESAEs were consistent across the 3 safety populations, occurring in 32.1%, 26.9%, and 30.8% of participants in Group D, the Whole Study 20 mg BID population, and the Whole Study SAF, respectively (**Table 60**).

In Group D, TESAEs reported in >2.5% of participants were diarrhea and disease progression, which were reported in 6.2% of participants each. TESAEs were considered study drug-related by the investigator in 13.6% of participants in Group D. The drug-related TESAEs reported in ≥2 participants included diarrhea, nausea, and hepatic function abnormal.

In the Whole Study 20 mg BID population, TESAEs reported in >2.5% of participants were diarrhea (3.7%), disease progression (3.4%), pneumonia (3.0%), and vomiting (2.6%). TESAEs were considered study drug-related by the investigator in 10.4% of participants in the Whole Study 20 mg BID population. The drug-related TESAEs reported in ≥2 participants included diarrhea, vomiting, nausea, hepatic function abnormal, decreased appetite, and pneumonia.

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Approximately two thirds of participants experiencing TESAEs had Grade 3 events (as the worst grade): 22.2% of participants in Group D and 18.3% of participants in the Whole Study 20 mg BID population (*Module 5.3.5.2, B003047, Table 8.3.2.2/2 [Datasets ADSL, ADAE and ADD]*). TESAEs with a worst grade of 4 occurred in 1.2% and 1.1%, respectively. TESAEs with a fatal outcome (Grade 5 events) occurred in 7.4% and 6.0%, respectively, see Section “Deaths” above.

The FDA’s Assessment:

As previously described, FDA considers all treatment-emergent AEs in its analysis, and cautions that attribution cannot be determined in the context of a single-arm trial. For the combined Groups D + E and pooled 20mg patients, all-grade SAEs occurred in 31% and 27% patients, respectively. SAEs in >1% of the combined Groups D + E and pooled 20 mg patient populations are listed in FDA **Table 61**. The risk of serious dyspnea, pulmonary embolism, pneumonia, and pleural effusion appear consistent with the expected incidence in this disease population. The SAE of hepatic function abnormal occurred in >1% of patients; refer to additional discussion of this issue in Section 8.2.5, Any Grade SAEs of arrhythmia occurred in 1.1% of patients; refer to 8.2.5 for an analysis of this signal. The remainder of the SAEs were rare, occurring in <1% of either safety population.

Table 61. Treatment-Emergent SAEs in >1%

	Groups D + E		Pooled 20mg patients	
	N = 136		N = 268	
	%		%	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any SAE	31	24	27	19
Diarrhea (GT)	6	5	4.1	3.7
Vomiting (GT)	1.5	0.7	3	2.6
Nausea	1.5	0.7	1.1	0.7
Malaise	1.5	0.7	0.7	0.4
Arrhythmia (GT)	1.5	1.5	1.1	0.7
Pericardial effusion	1.5	1.5	0.7	0.7
Pericarditis	1.5	0.7	0.7	0.4
Pneumonia (GT)	3.7	3.7	3	2.2
Pleural effusion	2.2	1.5	1.5	0.7
Dyspnea (GT)	2.2	1.5	1.9	0.7

	Groups D + E		Pooled 20mg patients	
	N = 136		N = 268	
	%		%	
	All	Grade	All	Grade
	Grade	Grade	3-4	
Hepatic function abnormal	1.5	1.5	1.1	1.1
Hypokalemia	1.5	1.5	0.7	0.7
Acute kidney injury (GT)	1.5	1.5	1.5	1.5

Source: FDA analysis of adae.xpt

Note: Custom grouped terms are designated by '(GT)'.

Acute kidney injury (GT) includes: Acute kidney injury, and Renal failure.

Arrhythmia (GT) includes: Arrhythmia, Atrial fibrillation, Atrioventricular block complete, and Sinus tachycardia.

Diarrhea (GT) includes: Diarrhea, and Enterocolitis.

Dyspnea (GT) includes: Dyspnea.

Pneumonia (GT) includes: Pneumonia.

Vomiting (GT) includes: Hematemesis, and Vomiting.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs leading to discontinuation of the study drug are summarized by PT for Group D, the Whole Study 20 mg BID and the Whole Study SAF safety populations in **Table 62**.

Table 62. TEAEs Leading to Permanent Treatment Discontinuation of Study Drug in Study 21607 (SAF)

Preferred term	Worst CTCAE grade	Study drug-related (Yes/No)	Group D 20 mg BID N=81 (100%) n (%)	Whole Study 20 mg BID N=268 (100%) n (%)	Whole Study SAF N=357 (100%) n (%)
Any	Any		4 (4.9%)	6 (2.2%)	9 (2.5%)
Corneal epithelial microcysts	Grade 3	Yes	1 (1.2%)	1 (0.4%)	1 (0.3%)
Dyspnoea	Grade 3	Yes	1 (1.2%)	1 (0.4%)	1 (0.3%)
Electrocardiogram QT prolonged	Grade 3	Yes	1 (1.2%)	1 (0.4%)	1 (0.3%)
Visual acuity reduced	Grade 1	Yes	1 (1.2%)	1 (0.4%)	1 (0.3%)
Hepatic function abnormal	Grade 1	Yes	1 (1.2%)	1 (0.4%)	1 (0.3%)
Renal failure	Grade 3	Yes	0	1 (0.4%)	1 (0.3%)
Pain in extremity	Grade 2	Yes	0	1 (0.4%)	1 (0.3%)
Alanine aminotransferase increased	Grade 2	Yes	0	0	1 (0.3%)
Metastases to meninges	Grade 2	No	0	0	1 (0.3%)
Pneumonitis	Grade 1	Yes	0	0	1 (0.3%)

Table 62. TEAEs Leading to Permanent Treatment Discontinuation of Study Drug in Study 21607 (SAF)

Preferred term	Worst CTCAE grade	Study drug-related (Yes/No)	Group D 20 mg BID N=81 (100%) n (%)	Whole Study 20 mg BID N=268 (100%) n (%)	Whole Study SAF N=357 (100%) n (%)

BID=Twice daily; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical dictionary for regulatory activities; N=Total number of participants; n=number of participants with the event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

This table contains counts of participants. If a participant experienced more than one episode of a TEAE, the participant is counted only once within a preferred term. Participants may have more than one entry.

Sorted by preferred term incidences in Group D.

MedDRA version 27.1, CTCAE version 5

Source: Module 5.3.5.2, Report B003047, t_14_3_1_adae_tea_wst.sas and t_14_3_1_adae_tesdrae_wst.sas (Datasets ADSL, ADAE and ADDS)

The Applicant's Position:

The overall incidence of TEAEs leading to permanent discontinuation of the study drug was low across the 3 safety populations (**Table 62**). In Group D, 4 participants (4.9%) had at least one TEAE leading to permanent discontinuation of the study drug. In the Whole Study 20 mg BID, 6 participants (2.2%) had TEAEs leading to permanent discontinuation of the study drug. All of these events were considered related to the study drug by the investigator. None of the events leading to treatment discontinuation occurred in >1 participant across the safety populations.

The FDA's Assessment:

FDA agrees that there were few study drug discontinuations due to TEAEs. For the Group D + E and pooled 20 mg patient populations, 3.7% and 2.2% of patients, respectively, discontinued sevabertinib due to a TEAE. TEAEs associated with drug discontinuation are listed in FDA **Table 63**. Each TEAE leading to drug discontinuation occurred in one patient. Hepatotoxicity and ocular toxicity are addressed in the product warnings.

Table 63. TEAEs Associated With Study Drug Discontinuation (All Grade)

	Groups D + E	Pooled 20mg patients
	N = 136	N = 268
	%	%
Any TEAE	3.7	2.2
Arrhythmia (GT)	0.7	0.4
Dyspnea (GT)	0.7	0.4
Eye disorder (GT)	0.7	0.4
Hepatic function abnormal	0.7	0.4

	Groups D + E	Pooled 20mg patients
	N = 136	N = 268
	%	%
Musculo-skeletal pain (GT)	0.7	0.4
Acute kidney injury (GT)	0	0.4

Source: FDA analysis of adae.xpt

Note: Custom grouped terms are designated by '(GT)'.

Acute kidney injury (GT) includes: Renal failure.

Arrhythmia (GT) includes: Electrocardiogram QT prolonged.

Dyspnea (GT) includes: Dyspnea.

Eye disorder (GT) includes: Corneal epithelial microcysts, and Visual acuity reduced.

Musculoskeletal pain (GT) includes: Pain in extremity.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

Overall, the incidence of TEAEs **leading to dose reduction** was consistent across the 3 safety populations (Group D: 20 participants, 24.7%; Whole Study 20 mg BID: 73 participants, 27.2%; and Whole Study SAF: 95 participants, 26.6%). In Group D, TEAEs leading to dose reduction, reported in $\geq 2\%$ of participants were diarrhea (11.1%), and hepatic function abnormal, conjunctivitis viral, ALT increased, and AST increased (2.5% each). Based on the investigator assessment, of these TEAEs, all, except conjunctivitis viral event in 1 participant, were considered related to the study drug. In the Whole Study 20 mg BID, TEAEs leading to dose reduction, reported in $\geq 2\%$ of participants, were diarrhea (11.6%) and ALT increased (2.6%). All of these TEAEs were considered related to the study drug. In the Whole Study SAF, TEAEs leading to dose reduction, reported in $\geq 2\%$ of participants, were diarrhea (11.5%), ALT increased (2.5%), and hypokalemia (2.2%). All of these TEAEs except hypokalemia in 1 participant were considered related to the study drug (*Module 5.3.5.2, B003047, Tables 8.3.1.1/10 and 8.3.1.2/8 [Datasets ADSL, ADAE and ADDS]*).

Overall, the incidence of TEAEs **leading to dose interruption/delay** was consistent across the 3 safety populations (Group D: 35 participants, 43.2%; Whole Study 20 mg BID: 113 participants, 42.2%; and Whole Study SAF: 154 participants, 43.1%). In Group D, the most common TEAEs (reported in $>5\%$ of participants), leading to dose interruption/delay, were diarrhea (16.0%) and hypokalemia (8.6%). Based on the investigator assessment, in all participants with TEAEs of diarrhea leading to dose interruption/delay in Group D, the events were considered related to the study drug, while in 4.9% of participants, hypokalemia, that led to dose interruption/delay, was considered related to the study drug. In the Whole Study 20 mg BID population, 42.2% of participants had TEAEs leading to dose interruption/delay. The most common TEAEs (reported in $>5\%$ of participants), leading to dose interruption/delay, were

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diarrhea (15.3%) and hypokalemia (6.3%). In the Whole Study SAF, the most common TEAEs (reported in >5% of participants) leading to dose interruption/delay were diarrhea (15.4%) and hypokalemia (5.9%) (*Module 5.3.5.2, B003047, Tables 8.3.1.1/12 and 8.3.1.2/10 [Datasets ADSL, ADAE and ADDS]*).

The Applicant’s Position:

Toxicity was effectively managed via dose interruptions/delays and dose reductions, with low rates of permanent discontinuation of the study drug due to TEAEs (<5% in all safety populations).

Overall, the incidence of TEAEs leading to dose interruption/delay was consistent (42.2% to 43.2%) across the 3 safety populations. The most common reason for dose interruptions/delays across the populations was diarrhea (15.3% to 16.0%).

Similarly, the percentage of participants with TEAEs leading to dose reduction was consistent across the 3 safety populations (24.7% to 27.2%), with diarrhea being the most common reason for dose reduction (11.1% to 11.6%).

The FDA’s Assessment:

FDA agrees with Applicant’s position.

For the Group D + E and the pooled 20 mg patient populations, dose reductions of sevabertinib due to a TEAE occurred in 28% and 27% of patients, respectively. TEAEs associated with dose reductions in these populations are listed in FDA **Table 64** and were mostly consistent between populations. The most common TEAEs leading to dose reductions in the pooled 20 mg safety population were diarrhea, ALT increased, and rash. These risks are adequately addressed in product labeling.

For the Group D + E and the pooled 20mg patient populations, dose interruptions of sevabertinib due to a TEAE occurred in 46 and 42% of patients, respectively. TEAEs associated with dose interruptions in these populations are listed in FDA **Table 65** and were mostly consistent among the populations. TEAEs which required dose interruptions in >2% of either population were diarrhea, hypokalemia, pneumonia, nausea, vomiting, decreased appetite, ALT increased, AST increased, Covid-19, dyspnea, amylase increased, stomatitis, and rash.

Table 64. TEAEs Associated With Study Drug Dose Reduction

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	Group D + E	Pooled 20mg patients
	N = 136	N = 268
	%	%
Any TEAE	28	27
Diarrhea (GT)	11	12
Alanine aminotransferase increased	1.5	2.6
Hepatic function abnormal	1.5	1.1
Aspartate aminotransferase increased	1.5	1.1
Arrhythmia (GT)	1.5	0.7
Conjunctivitis viral	1.5	0.7
Hypokalaemia	2.2	1.9
Stomatitis (GT)	1.5	1.9
Nausea	1.5	1.9
Decreased appetite	1.5	1.1
Weight decreased	1.5	1.1
Eye disorder (GT)	1.5	0.7
Vomiting (GT)	0.7	0.7
Pericardial effusion	0.7	0.4
Duodenitis	0.7	0.4
Meibomian gland dysfunction	0.7	0.4
Pyrexia (GT)	0.7	0.4
Rash (GT)	2.2	2.2
Amylase increased	0.7	0.4
Pruritus	0.7	0.4
Paronychia	0	0.7
Epilepsy	0	0.4
Metastases to meninges	0	0.4
Acute kidney injury (GT)	0	0.4
Fatigue (GT)	0	0.4
Hypocalcaemia	0	0.4
Malaise	0	0.4

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	Group D + E	Pooled 20mg patients
	N = 136	N = 268
	%	%
Taste disorder	0	0.4

Source FDA analysis of adae.xpt

USUBJID, COLGROUP, ATOXGRN, AEDECOD, AEBODSYS, TRTEMFL, AEACN = 'DOSE REDUCED'

Note: Custom grouped terms are designated by '(GT)'.

Acute kidney injury (GT) includes: Renal failure.

Arrhythmia (GT) includes: Atrioventricular block complete, and Electrocardiogram QT prolonged.

Diarrhea (GT) includes: Diarrhea.

Eye disorder (GT) includes: Blindness unilateral, and Conjunctivitis.

Fatigue (GT) includes: Fatigue.

Pyrexia (GT) includes: Pyrexia.

Rash (GT) includes: Dermatitis, Dermatitis acneiform, Palmar-plantar erythrodysesthesia syndrome, Rash, and Rash maculo-papular.

Stomatitis (GT) includes: Stomatitis.

Vomiting (GT) includes: Vomiting.

Table 65. TEAEs Associated With Study Drug Dose Interruption

	Groups D + E	Pooled 20mg patients
	N = 136	N = 268
	%	%
Any TEAE	46	42
Diarrhea (GT)	18	15
Hypokalemia	8	6
Pneumonia (GT)	4.4	3
Nausea	5	4.9
Vomiting (GT)	2.2	4.1
Decreased appetite	3.7	3.4
Alanine aminotransferase increased	2.2	2.2
Aspartate aminotransferase increased	2.2	1.9
COVID-19	2.2	1.5
Malaise	1.5	1.5
Hepatic function abnormal	1.5	1.1

	Groups D + E	Pooled 20mg patients
	N = 136	N = 268
	%	%
Pruritus	1.5	1.1
Dyspnea (GT)	2.2	1.9
Amylase increased	2.2	1.1
Stomatitis (GT)	1.5	2.2
Acute kidney injury (GT)	1.5	1.5
Arrhythmia (GT)	1.5	1.1
Weight decreased	1.5	1.1
Pyrexia (GT)	0.7	1.5
Lipase increased	0.7	0.7
Dysphagia	0.7	0.7
Paronychia	0.7	0.7
Dizziness (GT)	0.7	0.7
Duodenal ulcer perforation	0.7	0.4
Duodenitis	0.7	0.4
Eye disorder (GT)	0.7	0.4
General physical health deterioration	0.7	0.4
Oral cavity fistula	0.7	0.4
Pericardial effusion	0.7	0.4
Pericardial effusion malignant	0.7	0.4
Pulmonary embolism	0.7	0.4
Vascular device infection	0.7	0.4
Conjunctivitis viral	0.7	0.4
Gastroenteritis	0.7	0.4
Neuropathy peripheral (GT)	0.7	0.4
Radiation pneumonitis	0.7	0.4
Respiratory tract inflammation	0.7	0.4

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	Groups D + E	Pooled 20mg patients
	N = 136	N = 268
	%	%
Tooth disorder	0.7	0.4
Tumor biopsy	0.7	0.4
Viral infection	0.7	0.4
Rash (GT)	2.2	2.2
Seizure	1.5	0.7
Blood bilirubin increased	1.5	0.7
Duodenal ulcer	0.7	0.7
Metastases to meninges	0.7	0.7
Fatigue (GT)	0.7	0.7
Influenza	0.7	0.7
Platelet count decreased	0.7	0.7
Coma	0.7	0.4
Device related sepsis	0.7	0.4
Hypomagnesaemia	0.7	0.4
Hypotension (GT)	0.7	0.4
Pericarditis	0.7	0.4
Blood creatinine increased	0	0.7
Anemia	0	0.4
Dehydration	0	0.4
Gastric ulcer	0	0.4
Pneumomediastinum	0	0.4
Sepsis	0	0.4
Tooth abscess	0	0.4
Chest discomfort	0	0.4
Musculoskeletal pain (GT)	0	0.4
Taste disorder	0	0.4

Source: FDA analysis of adae.xpt

Note: Custom grouped terms are designated by '(GT)':

Acute kidney injury (GT) includes: Acute kidney injury, Nephropathy toxic, and Renal impairment.

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Arrhythmia (GT) includes: Atrial fibrillation, Electrocardiogram QT prolonged, and Supraventricular extrasystoles.

Diarrhea (GT) includes: Diarrhea, and Enterocolitis.

Dizziness (GT) includes: Dizziness, and Vertigo positional.

Dyspnea (GT) includes: Dyspnea.

Eye disorder (GT) includes: Visual acuity reduced.

Fatigue (GT) includes: Asthenia, and Fatigue.

Hypotension (GT) includes: Hypotension.

Musculoskeletal pain (GT) includes: Pain in extremity.

Neuropathy peripheral (GT) includes: Peripheral sensory neuropathy.

Pneumonia (GT) includes: Pneumocystis jirovecii pneumonia, and Pneumonia.

Pyrexia (GT) includes: Pyrexia.

Rash (GT) includes: Dermatitis acneiform, and Rash.

Stomatitis (GT) includes: Stomatitis.

Vomiting (GT) includes: Hematemesis, and Vomiting.

Significant Adverse Events

Data:

For the purposes of this section, CTCAE Grade 3 and 4 TEAEs are considered to be significant. Worst Grade 3 ($\geq 1\%$ participants) and all worst Grade 4 TEAEs are presented in **Table 66**.

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Table 66. Worst Grade 3 TEAEs Occurring in ≥1% of Participants^a and All Worst Grade 4 TEAEs in Study 21607 (SAF)

Preferred term	Group D 20 mg BID N=81 (100%) n (%)	Whole Study 20 mg BID N=268 (100%) n (%)	Whole Study SAF N=357(100%) n (%)
Worst Grade 3 TEAE			
Diarrhoea	19 (23.5%)	39 (14.6%)	53 (14.8%)
Hypokalaemia	9 (11.1%)	21 (7.8%)	26 (7.3%)
Vomiting	3 (3.7%)	9 (3.4%)	12 (3.4%)
Decreased appetite	3 (3.7%)	6 (2.2%)	7 (2.0%)
Pericardial effusion	2 (2.5%)	2 (0.7%)	3 (0.8%)
Nausea	2 (2.5%)	6 (2.2%)	7 (2.0%)
Hepatic function abnormal	2 (2.5%)	3 (1.1%)	3 (0.8%)
Pneumonia	2 (2.5%)	7 (2.6%)	13 (3.6%)
Urinary tract infection	2 (2.5%)	2 (0.7%)	3 (0.8%)
Alanine aminotransferase increased	2 (2.5%)	5 (1.9%)	7 (2.0%)
Aspartate aminotransferase increased	2 (2.5%)	4 (1.5%)	4 (1.1%)
Pruritus	2 (2.5%)	2 (0.7%)	3 (0.8%)
Anaemia	1 (1.2%)	4 (1.5%)	6 (1.7%)
Arrhythmia	1 (1.2%)	1 (0.4%)	1 (0.3%)
Atrioventricular block complete	1 (1.2%)	1 (0.4%)	1 (0.3%)
Pericardial effusion malignant	1 (1.2%)	1 (0.4%)	1 (0.3%)
Pericarditis	1 (1.2%)	1 (0.4%)	1 (0.3%)
Sinus tachycardia	1 (1.2%)	1 (0.4%)	1 (0.3%)
Blindness unilateral	1 (1.2%)	1 (0.4%)	1 (0.3%)
Corneal epithelial microcysts	1 (1.2%)	1 (0.4%)	1 (0.3%)
Visual acuity reduced	1 (1.2%)	1 (0.4%)	1 (0.3%)
Duodenitis	1 (1.2%)	1 (0.4%)	1 (0.3%)
Enterocolitis	1 (1.2%)	1 (0.4%)	1 (0.3%)
Oral cavity fistula	1 (1.2%)	1 (0.4%)	1 (0.3%)
Stomatitis	1 (1.2%)	2 (0.7%)	3 (0.8%)
Malaise	1 (1.2%)	1 (0.4%)	1 (0.3%)
Conjunctivitis viral	1 (1.2%)	1 (0.4%)	1 (0.3%)
Gastric infection	1 (1.2%)	1 (0.4%)	1 (0.3%)
Gastroenteritis	1 (1.2%)	1 (0.4%)	1 (0.3%)
Vascular device infection	1 (1.2%)	1 (0.4%)	1 (0.3%)
Femur fracture	1 (1.2%)	1 (0.4%)	1 (0.3%)
Blood creatinine increased	1 (1.2%)	1 (0.4%)	2 (0.6%)
Electrocardiogram QT prolonged	1 (1.2%)	2 (0.7%)	3 (0.8%)
Lipase increased	1 (1.2%)	2 (0.7%)	2 (0.6%)
Lymphocyte count decreased	1 (1.2%)	1 (0.4%)	1 (0.3%)
Platelet count decreased	1 (1.2%)	1 (0.4%)	1 (0.3%)
Weight decreased	1 (1.2%)	2 (0.7%)	3 (0.8%)
Hyperglycaemia	1 (1.2%)	1 (0.4%)	2 (0.6%)
Hypoalbuminaemia	1 (1.2%)	1 (0.4%)	1 (0.3%)
Hypophosphataemia	1 (1.2%)	1 (0.4%)	1 (0.3%)
Non-small cell lung cancer metastatic	1 (1.2%)	1 (0.4%)	1 (0.3%)
Cerebrovascular accident	1 (1.2%)	1 (0.4%)	2 (0.6%)
Syncope	1 (1.2%)	1 (0.4%)	1 (0.3%)
Pleural effusion	1 (1.2%)	2 (0.7%)	5 (1.4%)
Pulmonary embolism	1 (1.2%)	1 (0.4%)	2 (0.6%)
Acute kidney injury	0	3 (1.1%)	4 (1.1%)
Rash	0	3 (1.1%)	3 (0.8%)
Hypertension	0	3 (1.1%)	4 (1.1%)

Version date: March 1, 2024 (ALL NDA/ BLA reviews)

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

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Table 66. Worst Grade 3 TEAEs Occurring in ≥1% of Participants^a and All Worst Grade 4 TEAEs in Study 21607 (SAF)

Preferred term	Group D 20 mg BID N=81 (100%) n (%)	Whole Study 20 mg BID N=268 (100%) n (%)	Whole Study SAF N=357(100%) n (%)
Worst Grade 4 TEAE			
Duodenal ulcer perforation	1 (1.2%)	1 (0.4%)	1 (0.3%)
Dyspnoea	1 (1.2%)	2 (0.7%)	3 (0.8%)
Hypocalcaemia	1 (1.2%)	1 (0.4%)	1 (0.3%)
Hypokalaemia	0	3 (1.1%)	5 (1.4%)
Depression	0	1 (0.4%)	1 (0.3%)
Hypertransaminasaemia	0	0	1 (0.3%)
Pneumonitis	0	0	1 (0.3%)

BID=Twice daily; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of participants; n=number of participants with the event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

This table contains counts of participants. If a participant experienced more than one episode of a TEAE, the participant is counted only once within a preferred term. Participants may have more than one entry.

Sorted by preferred term incidences in Group D.

a: The cut-off applies to TEAEs that occurred in ≥1% of participants in either Group D or the Whole Study 20 mg BID population. MedDRA version 27.1

Source: Module 5.3.5.2, Report B003047, t_14_3_1_adae_tea_wst0.sas (Datasets ADSL, ADAE and ADDS)

The Applicant's Position:

The overall incidence of **TEAEs with Grade 3 as the worst grade** in severity was consistent across the 3 safety populations (36.1% to 42.0%) (**Table 67**). The most common TEAEs with Grade 3 as the worst grade were diarrhea and hypokalemia, occurring in 23.5% and 11.1% of participants in Group D, and in 14.6% and 7.8% of participants in the Whole Study 20 mg BID population, respectively. In the majority of participants who experienced TEAEs with Grade 3 as the worse grade in severity, the events were considered study drug-related by the investigator.

The incidence of **TEAEs with Grade 4 as the worst grade** in severity was consistent across the safety populations (2.2% to 2.5%) (**Table 67**). In Group D, the Grade 4 TEAEs reported were duodenal ulcer, dyspnea, and hypocalcemia in 1 participant each (1.2%). In the Whole Study 20 mg population, the only TEAE with a worst grade of Grade 4, occurring in >1% of participants, was hypokalemia (1.1%). Study drug-related TEAEs with Grade 4 as the worst grade occurred in 1 participant (1.2%) in Group D and in 3 participants (1.1%) in the Whole Study 20 mg population including dyspnea in 1 participant (in Group D) and hypokalemia in 2 participants.

Source (study drug-related TEAEs): Module 5.3.5.2 B003047, Table 8.3.1.2/2 [Datasets ADSL, ADAE and ADDS]

The FDA's Assessment:

While the FDA agrees that treatment emergent adverse events (TEAEs) that are Grade 3-4 are significant events it also considers other TEAEs including interstitial lung disease (ILD)/pneumonitis to be significant regardless of grade. These adverse events of special interest,

additional identified risks are addressed in detail in Section 8.2.5. Grade 3-4 TEAEs are addressed in the section Treatment Emergent Adverse Events and Adverse Reactions below.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

An overview of TEAEs in Study 21607 and the most common TEAEs ($\geq 10\%$ in any group) by MedDRA PT are presented in **Table 67** and **Table 68**, respectively.

Undesirable effects of sevabertinib, including ADRs and laboratory test abnormalities, were determined based on a comprehensive review of all safety data included in this application. A detailed rationale for the ADR determination can be found in Module 1.14.1.5, ADR justification document. The ADR and laboratory abnormalities tables, **Table 69** and **Table 70**, respectively, are ^{(b) (4)} Adverse Reactions.

Table 67. Overview of TEAEs in Study 21607 (SAF)

Number (%) of participants with	Group D 20 mg BID N=81 (100%) n (%)	Whole Study 20 mg BID N=268 (100%) n (%)	Whole Study SAF N=357 (100%) n (%)
Any TEAE ^a	81 (100.0%)	266 (99.3%)	354 (99.2%)
Worst grade			
Grade 1	9 (11.1%)	35 (13.1%)	50 (14.0%)
Grade 2	30 (37.0%)	111 (41.4%)	140 (39.2%)
Grade 3	34 (42.0%)	98 (36.6%)	129 (36.1%)
Grade 4	2 (2.5%)	6 (2.2%)	9 (2.5%)
Grade 5 (death)	6 (7.4%)	16 (6.0%)	26 (7.3%)
Grade 1 or 2	39 (48.1%)	146 (54.5%)	190 (53.2%)
Grade 3 or 4	36 (44.4%)	104 (38.8%)	138 (38.7%)
TESAE	26 (32.1%)	72 (26.9%)	110 (30.8%)
TEAE leading to dose reduction	20 (24.7%)	73 (27.2%)	95 (26.6%)
TEAE leading to dose interruption/delay	35 (43.2%)	113 (42.2%)	154 (43.1%)
TEAE leading to permanent discontinuation of study drug	4 (4.9%)	6 (2.2%)	9 (2.5%)
Any drug-related TEAE ^a	78 (96.3%)	257 (95.9%)	336 (94.1%)
Worst grade			
Grade 1	16 (19.8%)	56 (20.9%)	83 (23.2%)
Grade 2	31 (38.3%)	121 (45.1%)	154 (43.1%)
Grade 3	30 (37.0%)	76 (28.4%)	94 (26.3%)
Grade 4	1 (1.2%)	3 (1.1%)	4 (1.1%)
Grade 5 (death)	0	1 (0.4%)	1 (0.3%)
Grade 1 or 2	47 (58.0%)	177 (66.0%)	237 (66.4%)
Grade 3 or 4	31 (38.3%)	79 (29.5%)	98 (27.5%)
TESAE	11 (13.6%)	28 (10.4%)	33 (9.2%)
TEAE leading to dose reduction	19 (23.5%)	70 (26.1%)	92 (25.8%)
TEAE leading to dose interruption/delay	25 (30.9%)	88 (32.8%)	114 (31.9%)
TEAE leading to permanent discontinuation of study drug	4 (4.9%)	6 (2.2%)	8 (2.2%)

BID=Twice daily; CTCAE=Common Terminology Criteria for Adverse Events; n=Number of participants with an event; N=Total number of participants; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event; TESAE=Treatment-emergent serious adverse event

a: Any TEAE also includes participants with grade not available for all TEAEs.

CTCAE v. 5.0

Source: Module 5.3.5.2, Report B003047, t_14_3_1_adae_overview.sas (Datasets ADSL and ADAE)

Table 68. TEAEs (Any Grade) Occurring in ≥10% of Participants^a in Study 21607 (SAF)

Preferred term	Group D 20 mg BID N=81 (100%) n (%)			Whole Study 20 mg BID N=268 (100%) n (%)			Whole Study SAF N=357 (100%) n (%)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any TEAE	81 (100.0%)	34 (42.0%)	2 (2.5%)	266 (99.3%)	98 (36.6%)	6 (2.2%)	354 (99.2%)	129 (36.1%)	9 (2.5%)
Diarrhoea	68 (84.0%)	19 (23.5%)	0	230 (85.8%)	39 (14.6%)	0	293 (82.1%)	53 (14.8%)	0
Rash	41 (50.6%)	0	0	121 (45.1%)	3 (1.1%)	0	141 (39.5%)	3 (0.8%)	0
Paronychia	22 (27.2%)	0	0	61 (22.8%)	1 (0.4%)	0	82 (23.0%)	1 (0.3%)	0
Hypokalaemia	21 (25.9%)	9 (11.1%)	0	72 (26.9%)	21 (7.8%)	3 (1.1%)	86 (24.1%)	26 (7.3%)	5 (1.4%)
Weight decreased	20 (24.7%)	1 (1.2%)	0	43 (16.0%)	2 (0.7%)	0	53 (14.8%)	3 (0.8%)	0
Anaemia	19 (23.5%)	1 (1.2%)	0	46 (17.2%)	4 (1.5%)	0	67 (18.8%)	6 (1.7%)	0
Aspartate aminotransferase increased	16 (19.8%)	2 (2.5%)	0	39 (14.6%)	4 (1.5%)	0	50 (14.0%)	4 (1.1%)	0
Dry skin	16 (19.8%)	0	0	47 (17.5%)	0	0	66 (18.5%)	0	0
Nausea	16 (19.8%)	2 (2.5%)	0	53 (19.8%)	6 (2.2%)	0	73 (20.4%)	7 (2.0%)	0
Vomiting	16 (19.8%)	3 (3.7%)	0	51 (19.0%)	9 (3.4%)	0	69 (19.3%)	12 (3.4%)	0
Alanine aminotransferase increased	15 (18.5%)	2 (2.5%)	0	39 (14.6%)	5 (1.9%)	0	49 (13.7%)	7 (2.0%)	0
Decreased appetite	15 (18.5%)	3 (3.7%)	0	46 (17.2%)	6 (2.2%)	0	63 (17.6%)	7 (2.0%)	0
Stomatitis	15 (18.5%)	1 (1.2%)	0	57 (21.3%)	2 (0.7%)	0	71 (19.9%)	3 (0.8%)	0
Pruritus	14 (17.3%)	2 (2.5%)	0	32 (11.9%)	2 (0.7%)	0	48 (13.4%)	3 (0.8%)	0
Amylase increased	13 (16.0%)	0	0	37 (13.8%)	2 (0.7%)	0	53 (14.8%)	3 (0.8%)	0
Blood creatinine increased	12 (14.8%)	1 (1.2%)	0	34 (12.7%)	1 (0.4%)	0	46 (12.9%)	2 (0.6%)	0
Lipase increased	12 (14.8%)	1 (1.2%)	0	38 (14.2%)	2 (0.7%)	0	46 (12.9%)	2 (0.6%)	0
Dermatitis acneiform	10 (12.3%)	0	0	28 (10.4%)	0	0	41 (11.5%)	0	0
Pyrexia	9 (11.1%)	0	0	20 (7.5%)	0	0	26 (7.3%)	0	0

BID=Twice daily; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical dictionary for regulatory activities; N=Total number of participants; n=number of participants with an event; SAF=Safety analysis set; TEAE=Treatment-emergent adverse event

This table contains counts of participants. If a participant experienced more than one episode of a TEAE, the participant is counted only once within a preferred term. Participants may have more than one entry.

Sorted by preferred term incidences in Group D.

a: The cut-off applies to TEAEs that occurred in ≥10% of participants either in Group D or in the Whole Study 20 mg BID population

MedDRA v. 27.1, CTCAE v. 5.0

Source: Module 5.3.5.2, Report B003047, t_14_3_1_adae_teae_wst0.sas and t_14_3_1_adae_teae_by_ir.sas (Datasets ADSL, ADAE and ADDS)

Table 69. Adverse Reactions (≥10%) in Patients From Study 21607 (Group D)

Adverse Reaction*	N = 81		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders			
Diarrhea	84	24	0
Stomatitis ¹	33	1.2	0
Vomiting	20	3.7	0
Nausea	20	2.5	0
Abdominal pain ²	12	0	0
Skin and subcutaneous tissue disorders			
Rash ³	75	0	0
Paronychia ⁴	36	0	0
Dry skin ⁵	22	0	0
Pruritus	17	2.5	0
Metabolism and nutrition disorders			
Decreased appetite	19	3.7	0
Investigations			
Weight decreased	25	1.2	0
General disorders and Administration site conditions			
Fatigue ⁶	11	0	0
Eye Disorders			
Ocular toxicity ⁷	10	1.2	0

* Graded per NCI CTCAE version 5

¹ Stomatitis includes cheilitis, mouth ulceration, mucosal inflammation stomatitis

² Abdominal pain includes abdominal distention, abdominal pain, abdominal pain upper

³ Rash includes acne, acne varioliformis, dermatitis acneiform, eczema, erythema, folliculitis, rash, rash erythematous, rash maculopapular, rash pruritic, skin exfoliation

⁴ Paronychia includes ingrowing nail, nail disorder, onycholysis, paronychia

⁵ Dry skin includes dry skin, xeroderma

⁶ Fatigue includes asthenia, fatigue

⁷ Ocular toxicity includes blindness unilateral, corneal epithelial microcysts, dry eye, ocular toxicity, visual acuity reduced, visual impairment, xerophthalmia

Source: Module 1.14.1.5, ADR justification document (for the USPI)

Table 70. Laboratory Abnormalities (≥ 20%) in Patients From Study 21607 (Group D)

Laboratory Abnormality*	Study 21607 Group D N=81 ¹		
	All Grades (%) ²	Grade 3 (%)	Grade 4 (%)
Hematology			
Anemia	46	1.3	0
Lymphocyte count decreased	31	7	0
White blood cell decreased	22	1.3	0
Chemistry			
Lipase increased ³	51	13	0
Aspartate aminotransferase increased	46	5	0
Alanine aminotransferase increased	41	5	0
Hypokalemia	41	10	0
Hyperglycemia ³	33	1.3	0
Creatinine increased	33	0	0
Serum amylase increased	32	1.3	0
Alkaline phosphatase increased	26	0	0
Hyponatremia	26	0	0

* Laboratory abnormalities worsening from baseline

¹ The denominator used to calculate the rate varied from 61 to 80 based on the number of patients with a baseline value and at least one post-treatment value.

² Graded per NCI CTCAE version 5 using only numeric values.

³ Graded per NCI CTCAE version 4.03 using only numeric values.

Source: Module 1.14.1.5, ADR justification document (for the USPI)

The Applicant's Position:

Overall, the TEAE profile was consistent across the safety populations and sevabertinib was generally well tolerated at 20 mg BID (RP2D). In general, the majority of study drug-related TEAEs were of Grade 1 or 2 in severity. Grade 3 study drug-related TEAEs occurred in 26.3% to 37.0% of participants across the safety populations, and Grade 4 study drug-related TEAEs occurred in <1.5% of participants. 1 study drug-related Grade 5 TEAE was reported in the Whole Study 20 mg BID population, see Section “Deaths” for details. Permanent discontinuation of the study drug, due to any TEAE, was required for <5% of participants (**Table 67**).

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The **most commonly reported TEAEs** were consistent across the 3 safety populations (**Table 68**). Diarrhea and rash were the most common TEAEs across the safety populations. Diarrhea and rash were reported in 84.0% and 50.6% of participants in Group D, respectively, and in 85.8% and 45.1% of participants in the Whole Study 20 mg BID population, respectively.

The incidence of common TEAEs over time shows that diarrhea and rash were observed at earlier cycles of treatment (Months 1-3) in most participants who had these events as of the database cut-off (*source: Module 5.3.5.2, B003047, Table 8.3.1.1/15 [Datasets ADSL, ADAE, and DS]*).

In line with the most common TEAEs, diarrhea and rash were also the most commonly reported TEAEs assessed as study drug-related by the investigator, occurring in 84.0% and 49.4% of participants in Group D, respectively and in 84.3% and 44.0% of participants in the Whole Study 20 mg BID population, respectively (*source: Module 5.3.5.2, Report B003047, Table 8.3.1.2/4 [Datasets ADSL, ADAE, and ADDS]*). Diarrhea and rash are discussed in Section **8.2.4** as part of special topics TEAEs (AE groupings), which are events/disorders representing potential or known risks associated with EGFR/HER2 TKI class drugs.

Undesirable effects of sevabertinib, including ADRs and laboratory test abnormalities were determined based on a comprehensive review of safety data included in this application. The ADR and Laboratory Abnormalities **Table 69** and **Table 70** are proposed to be included in the sevabertinib USPI section 6 ‘Adverse Reactions’. As agreed with the FDA, Bayer is using the primary safety population, Group D (81 participants), to inform the Adverse Reactions Section of the USPI and the Pooled Whole Study 20 mg BID population (268 participants) to inform the Warnings and Precautions Section of the USPI.

The FDA’s Assessment:

The FDA generally agrees with the most commonly reported TEAEs by the Applicant; however, FDA disagrees with any attribution determinations in the context of this single-arm trial. FDA also agrees that most TEAEs were low grade and did not require treatment or impact dosage. The FDA’s independent analysis of the most commonly reported TEAEs for both Group D + E and pooled 20 mg populations are presented in FDA **Table 71**. The most common TEAEs of any Grade (occurring in $\geq 20\%$ of patients in either population) were diarrhea, stomatitis, nausea, rash, and paronychia. The most common Grade 3-4 TEAEs (occurring in $\geq 2\%$ in either population) were diarrhea, nausea, vomiting, pneumonia, and decreased appetite. TEAEs of interest are discussed in detail in Section **8.2.5**. Note that FDA’s analysis of laboratory-abnormality-based adverse reactions (i.e., anemia, ALT increase, amylase increase) are performed using the laboratory value dataset (adlb.xpt) and are excluded from FDA’s tables of adverse reactions

Table 71. FDA Analysis of TEAEs Occurring in $\geq 10\%$ by Grouped Terms

	Groups D + E	Pooled 20mg patients
	N = 136	N = 268

	%		%	
	All	Grade	All	Grade
	Grade	3-4	Grade	3-4
Any TEAE	100	43	99	39
Gastrointestinal disorders				
Diarrhea (GT)	87	18	86	15
Nausea	29	1.5	34	0.7
Vomiting (GT)	21	1.5	20	2.2
Stomatitis (GT)	15	2.2	19	3.7
Abdominal pain (GT)	10	0	10	0
Skin and subcutaneous tissue disorders				
Rash (GT)	66	1.5	62	1.1
Dry skin (GT)	20	0	18	0
Paronychia (GT)	33	0	23	0.4
Pruritus	14	1.5	12	0.7
Respiratory, thoracic and mediastinal disorders				
Dyspnea (GT)	10	1.5	7	1.1
Investigations				
Weight decreased	19	0.7	16	0.7
Infections and infestations				
Urinary tract infection (GT)	7	1.5	6	0.7
Pneumonia (GT)	7	4.4	7	2.6
Metabolism and nutrition disorders				
Decreased appetite	18	2.9	17	2.2
General disorders and administration site conditions				
Fatigue (GT)	13	0.7	14	0.4
Edema (GT)	10	0.7	8	0.4
Pyrexia (GT)	8	0	7	0
Eye disorders				
Eye disorder (GT)	16	0.7	14	0.4
Musculoskeletal and connective tissue disorders				

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Musculoskeletal pain (GT)	13	0	13	0.4

Source: FDA analysis of adae.xpt.

Note: Custom grouped terms are designated by '(GT)'.

Abdominal pain (GT) includes: Abdominal discomfort, Abdominal pain, and Abdominal pain upper.

Diarrhea (GT) includes: Colitis, Diarrhea, and Enterocolitis.

Dry skin includes dry skin, xeroderma.

Dyspnoea (GT) includes: Dyspnea, and Dyspnea exertional.

Eye disorder (GT) includes: Blindness unilateral, Cataract, Conjunctivitis, Conjunctivitis allergic, Corneal epithelial microcysts, Dry eye, Eye discharge, Eye pain, Eye swelling, Lacrimation increased, Ocular hyperemia, Ocular hypertension, Ocular toxicity, Punctate keratitis, Vision blurred, Visual acuity reduced, Visual impairment, and Xerophthalmia.

Fatigue (GT) includes: Asthenia, and Fatigue.

Musculoskeletal pain (GT) includes: Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, and Spinal pain.

Edema (GT) includes: Eyelid oedema, Face oedema, Lip oedema, Localized oedema, Oedema, and Oedema peripheral.

Paronychia: Includes ingrowing nail, nail disorder, onychoclasia, onycholysis, onychomadesis, paronychia.

Pneumonia (GT) includes: Pneumocystis jirovecii pneumonia, and Pneumonia.

Pyrexia (GT) includes: Pyrexia.

Rash (GT) includes: Dermatitis, Dermatitis acneiform, Eczema, Eczema asteatotic, Palmar-plantar erythrodysesthesia syndrome, Rash, Rash erythematous, Rash maculo-papular, Rash pruritic, Rash pustular, and Skin exfoliation.

Stomatitis (GT) includes: Aphthous ulcer, Cheilitis, Mouth ulceration, Mucosal inflammation, and Stomatitis.

Urinary tract infection (GT) includes: Cystitis, and Urinary tract infection.

Vomiting (GT) includes: Hematemesis, and Vomiting.

Laboratory Findings

Data:

Changes in hematology and chemistry laboratory parameters were analyzed for participants with both baseline and post-baseline values in Study 21607. Hematology and general chemistry abnormalities that worsened from baseline during the treatment period are presented in **Table 72**.

In **Group D**, the following laboratory abnormalities worsened post-baseline in >20% of participants: lipase increased (51.3%), anemia (46.3%), AST increased (46.3%), ALT increased (41.3%), hypokalemia (41.3%), creatinine increased (32.5%), hyperglycemia (32.5%), serum amylase increased (32.1%), lymphocyte count decreased (31.1%), alkaline phosphatase increased (26.3%), hyponatremia (26.3%), and white blood cell decreased (21.5%).

- Worsening to Grade 3 was observed in lipase increased (12.8%), hypokalemia (10.0%), lymphocyte count decreased (6.6%), AST increased (5.0%), ALT increased (5.0%), anemia (1.3%), hyperglycemia (1.3%), serum amylase increased (1.3%), and white blood cell decreased (1.3%).
- No worsening of laboratory values to Grade 4 was observed in Group D.

In the **Whole Study 20 mg BID**, the following laboratory abnormalities worsened post-baseline in >20% of participants: hypokalemia (42.6%), anemia (41.9%), lipase increased (39.9%), hyperglycemia (35.7%), AST increased (35.5%), ALT increased (34.7%), serum amylase

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increased (31.7%), creatinine increased (29.1%), lymphocyte count decreased (25.4%), hyponatremia (24.2%), and alkaline phosphatase increased (21.5%).

- Worsening to Grade 3 was observed in hypokalemia (10.9%), lipase increased (9.1%), lymphocyte count decreased (4.9%), ALT increased (2.3%), AST increased (2.3%), serum amylase increased (2.3%), anemia (1.5%), hyperkalemia (0.8%), neutrophil count decreased (0.5%), lymphocyte count increased (0.5%), hyperglycemia (0.4%), white blood cell decreased (0.4%), and creatinine increased (0.4%).
- Worsening to Grade 4 was observed in hypokalemia (0.8%), lipase increased (0.8%), serum amylase increased (0.8%), neutrophil count decreased (0.5%), and creatinine increased (0.4%).

Table 72. Laboratory Abnormalities Worsening From Baseline in Study 21607 (SAF)

Laboratory category CTCAE term	Worst CTCAE grade ^a	Group D 20 mg BID	Whole Study 20 mg BID	Whole Study SAF
General chemistry				
Lipase increased	N ^b	78 (100%)	263 (100.0%)	352 (100.0%)
	All categories	40 (51.3%)	105 (39.9%)	142 (40.3%)
	Grade 3 (>2.0 - 5.0 x ULN)	10 (12.8%)	24 (9.1%)	37 (10.5%)
	Grade 4 (>5.0 x ULN)	0	2 (0.8%)	2 (0.6%)
Aspartate aminotransferase increased	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	37 (46.3%)	94 (35.5%)	114 (32.2%)
	Grade 3	4 (5.0%)	6 (2.3%)	8 (2.3%)
	Grade 4	0	0	0
Alanine aminotransferase increased	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	33 (41.3%)	92 (34.7%)	116 (32.8%)
	Grade 3	4 (5.0%)	6 (2.3%)	8 (2.3%)
	Grade 4	0	0	0
Hypokalemia	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All categories	33 (41.3%)	113 (42.6%)	136 (38.4%)
	Grade 3 (<3.0 - 2.5 mmol/L)	8 (10.0%)	29 (10.9%)	34 (9.6%)
	Grade 4 (<2.5 mmol/L)	0	2 (0.8%)	4 (1.1%)
Creatinine increased	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	26 (32.5%)	77 (29.1%)	105 (29.7%)
	Grade 3	0	1 (0.4%)	2 (0.6%)
	Grade 4	0	1 (0.4%)	1 (0.3%)
Hyperglycemia	N ^b	77 (100.0%)	258 (100.0%)	345 (100.0%)
	All grades	25 (32.5%)	92 (35.7%)	128 (37.1%)
	Grade 3	1 (1.3%)	1 (0.4%)	3 (0.9%)
	Grade 4	0	0	0
Serum amylase increased	N ^b	78 (100%)	262 (100%)	351 (100%)
	All categories	25 (32.1%)	83 (31.7%)	111 (31.6%)
	Grade 3 (>2.0 - 5.0 x ULN)	1 (1.3%)	6 (2.3%)	8 (2.3%)
	Grade 4 (>5.0 x ULN)	0	2 (0.8%)	4 (1.1%)
Alkaline phosphatase increased	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	21 (26.3%)	57 (21.5%)	81 (22.9%)
	Grade 3	0	0	0
	Grade 4	0	0	0
Hyponatremia	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)

Table 72. Laboratory Abnormalities Worsening From Baseline in Study 21607 (SAF)

Laboratory category CTCAE term	Worst CTCAE grade ^a	Group D 20 mg BID	Whole Study 20 mg BID	Whole Study SAF
	All categories	21 (26.3%)	64 (24.2%)	85 (24.0%)
	Grade 3 (<125 - 120 mmol/L)	0	0	1 (0.3%)
	Grade 4 (<120 mmol/L)	0	0	0
Blood bilirubin increased	N ^b	80 (100.0%)	264 (100.0%)	353 (100.0%)
	All grades	10 (12.5%)	31 (11.7%)	39 (11.0%)
	Grade 3	0	0	1 (0.3%)
	Grade 4	0	0	0
Hypoglycemia	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	9 (11.3%)	17 (6.4%)	27 (7.6%)
	Grade 3	0	0	0
	Grade 4	0	0	0
Hyperkalemia	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	8 (10.0%)	28 (10.6%)	44 (12.4%)
	Grade 3	0	2 (0.8%)	2 (0.6%)
	Grade 4	0	0	0
Hypematremia	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	6 (7.5%)	11 (4.2%)	13 (3.7%)
	Grade 3	0	0	0
	Grade 4	0	0	0
Hematology				
Anemia	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	37 (46.3%)	111 (41.9%)	145 (41.0%)
	Grade 3	1 (1.3%)	4 (1.5%)	7 (2.0%)
	Grade 4	0	0	0
Lymphocyte count decreased	N ^b	61 (100.0%)	205 (100.0%)	285 (100.0%)
	All grades	19 (31.1%)	52 (25.4%)	82 (28.8%)
	Grade 3	4 (6.6%)	10 (4.9%)	16 (5.6%)
	Grade 4	0	0	0
White blood cell decreased	N ^b	79 (100.0%)	262 (100.0%)	351 (100.0%)
	All grades	17 (21.5%)	42 (16.0%)	60 (17.1%)
	Grade 3	1 (1.3%)	1 (0.4%)	1 (0.3%)
	Grade 4	0	0	0
Neutrophil count decreased	N ^b	65 (100.0%)	214 (100.0%)	297 (100.0%)
	All grades	9 (13.8%)	25 (11.7%)	36 (12.1%)
	Grade 3	0	1 (0.5%)	1 (0.3%)
	Grade 4	0	1 (0.5%)	1 (0.3%)
Platelet count decreased	N ^b	79 (100.0%)	262 (100.0%)	351 (100.0%)
	All grades	6 (7.6%)	29 (11.1%)	38 (10.8%)
	Grade 3	0	0	0
	Grade 4	0	0	0
Lymphocyte count increased	N ^b	61 (100.0%)	205 (100.0%)	285 (100.0%)
	All grades	2 (3.3%)	5 (2.4%)	5 (1.8%)
	Grade 3	0	1 (0.5%)	1 (0.4%)
	Grade 4	0	0	0
Hemoglobin increased	N ^b	80 (100.0%)	265 (100.0%)	354 (100.0%)
	All grades	1 (1.3%)	7 (2.6%)	8 (2.3%)
	Grade 3	0	0	0
	Grade 4	0	0	0
Leukocytosis	N ^b	79 (100.0%)	262 (100.0%)	351 (100.0%)
	All grades	0	0	0
	Grade 3	0	0	0
	Grade 4	0	0	0

Table 72. Laboratory Abnormalities Worsening From Baseline in Study 21607 (SAF)

Laboratory category CTCAE term	Worst CTCAE grade ^a	Group D 20 mg BID	Whole Study 20 mg BID	Whole Study SAF

BID=Twice daily; CTCAE=Common Terminology Criteria for Adverse Events; N=Total number of participants; SAF=Safety analysis set

All laboratory data collected after the start of first dose up to 30 days after the last administration of sevabertinib were considered in this table.

a: Grading was based on CTCAE v. 5.0 using only numeric values. The worst grade during treatment-emergent period is reported, if worsening from baseline. Hyperglycemia was graded based on CTCAE v. 4.03 numeric values. For hypokalemia, hyponatremia, lipase increased, and serum amylase increased, worsening from baseline categories were obtained from the grade definitions in CTCAE v. 5.0 but are based on laboratory measurements only.

b: Denominator, which includes participants with a baseline and at least one non-missing value during treatment-emergent period for the laboratory test, including scheduled and unscheduled visits.

Ordered based on decreasing incidence of "All grades" in Group D.

Source: Module 5.3.5.2, Report B003047, t_14_3_4_3_adlb_ctcae5_grd.sas and t_s1_14_3_4_adlbctc_ctcae5_summary.sas (Datasets ADSL, ADLB and ADLBCTC)

Liver function

Liver enzyme abnormalities, potential Hy's Law cases, and potential DILI cases from Study 21607 were reviewed to assess hepatotoxicity.

Liver function test values (ALT, AST, ALP, and blood bilirubin) most commonly worsened to Grade 1 as the worst grade during treatment, with no values worsening to Grade 4 (**Table 72**). There were no notable changes in mean laboratory values during treatment.

In terms of TEAEs, Grade ≥ 3 TEAEs of ALT increased and AST increased were reported at low levels. Grade 3 AST increased and ALT increased were reported in 2 participants each (2.5%) in Group D, and in 4 participants (1.5%) and in 5 participants (1.9%), respectively, in the Whole Study 20 mg BID population. No Grade 4 TEAEs were reported. No Grade ≥ 3 TEAEs of ALP increased or bilirubin increased were reported in Group D or the Whole Study 20 mg BID population (**Table 66**). There were no TESAEs or TEAEs leading to study drug discontinuation due to AST increased, ALP increased, or bilirubin increased in any of the safety populations. 1 participant in the Whole Study SAF (receiving 10 mg BID dose) discontinued treatment due to Grade 2 ALT increased (**Table 62**). Additionally, study drug-related Grade 3 hepatic function abnormal was reported as a TESA in 2 participants (2.5%) in Group D and in 3 participants (1.1%) in the Whole Study 20 mg BID population (**Table 60**). 1 participant (included in both populations) discontinued the study drug permanently due to hepatic function abnormal (**Table 62**).

A potential Hy's Law case was defined as having any post baseline total bilirubin ≥ 2 x ULN within 30 days after a post baseline ALT or AST ≥ 3 x ULN, and concurrent ALP < 2 x ULN in the treatment-emergent period. Altogether, 2 participants fulfilled the biochemical criteria of Hy's Law for bilirubin and ALT/AST: 1 participant in the Whole Study 20 mg BID population (from 20 mg BID TAB group in the DE/BF part) and 1 participant in the 40 mg QD LSF dose level group in the DE/BF part. These cases were assessed further in the clinical context, including alternative causes for the laboratory abnormality. Although the participants fulfilled

the laboratory criteria for bilirubin and ALT/AST, they were not definite cases of Hy's Law.

The Applicant's Position:

Across the 3 safety populations, laboratory abnormalities that worsened from baseline during the treatment mostly worsened to Grade 1 or 2 as the worst CTCAE grade v. 5.0 (**Table 72**).

In the primary safety population, Group D, the most common laboratory abnormalities (>40% of participants with a baseline value and at least 1 value during the treatment-emergent period available) worsening post-baseline were lipase increased (51.3%), anemia (46.3%), AST increased (46.3%), ALT increased (41.3%), and hypokalemia (41.3%).

Worsening to Grade 3 was observed in lipase increased (12.8%), hypokalemia (10.0%), lymphocyte count decreased (6.6%), AST increased (5.0%), ALT increased (5.0%), anemia (1.3%), hyperglycemia (1.3%), serum amylase increased (1.3%), and white blood cell decreased (1.3%). No laboratory value worsened to Grade 4 in Group D. The results were generally comparable between Group D and the Whole Study 20 mg BID population; however, worsening to Grade 4 was observed in the Whole Study 20 mg BID for hypokalemia, lipase increased, serum amylase increased, neutrophil count decreased, and creatinine increased.

Overall, while increased aminotransferases were observed with sevabertinib use in Study 21607, the elevations were mostly of Grade 1 or Grade 2 in severity, with no Grade 4. No cases of Hy's Law were identified.

The FDA's Assessment:

FDA's analysis of the most commonly reported lab abnormalities ($\geq 10\%$) for Groups D + E and pooled 20 mg populations is presented in FDA **Table 73**. The most common ($\geq 2\%$) Grade 3 or 4 laboratory abnormalities were AST increased, ALT increased, lymphocytes decreased, hypokalemia, amylase increased, lipase increased, and hyponatremia. Hepatotoxicity is an identified risk and is discussed further in Section 8.2.5. FDA agrees there were no incidences of Hy's law cases.

As there was a relatively high incidence of Grade 3-4 elevation of pancreatic enzymes, FDA investigated this further. There were no TEAEs described as pancreatitis in either safety population. Narrative review did not reveal a clear association with pancreatic enzyme elevation alongside abdominal pain as a TEAE. However, given the frequency of Grade 3-4 pancreatic enzyme elevation, the FDA has determined that providers should be made aware of this risk to inform patient monitoring and it will be included as a Warning in Section 5 of the product label.

FDA's analysis considered only laboratory values with an associated CTCAE toxicity Grade. Patients with a baseline and at least one post-baseline laboratory value were counted as the denominator for each test (evaluative patients). The denominator varied from test to test. CTCAE version 5.0 considers non-numerical aspects of a subset of laboratory tests when determining Grade (i.e. accompanying symptoms, intervention indicated, or hospitalization). In our independent analysis, this was relevant to four laboratory abnormalities: decreased potassium, increased lipase, increased amylase, and decreased sodium. For these laboratory tests, only the

numerical value was used in the Applicant’s dataset, and in our analysis for confirming toxicity Grade, without accounting for non-numerical factors. For example, CTCAE version 5.0 distinguishes Grade 2 and Grade 3 lipase increase >2-5x the upper limit of normal (ULN) based on the presence of symptoms.

Table 73. Laboratory Abnormalities Occurring in ≥10% of Patients

	Groups D + E		Pooled 20mg	
	N = 136		N = 268	
	%		%	
	All	Grade	All	Grade
	Grade	3-4	Grade	3-4
General Chemistry				
Aspartate Aminotransferase (U/L) – Increased	41	3	35	2.3
Magnesium (mg/dL)– Decreased	40	0	35	0.4
Alanine Aminotransferase (U/L)– Increased	37	3	35	2.3
Glucose (mg/dL), Fasting,– Increased	36	0.7	37	0.4
Albumin (g/dL)– Decreased	32	1.5	30	0.8
Creatinine (mg/dL)– Increased	27	0	29	0.8
Calcium Corrected (mg/dL)– Decreased	28	1.5	28	1.5
Alkaline Phosphatase (U/L – Increased)	24	0	22	0
Triglycerides (mg/dL)– Increased	22	0	28	0.4
Bilirubin (mg/dL)– Increased	14	0	12	0
Cholesterol (mg/dL)– Increased	10	0	10	0
Glucose (mg/dL), Fasting,– Decreased	7	0	6	0
Potassium (mmol/L)– Increased	9	0.7	11	0.8
Potassium (mmol/L)– Decreased	45	13	43	12
Triacylglycerol Lipase (U/L) – Increased	48	12	40	10
Amylase, unspecified (U/L) – Increased	31	3.8	32	3.1

	Groups D + E		Pooled 20mg	
	N = 136		N = 268	
	%		%	
	All	Grade	All	Grade
	Grade	3-4	Grade	3-4
Sodium (mmol/L)– Decreased	26	4.4	24	4.5
Hematology				
Hemoglobin decreased	47	1.5	42	1.5
Lymphocytes decreased	32	6	25	4.9
Leukocytes decreased	21	0.7	16	0.4
Neutrophils decreased	16	0.9	12	0.9
Platelet decreased	13	0	11	0

Denominators for laboratory analyses are based on patients with a baseline and at least one on-study value. Patients must have had at least one grade worsening on study to be counted in analyses and only worst grade will be included in the analyses.

Source: FDA analysis based on adlb.xpt

Vital Signs

Data and the Applicant’s Position:

Summary statistics and changes from baseline in vital sign parameters were summarized over time. There were no clinically meaningful findings in the vital signs measurements (blood pressure, heart rate, temperature, body weight, BMI, and respiratory rate) related to safety in Study 21607 (Module 5.3.5.2, Report B003047, Tables 8.3.5.2/8 to 8.3.5.2/14 [Datasets ADSL and ADEGM]).

The FDA’s Assessment:

FDA agrees with the Applicant’s position. There was no clinically meaningful change from baseline in heart rate, systolic and diastolic blood pressure, temperature, and peripheral oxygen saturation in Study SOHO-01.

Electrocardiograms (ECGs)

Data and The Applicant’s Position:

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Single or triplicate 12-lead ECGs were obtained, as defined in the Schedule of Activities in the protocol. Mean changes in the ECGs in the Whole Study SAF population were small and not clinically significant (*Module 5.3.5.2, B003047, Tables 8.3.5.2/8 to 8.3.5.2/14 [Datasets ADSL and ADEGM]*). Cardiac disorders were relatively infrequent across the safety populations (see Section 8.2.4).

Echocardiograms revealed no clinically meaningful changes in cardiac function values. The changes in mean LVEF were generally small, and the safety follow-up visits showed minimal changes from baseline. LVEF values were similar across all 3 safety populations.

For the results of the concentration-QTc analysis, please see Section “QT” below.

The FDA’s Assessment:

FDA’s analysis identified 6% of patients in the Group D +E safety population with an event of cardiac arrhythmia. As discussed in Section 8.2.4.5, FDA determined there were multiple possible confounding factors including concomitant use of anti-diarrheal medications and electrolyte disturbances from diarrhea. For these reasons FDA determined that cardiac arrhythmia did not warrant a specific warning in the USPI but did warrant inclusion within the USPI in Section 6.

FDA agrees the Applicant’s position as it concern echocardiograms. FDA’s independent analysis of QT prolongation is discussed below.

QT

Data:

A concentration-QTc analysis was performed and is reported separately (Cardiac safety risk assessment including concentration–QTc analysis, Module 5.3.3.5, Report B003828).

The Applicant’s Position:

The analysis of the association between time-matched plasma concentrations and baseline corrected QTcF (Δ QTcF), based on high-quality triplicate ECG data, in Study 21607 showed a statistically significant increase in Δ QTcF with increasing sevabertinib plasma concentration. The mean change from baseline in QTcF interval was well below 10 ms, and the upper limit of the 90% CI of the predicted Δ QTcF remained well below the threshold of regulatory concern of a Δ QTcF of 20 ms at doses up to 2 times the recommended TDD.

Based on a concentration-QTc(F) analysis, cardiologist evaluation, and central tendency analysis of relevant cardiac intervals (PR, QRS, RR, and QT), the risk of cardiovascular events due to sevabertinib treatment, as observable from ECGs, is considered low.

The FDA’s Assessment:

FDA independent analysis concluded that sevabertinib does not cause mean QTc interval

prolongation ≥ 20 msec based on data from SOHO-01. Without a placebo control, however, FDA cannot conclude that sevabertinib has no effect on the QTc interval.

Immunogenicity

Data and the Applicant's Position:

Not applicable; no immunogenicity assessments were conducted as part of Study 21607.

The FDA's Assessment:

Not applicable

8.2.4. Analysis of Submission-Specific Safety Issues

Data:

A safety analysis of AEs characteristic of the pharmacological class was performed in Study 21607 by grouping of TEAEs representing similar medical conditions. The special safety topics for this analysis were selected based on toxicities reported within the sevabertinib program and class toxicities of TKIs targeting HER2 and/or EGFR, and included gastrointestinal toxicities, skin-related toxicities, ILD/pneumonitis, ocular toxicity, and cardiac toxicities. The Sponsor defined each of the queries for these special topics using SMQs, SOCs, HLTs, PTs or Sponsor generated MLGs as shown in **Table 53**.

8.2.4.1. Gastrointestinal toxicities

Gastrointestinal toxicity, especially diarrhea is the most frequently reported and well described toxicity with HER2/EGFR TKIs, with incidence rates varying depending on the agent used and dosage, and occur as frequent as in >95% of patients (42). Diarrhea is caused by intestinal epithelial cell damage and inflammation, and HER2 inhibition leads to excessive chloride translocation into the intestinal lumen, resulting in secretory diarrhea (43, 44).

In Study 21607, TEAEs within the SOC of gastrointestinal disorders were the most commonly reported events across the safety populations, with 88.9% of participants in Group D and 90.7% of participants in the Whole Study 20 mg BID population. TEAE incidences within this SOC were mostly driven by PT diarrhea, followed by nausea, vomiting, and stomatitis, as summarized below.

Diarrhea, nausea, and vomiting

Diarrhea (individual PT) was the most common TEAE in Study 21607, occurring in >80% of participants across the safety populations (**Table 68**). The events were considered study drug-related in all participants experiencing diarrhea in Group D (84.0%). Overall, the incidence and severity profile of diarrhea was consistent across the 3 safety populations.

In the majority of participants with diarrhea, the events were of Grade 1 or 2 in severity (worst grade). Diarrhea was the most common TEAE with Grade 3 as the worst grade, affecting 23.5% and 14.6% of participants in Group D and the Whole Study 20 mg BID population, respectively. No Grade 4 events of diarrhea were reported (**Table 68**). Diarrhea was also the most common TEAE leading to study drug interruption/delay (16.0% and 15.3%) or study drug dose reduction (11.1% and 11.6%) in Group D and the Whole Study 20 mg BID population, respectively (see Section “Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects”). Serious events of diarrhea were reported in 6.2% of participants in Group D and in 3.7% of participants in the Whole Study 20 mg BID population (**Table 60**). No permanent discontinuations were required due to diarrhea (**Table 62**).

The median time to the first TEAE of diarrhea was 4 days (range: 1 day to 6.2 months) after the start of study treatment in both Group D and in the Whole Study 20 mg BID population. The median time to recovery of the first TEAE of diarrhea was 4.9 months (range: 1 day to 5.9 months) in Group D and 3.6 months (range: 1 day to 16.7 months) in the Whole Study 20 mg BID population. Most of the participants with a TEAE of diarrhea in Group D (83.8%) and in the Whole Study 20 mg BID population (74.8%) received anti-diarrhea medication for the TEAE concomitantly with sevabertinib (*Source: Module 5.3.5.2, B003047, Tables 8.3.1.4/12, 8.3.1.4/14 and 8.3.1.4/16 [Datasets ADSL, ADTTE, ADAE and ADCM]*).

The incidence and severity of **nausea and vomiting** (individual PTs) were consistent across the safety populations, with both occurring in approximately 20% of participants in Group D and in the Whole Study 20 mg BID population. The events were of Grade 1 or 2 in severity in most participants experiencing these TEAEs (**Table 68**). Further details on gastrointestinal toxicities are provided in Module 2.7.4, Section 2.1.4.2.1.

Stomatitis

Stomatitis is a common class toxicity of EGFR TKIs and was a common TEAE with sevabertinib across the safety populations (**Table 68**). The HLT of stomatitis and ulceration was used to evaluate stomatitis in Study 21607. Overall, the incidence and severity of stomatitis were consistent across the 3 safety populations (*Module 5.3.5.2, B003047, Table 8.3.1.4/5s1 [Datasets ADSL and ADAE]*).

Stomatitis occurred in 25.9% of participants in Group D and in 29.1% of participants in the Whole Study 20 mg BID population. In the vast majority of participants with stomatitis, the events were of Grade 1 or 2 in severity and were assessed as related to the study drug by the investigator. There were no TESAEs or permanent treatment discontinuations due to stomatitis. Dose reduction and dose interruptions/delays due to stomatitis were uncommon, ranging from

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1.2% to 2.2% of participants in both populations. Further details on stomatitis are provided in Module 2.7.4, Section 2.1.4.2.2.

8.2.4.2. Skin-related toxicities

Skin-related toxicities, including events such as rash and paronychia, are known risks of EGFR TKIs (42).

In Study 21607, TEAEs within the SOC skin and subcutaneous tissue disorders were reported in 85.2% of participants in Group D and in 75.7% of participants in the Whole Study 20 mg BID population (*Module 5.3.5.2, B003047, Table 8.3.1.1/4 [Datasets ADSL, ADAE and ADDS]*). PTs rash and paronychia were among the most commonly reported TEAEs across the safety populations (**Table 68**). They were also analyzed using grouped terms, as summarized below.

Rash

A fully reversible mode of action-related degenerative effect on the epidermis was observed in repeat-dose toxicity studies of sevabertinib in rats (Module 2.6.6, Section 3.1.4).

No specific dermatological exclusion criteria were included in Study 21607. Dermatological treatment was to be started for participants with skin reactions of any grade. It was recommended that participants should follow sun protection measures during the study.

A database search, with a combination of MLGs rash and skin erythema, and PTs of dermatitis, dermatitis acneiform, and acne, was performed for evaluation of rash. Rash events were the second most reported events, occurring in 71.6% and 62.7% of participants in Group D and in the Whole Study 20 mg BID population, respectively. In almost all participants with rash, the events were of Grade 1 or 2 in severity and assessed as related to the study drug by the investigator. Rash, with Grade 3 as the worst grade, occurred in 1.1% of participants in the Whole Study 20 mg BID population, with no Grade 3 events in Group D. No Grade 4 events of rash were reported. None of the participants in Group D and 1 participant (0.4%) in the Whole Study 20 mg BID population had a TESAE of rash, and no permanent discontinuations were required due to rash events. Rash rarely led to dose reduction or dose interruption/delay (none of the participants in Group D and in <3% of participants in the Whole Study 20 mg BID population) (*Module 5.3.5.2, Report B003047, Table 8.3.1.4/6s1 [Datasets ADSL and ADAE]*).

Paronychia

Paronychia is also a known class toxicity of EGFR TKIs. The analysis of paronychia was performed with a grouped term search, including PTs of paronychia, nail infection, nail bed infection and HLT nail and nail bed conditions (excluding infections and infestations). Paronychia, as a grouped term, was reported in 35.8% and 28.0% of participants in Group D and in the Whole Study 20 mg BID population, respectively. In almost all participants with paronychia, the events were of Grade 1 or 2 in severity and assessed as related to the study drug by the investigator. Paronychia, with Grade 3 as the worst grade, occurred in 1 participant (0.4%) in the Whole Study 20 mg BID population, with no Grade 3 events in Group D. None of the participants experienced a TESAE of paronychia, and none discontinued study treatment due to

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paronychia. Paronychia rarely led to dose reduction or dose interruption/delay (*Module 5.3.5.2, B003047, Table 8.3.1.4/7s1 [Datasets ADSL and ADAE]*).

Further details on skin-related toxicities are provided in Module 2.7.4, Section 2.1.4.2.3.

8.2.4.3. ILD/pneumonitis

Interstitial lung disease (ILD) is a known and potentially serious adverse event associated with some EGFR TKIs. The incidence, severity, and risk factors for ILD vary depending on the specific TKI, patient population, and underlying lung conditions (42). No pulmonary toxicity was observed in the pre-clinical toxicology studies of sevabertinib (Module 2.6.6, Section 3). Patients with a past medical history of pneumonitis/ILD, drug induced pneumonitis/ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from participation in sevabertinib studies.

A SMQ search of ILD (narrow search) was conducted for analysis of ILD/pneumonitis (*Module 5.3.5.2, B003047, Tables 8.3.1.4/8s1, 8.3.1.4/2, 8.3.2.2/8, 8.3.2.2/6 [Datasets ADSL, ADAE and ADDS]*).

The search results for Group D showed that none of the participants had TEAEs of ILD or pneumonitis. Grade 1 lung opacity and Grade 2 radiation pneumonitis were reported in 1 participant each (both non-related). In addition to the TEAEs retrieved from Group D, 1 participant in the Whole Study 20 mg BID population had a serious, study drug-related Grade 3 ILD (PID [REDACTED]^{(b) (6)} with an EGFR mutation from Group A). None of the events in Group D or in the Whole Study 20 mg BID population led to permanent discontinuation of study treatment.

In addition, 1 study-drug related Grade 1 pneumonitis (PID [REDACTED]^{(b) (6)}) and one serious, non-related Grade 4 pneumonitis (PID [REDACTED]^{(b) (6)}) were reported in the Whole Study SAF. The narratives of the SAEs Grade 3 ILD and Grade 4 pneumonitis are provided in Module 5.3.5.2, Report B003047, Section 9. Further details on the analysis of ILD/pneumonitis are provided in Module 2.7.4, Section 2.1.4.2.4.

8.2.4.4. Ocular toxicity

Ocular toxicity is considered a class toxicity of HER2/EGFR TKIs (42). Minimal and non-reproducible ocular toxicity at a lower dose level of sevabertinib was observed in a 2-week rat study (although no explanation could be provided) (Module 2.6.6, Section 3.1.1). In a 13-week toxicology study in rats, ophthalmological examinations did not reveal any test item-related findings, up to the highest dose of 10 mg/kg/day (Module 2.6.6, Section 3.1.4).

In Study 21607, participants were closely monitored for ocular toxicity. Full ophthalmologic examination, including slit lamp examination, was performed at screening and when clinically indicated during the treatment period, as well as at the end of the study.

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A detailed review of eye disorders SOC was performed for ocular toxicity. Overall, the incidence and severity of TEAEs within the SOC of eye disorders were consistent across the safety populations. Ocular toxicity TEAEs were reported in 18.5% of participants in Group D and in 13.1% of participants in the Whole Study 20 mg BID population, and the events were considered related to the study drug in 9.9% and 8.6% of participants, respectively. The most reported ocular TEAE was dry eye for both Group D (4.9%) and the Whole Study 20 mg BID population (5.6%). Ocular toxicities were predominately of Grade 1 or 2 in severity, with no events deemed serious in Group D and in the Whole Study 20 mg BID population. Ocular toxicities led to discontinuation of the study treatment in 1 participant from Group D (**Table 62**) (Grade 3 TEAE corneal epithelial microcysts, PID (b) (6)) (Module 5.3.5.2, B003047, Tables 8.3.1.4/9s1 and 8.3.1.4/2 [Datasets ADSL, ADAE, and ADDS]).

Further details on ocular toxicities are provided in Module 2.7.4, Section 2.1.4.2.5.

8.2.4.5. Cardiac toxicities

Cardiac toxicities, particularly decreases in LVEF have been observed with anti-*HER2* therapies (42, 45).

Based on the eligibility criteria in Study 21607, the participants with a resting QTcF >450 ms or with a history of congestive heart failure of Class>II according to the New York Heart Association Functional Classification or serious cardiac arrhythmias requiring treatment or any clinically important abnormalities in rhythm, conduction, or morphology, were excluded from the study. Baseline and periodic (every 12 weeks) LVEF evaluations (echocardiogram) were performed during the study. Frequent ECG monitoring was also performed.

No cardiotoxicity was observed in pre-clinical toxicology studies with sevabertinib. *In vivo*, in telemetered dogs, delayed cardiac ventricular repolarization (QTc interval prolongation) was observed when sevabertinib was administered at approximately 12 times the human exposure at 20 mg BID (relative to unbound C_{max} at steady state) (Module 2.6.6, Section 3, Module 2.7.2, Section 3.5.1).

TEAEs of electrocardiogram QT prolonged were reported in 2 participants (2.5%) in Group D and in 6 participants (2.2%) in the Whole Study 20 mg BID population, and were all considered related to the study drug by the investigator. None of the events were considered serious. 1 participant discontinued study treatment due to Grade 3 TEAE of electrocardiogram QT prolonged (**Table 62**) (Module 5.3.5.2, B003047, Tables 8.3.1.1/4, 8.3.1.2/2 and 8.3.2.2/2 [Datasets ADSL, ADAE, and ADDS]).

The SOC of cardiac disorders was used to analyze cardiac toxicities (Module 5.3.5.2, B003047, Table 8.3.1.4/10s1 [Datasets ADSL and ADAE]). Overall, the incidence and severity of cardiac TEAEs were consistent across the safety populations. Cardiac TEAEs were reported in 9.9% of participants in Group D and in 7.8% of participants in the Whole Study 20 mg BID population. In approximately half of the participants with cardiac disorders, the events were assessed as related to the study drug by the investigator.

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In Group D, the cardiac events were of Grade 3 as the worst severity in most participants (7.4%), while in the Whole Study 20 mg BID population, the events were mostly Grade 1 or 2 as the worst grade (5.2%). No Grade 4 cardiac events were reported. 1 participant in the Whole Study 20 mg population had Grade 5 cardio-respiratory arrest, assessed as related to the study drug (see Section Deaths for a brief summary).

In Group D, TESAEs of cardiac disorders were reported in 6 participants (7.4%) and were all reported with Grade 3 as the worst grade: pericardial effusion in 2 participants, atrioventricular block complete, pericardial effusion malignant, and pericarditis in 1 participant each, and 1 participant had both arrhythmia and sinus tachycardia (*Module 5.3.5.2, B003047, Table 8.3.2.2/8 and Listing 10.2.7/1 [Datasets ADSL, ADAE and ADDS]*). None of the events reported within the SOC of cardiac disorders led to permanent discontinuation of study treatment. Further details on cardiac toxicities are provided in Module 2.7.4, Section 2.1.4.2.6.

The Applicant's Position:

- In Study 21607, the observed gastrointestinal TEAEs, including diarrhea, nausea, vomiting, and stomatitis, were consistent with the class effect of HER2/EGFR TKIs. The events were generally tolerable, monitorable, and manageable with standard supportive care (e.g., anti-diarrheal medication for diarrhea and antiemetic medications for nausea and/or vomiting) and rarely led to permanent treatment discontinuation. As gastrointestinal toxicities are associated with HER2/EGFR TKIs and were commonly reported across the safety populations, diarrhea, stomatitis (grouped term), nausea, and vomiting were considered clinically relevant ADRs. Diarrhea was identified as an important risk for sevabertinib.
- Overall, skin-related toxicities were generally tolerable, monitorable, and manageable with standard supportive care. The most commonly reported study drug-related TEAEs were of Grade 1 or 2 in severity, and were reversible, monitorable, and manageable. As skin-related toxicities are known risks of EGFR TKIs and were commonly reported across the safety populations, rash (grouped term), paronychia (grouped term), dry skin (grouped term), pruritus, alopecia, and palmar-plantar erythrodysesthesia syndrome were considered clinically relevant ADRs.
- Based on the available data, ILD/pneumonitis is not identified as a risk of sevabertinib.
- Overall, the ocular toxicity TEAEs reported within the SOC of eye disorders were primarily of low grade and approximately one third (Whole Study 20 mg BID) to nearly half (Group D) were attributable to causes other than sevabertinib. As ocular toxicity is a class toxicity for HER2/EGFR TKIs, the study drug-related ocular TEAEs were grouped as ocular toxicity and were considered as a clinically relevant ADR.
- Overall, the incidence of TEAEs reported within the SOC of cardiac disorder was low and approximately half were attributable to causes other than sevabertinib. As cardiac toxicity is a class toxicity of HER2 TKIs and cardiac arrhythmias were most attributed to sevabertinib, TEAEs associated with arrhythmias were grouped as cardiac arrhythmia

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and were considered as a clinically relevant ADR. No clinically meaningful findings were observed based on ECG and echocardiogram measurements in Study 21607. Based on a concentration-QTc(F) analysis, cardiologist evaluation, and central tendency analysis of relevant cardiac intervals (PR, QRS, RR, and QT), the risk of cardiovascular events due to sevabertinib treatment, as observable from ECGs, is considered low.

The FDA's Assessment:

FDA performed an independent analysis of GI toxicity, skin toxicity, ILD/pneumonitis, ocular toxicity, and cardiac toxicity as specific safety issues but also identified hepatotoxicity and elevated pancreatic enzymes as detailed respectively in the following sections. FDA's analysis used grouped terms as described in **Table 74**.

Hepatotoxicity

In the pooled safety population, there were three cases of Grade 3 hepatic function abnormal and one case of Grade 3 cholecystitis. A total of 1.5 and 1.1% of patients in the combined Groups D + E and pooled 20 mg population had an event of Grade 3 hepatic function abnormal. One case (0.4%) of Grade 3 cholecystitis occurred in the pooled 20 mg population. As described under Laboratory Findings, FDA reviewed the narratives and agrees there were no Hy's law cases. The median time to onset for the GT hepatotoxicity (comprised of hepatic function abnormal, ALT, and AST increased) was 42 days for the combined Group D + E while increased bilirubin occurred at 70.5 days. For the pooled 20 mg population the median onset of hepatic function abnormal was 35.5 days, ALT increased was 42 days, AST increased was 22 days, and total bilirubin 64 days. Narratives for severe events in the hepatobiliary system were reviewed, with select narratives briefly discussed below.

- Patient ID (b) (6): This is a case of Grade 3 hepatic function abnormal with elevated AST and ALT aminotransferases; both the Investigator and Sponsor attributed this to study drug resulting in dose reduction and interruption. This was treated with ursodeoxycholic acid, cysteine hydrochloride, glycine, and glycyrrhizic acid and no other clear etiology could be determined from the narrative. The last reported assessment noted this as resolving which is corroborated by the pattern of provided liver function tests (LFTs). Approximately 3 weeks after this hepatic event, the patient experienced a Grade 5 event described as 'general physical health deterioration. FDA considers this an event of hepatotoxicity likely due to sevabertinib.
- Patient ID (b) (6): This is a case of Grade 3 hepatic function abnormal with elevated AST and ALT aminotransferases, alkaline phosphatase, and direct bilirubin. This occurred 42 days after start of treatment and was attributed to study drug by both Investigator and Sponsor. The patient initially recovered (corroborated by the pattern of AST but no other pertinent LFTs) after dose reduction and interruption but the TEAE

recurred resulting in treatment discontinuation 63 days after start of treatment. The patient was treated with methionine, glycine, glycyrrhizic acid, an unknown “Liver therapy,” methionine, and ursodeoxycholic acid. No other clear etiology could be gleaned from the narrative. FDA considers this an event of hepatotoxicity likely due to sevabertinib.

- Patient ID (b) (6): This is a case of Grade 3 hepatic function abnormal with elevated AST and ALT aminotransferases. This occurred 42 days after treatment initiation and was attributed to study drug by both the Investigator and the Sponsor. The patient was treated with cysteine, glutathione, magnesium, and diammonium glycyrrhizinate. No other etiology for this TEAE was provided in the narrative. The pattern of LFTs suggest the event was resolving but approximately one month later the patient permanently discontinued study treatment with the stated reason of progressive disease. FDA considers this an event of hepatotoxicity likely due to sevabertinib.

FDA reviewed LFT laboratory data from both the combined Groups D + E and the pooled 20 mg population. In the pooled population, Grade 3 – 4 AST elevation occurred in 2.3% of patients and ALT elevation occurred in 2.3% of patients. There were no cases of Grade 3 – 4 total bilirubin elevation, but 12% of patients had a Grade 1-2 elevation.

Considering the three cases of Grade 3 hepatotoxicity each requiring intervention, and the pattern of LFT elevation on laboratory findings, the FDA determined a specific warning in the USPI was warranted to advise providers of the potential for hepatotoxicity and the need for monitoring and potential treatment modifications.

GI toxicity

Diarrhea was the most common all grade and Grade 3-4 toxicity observed in the pooled safety population. Among the pooled population, 86% of patients experienced any Grade TEAE of diarrhea with 15% of patients experiencing Grade 3 – 4 diarrhea. Sixty-three percent (63%) of the pooled 20mg population required loperamide during treatment with sevabertinib. While the FDA agrees that there is no instance of study drug being withdrawn specifically due to diarrhea, it appears that diarrhea contributed to two cases of drug being withdrawn for arrhythmia (likely related to use of loperamide and electrolyte disturbances) or acute kidney injury (dehydration). Amongst the pooled 20mg population, diarrhea led to dose interruption in 15% and to dose reduction in 12% of patients. Median time to onset of diarrhea (as a grouped term) TEAE was 4.0 days with a wide range of 1 to 190 days. The instances of enterocolitis and colitis were very rare although there was one Grade 3 case of enterocolitis and one Grade 1 – 2 case of colitis in the pooled 20mg population. As was required by protocol in the SOHO-01 study, the warning will contain instructions that antidiarrheal treatment should be initiated at the first sign of diarrhea or increased bowel movement frequency.

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Stomatitis occurred at any grade in 34% of patients in the pooled 20mg population with 0.7% being Grade 3 – 4. Stomatitis caused dose interruption in 2.2% and dose reduction in 1.9% of patients.

In the combined Group D + E patients, all grade nausea occurred in 20% and vomiting occurred in 19%; Grade 3 – 4 nausea occurred in 1.5% of patients and vomiting in 2.2%. Events of nausea or vomiting led to dose interruption and reduction at combined rates of 2.7 and 9% and 2.2 and 2.6% respectively in these same populations. There were no cases of drug withdrawal attributed to either nausea or vomiting.

Skin toxicity

Rash was a commonly observed event (62% of patients in the pooled 20mg population), with the majority being low grade (1.1% Grade 3 – 4). There were no instances of drug withdrawal for rash, and AEs of rash led to dose interruptions and reductions in 2.2% of patients. Rash is included in the product label in Section 6 as a common adverse reaction; given the limited number of high-grade events and dose modifications, FDA did not consider a specific warning to be necessary.

Pancreatic enzyme elevation

During the safety review FDA identified a significant number of cases of elevated amylase and lipase. Among the pooled 20 mg safety population based on laboratory data, 32% of patients had elevated amylase with 3.1% Grade 3 or 4; 40% of patients had elevated lipase with 10% Grade 3 or 4. Median time to amylase/lipase elevation was 1.4 months (range 0.2 to 17 months). There was a wide range of time to onset for these two enzyme elevations from 1 to 316 days. Based on adverse event data, two patients (0.7%) required interruption of sevabertinib due to increased lipase and 3 (1.1%) required interruption of sevabertinib due to increased amylase. All narratives for elevated amylase or lipase were reviewed and no cases of pancreatitis were identified, nor were there clear associations between the TEAE of abdominal pain and evidence of elevation amylase or lipase serum levels. However, given the high rate of pancreatic enzyme elevation including high grade events, and the lack of routine monitoring for these events with this class of product, FDA considered a warning for pancreatic enzyme elevation to be warranted in the USPI.

Interstitial lung disease (ILD)/pneumonitis

ILD/pneumonitis is known adverse reaction for other anti-HER2 directed therapies and as such an extensive review was undertaken with respect to sevabertinib. FDA's analysis used a pooled term as described in **Table 74**. ILD/pneumonitis occurred in 0.7% of patients treated in the pooled 20mg population including 0.4% Grade 3. The median time to first onset of ILD/pneumonitis was 2.6 months (range 37 to 123 days). One patient required dose interruption.

Of note, patients with existing ILD/pneumonitis were excluded at enrollment. Narratives of pneumonitis cases were reviewed in detail as briefly summarized below:

- Patient ID (b) (6): This is an event of Grade 2 ILD/pneumonitis, with preferred term radiation pneumonitis; the narrative does not detail the rationale for ascribing pneumonitis to radiation, or describe the history of radiation therapy (i.e., timing, target, or dose administered). This TEAE was listed as recovered with no change in study drug dosage or administration.

Note: the following patients received dosages other than the recommended dosage.

- Patient ID (b) (6): This is an event of Grade 1 pneumonitis that occurred approximately one month after treatment initiation (40 mg QD) and resulted in treatment withdrawal; the event was attributed to study drug by at least the Investigator (Applicant attribution not provided). The patient was treated with a prednisone taper and Bactrim; there is no diagnosis of PJP pneumonia described in the narrative. The TEAE was listed as not recovered and the patient died approximately 6 months from this TEAE from the stated reason of progressive disease.
- Patient ID (b) (6): This is an event of Grade 4 ILD/pneumonitis which occurred 180 days from start of treatment while on active treatment with sevabertinib; this patient received sevabertinib 40 mg BID and is not included in the primary safety population. Treatment was permanently discontinued and the patient expired one day after the start of this TEAE. Both the Investigator and Sponsor considered that the event was not related to sevabertinib. While the timing of this adverse reaction is consistent with progressive disease being responsible for the Grade 5 event, the narrative offers few details concerning the etiology with no imaging data.

ILD/pneumonitis is a known adverse reaction associated with anti-HER2 therapy and many kinase inhibitors. Given the potential severity, the occurrence of cases resulting in study drug withdrawal and need for provider awareness of this adverse reaction, a warning for ILD/pneumonitis is warranted in Section 5 of the USPI.

Ocular Toxicity

Ocular toxicity is a potential class effect of anti-EGFR/HER2 therapy. FDA's analysis used a GT as detailed in **Table 74**. The median time to any Eye disorder (GT) was 21 and 21.5 days in the two safety populations with a range of 3 to 504 days. The GT Eye disorder occurred in 14% of the pooled 20 mg safety population of which 0.4% of patients had a Grade 3 event. The most common PT within the GT was Dry Eye (6% of patients). Narratives for serious or severe cases of ocular toxicity are described below.

- Patient ID (b) (6): This is an event of Grade 3 Eye disorder that resulted in unilateral blindness. The narrative does not describe pre-existing ocular conditions. Grade 3 conjunctivitis occurred 24 days from the start of treatment, resulting in dose reduction.

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The narrative indicates this was ascribed to viral conjunctivitis not considered related to study drug and the patient received tobramycin, dexamethasone, and saline eye drops. At 108 days after start of treatment and 3 days after the last dose of sevabertinib, the patient experienced Grade 3 unilateral blindness resulting in medication interruption. The investigator attributed this event to corneal microcysts, and not to the study drug. This event is listed as having recovered.

FDA considered that these events were at least possibly related to sevabertinib treatment, given the specific details described above, that corneal changes including microcysts have been observed in anti-EGFR or anti-HER2 directed therapy, and given the nonclinical findings in toxicology studies of sevabertinib. In light of the potential impact of ocular toxicity on patient quality of life, the need for provider awareness for prompt dose modification and ophthalmologic evaluation, FDA considered a warning for ocular toxicity in the USPI for sevabertinib as warranted.

Cardiac toxicity

As described in the dedicated QT section, FDA agrees that evidence does not suggest a large effect of sevabertinib on QTc prolongation. FDA evaluated the adverse event dataset for terms associated with reduced ejection fraction or heart failure, and did not find evidence for reduction in ejection fraction. However, the FDA disagrees with the Applicant's statement that there were no clinically significant findings with respect to arrhythmias among the pooled safety population. In the pooled population, 7% of patients had an arrhythmia (GT), including 1.5% Grade 3 – 4 events. Among the Grade 3-4 TEAEs, terms included QT prolonged (0.7%), arrhythmia (0.4%), atrioventricular block (AV block) complete (0.7%), and sinus tachycardia (0.4%).

FDA reviewed narratives of events of arrhythmia. All cases were confounded by at least one factor contributing to arrhythmia. The case of AV block occurred in a patient with prior history of mediastinal irradiation for Hodgkin lymphoma. Other cases were confounded by concomitant medication use (e.g., loperamide) and diarrhea with resulting electrolyte derangement. Notably the label for loperamide carries a black box warning for Torsades de Pointes and sudden death with higher than recommended doses of loperamide; cases of syncope and ventricular tachycardia have also been reported in adult patients receiving the recommended dosage of loperamide.

Cardiac event narratives were reviewed with one non-arrhythmia case described below.

- Patient ID (b)(6): This is a case of cardio-pulmonary arrest that occurred 45 days after starting treatment resulting in a Grade 5 toxicity. This occurred in a patient in Group F included in the pooled 20mg population but not in the combined Group D + E population. Sinus tachycardia was noted along with left anterior fascicular block and U wave changes. CT chest noted a shrinking left upper lobe mass next to the mediastinum as well as increasing bilateral exudative lesions, and involved mediastinal lymph nodes.

No further information on the etiology of the cardio-pulmonary arrest was available. The Investigator attributed the sinus tachycardia in this case to the study drug while the Applicant considered it unrelated. FDA considered that a contribution of sevabertinib could not be excluded.

Investigators attributed three Grade 3-4 cardiac arrhythmias to study drug (AV block complete, arrhythmia, and sinus tachycardia) and in all cases the Applicant disagreed with that attribution.

Due to the presence of multiple confounding causative factors for arrhythmias including use of concomitant anti-diarrheal medications and electrolyte disturbances from diarrhea, FDA considered that there was insufficient evidence of causality to support inclusion of a Warning; however the occurrence of arrhythmias will be included in Section 6 of the USPI.

Table 74. FDA Analysis of Adverse Events of Special Interest

	Groups D + E		Pooled 20mg patients	
	N = 136		N = 268	
	%		%	
	All	Grade	All	Grade
	Grade	3-4	Grade	3-4
Any TEAE	100	43	99	39
Hepatotoxicity (GT)				
Hepatic Function Abnormal	1.5	1.5	1.5	1.1
Alanine Aminotransferase Increased	16	1.5	15	1.9
Aspartate Aminotransferase Increased	17	1.5	15	1.5
Blood Bilirubin Increased	7	0	5	0
Gastrointestinal disorders				
Diarrhea (GT)	87	18	86	15
Nausea	29	1.5	34	0.7
Vomiting (GT)	21	1.5	20	2.2
Stomatitis (GT)	15	2.2	19	3.7
Abdominal pain (GT)	10	0	10	0
Skin and subcutaneous tissue disorders				

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Rash (GT)	66	1.5	62	1.1
Dry skin	18	0	18	0
Pruritus	14	1.5	12	0.7
Pancreatic enzyme elevation				
Amylase elevated	18	1.5	14	0.7
Lipase elevated	17	0.7	14	0.7
ILD/pneumonitis				
Radiation pneumonitis	0.7	0	0.4	0
Interstitial lung disease	0	0	0.4	0.4
Eye disorder (GT)				
Dry eye	6	0	6	0
Xerophthalmia	2.2	0	1.5	0
Cataract	1.5	0	0.7	0
Conjunctivitis	2.2	0	3.4	0
Ocular hyperaemia	0.7	0	0.7	0
Blindness unilateral	0.7	0.7	0.4	0.4
Corneal epithelial microcysts	0.7	0.7	0.4	0.4
Visual acuity reduced	0.7	0.7	0.4	0.4
Conjunctivitis allergic	0.7	0	0.4	0
Eye discharge	0.7	0	0.4	0
Eye pain	0.7	0	0.4	0
Ocular hypertension	0.7	0	0.4	0
Ocular toxicity	0.7	0	0.4	0
Visual impairment	0.7	0	0.4	0
Vision blurred	1.5	0	1.5	0
Lacrimation increased	0.7	0	0.4	0
Eye swelling	0	0	0.4	0
Punctate keratitis	0	0	0.4	0
Arrhythmia (GT)				
Electrocardiogram QT prolonged	2.9	1.5	2.2	0.7
Supraventricular extrasystoles	1.5	0	2.2	0

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Supraventricular tachycardia	0.7	0	0.7	0
Arrhythmia	0.7	0.7	0.4	0.4
Atrioventricular block complete	0.7	0.7	0.4	0.4
Sinus tachycardia	0.7	0.7	0.4	0.4
Sinus bradycardia	0.7	0	0.4	0
Sinus arrhythmia	0.7	0	0.4	0
Atrial fibrillation	0	0	1.1	0
Atrial tachycardia	0	0	0.7	0

Source: FDA analysis of adae.xpt

Variables used: USUBJID, COLGROUP, ATOXGRN, AEDECOD, AEBODSYS, and TRTEMFL.

Note: Custom grouped terms are designated by '(GT)'.

Arrhythmia (GT) includes: Arrhythmia, Atrial fibrillation, Atrial tachycardia, Atrioventricular block complete, Electrocardiogram QT prolonged, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Supraventricular

Cough (GT) includes: Cough, and Productive cough.

Diarrhoea (GT) includes: Colitis, Diarrhoea, and Enterocolitis.

Eye disorder (GT) includes: Blindness unilateral, Cataract, Conjunctivitis, Conjunctivitis allergic, Corneal epithelial microcysts, Dry eye, Eye discharge, Eye pain, Eye swelling, Lacrimation increased, Ocular hyperaemia, Ocular hypertension, Ocular toxicity, Punctate keratitis, Vision blurred, Visual acuity reduced, Visual impairment, and Xerophthalmia.

Pneumonitis (GT) includes: Interstitial lung disease.

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

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.2.6. Safety Analyses by Demographic Subgroups

Data:

Subgroup analyses for TEAEs were performed based on age (<65 years, ≥65 years), sex (male, female), race (Asian, White, Other), and geographical region (Asia, non-Asia).

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Due to the low number of participants in some of the subgroups for Group D, the results for subgroups showing a >10% point difference between the groups are summarized for the Whole Study 20 mg BID population below. As there is no comparator in Study 21607 and the subgroups are not numerically comparable in size, the results should be interpreted with caution.

Age: <65 years (N=153) vs. ≥65 years (N=115)

- The incidences of TEAEs leading to dose interruptions/delays tended to increase with age: 34.6% of participants <65 years and 52.2% of participants ≥65 years.

Sex: Male (N=94) vs. Female (N=174)

- Higher incidences of TEAEs leading to dose reduction were observed in females (31.0%) compared with males (20.2%).
- A similar pattern was observed for dose interruptions/delays (46.0% and 35.1%, respectively).

Geographical region: Asia (N=177) vs. Non-Asia (N=91)

- TEAEs leading to dose interruptions/delays showed a higher incidence in participants from Non-Asian region (53.8%) compared to participants from the Asian region (36.2%).

Race: Asian (N=179) vs. White (N=65)

- Similar to the geographical region subgroups, TEAEs leading to dose interruptions/delays showed a higher incidence in White participants (61.5%) compared to Asian participants (36.3%).
- In addition, the incidences of Grade 3 TEAEs (47.7% vs. 34.1%) and TESAEs (35.4% vs. 25.1%) were higher in White participants compared to Asian participants, respectively.

Source: Module 5.3.5.2, B003047, Tables 8.3.1.5/1s1, 8.3.1.5/2s1, 8.3.1.5/3s1, and 8.3.1.5/4s1 [datasets ADSL and ADAE]

The Applicant's Position:

In Study 21607, while some variations in the incidence of certain TEAE categories were observed among subgroups defined by age, sex, and race, and geographical region, no clinically meaningful differences were identified across these subgroups. However, due to the small numbers of participants in each subgroup, it is not possible to derive definitive conclusions regarding the potential differences in the safety profile of sevabertinib across the different subgroups.

Population PK data from Study 21607 showed that sevabertinib exposure was not affected by demographic factors, such as age, sex, race, or geographical region (see Section 6.3.2.2).

Based on data from Study 21607, no clinically meaningful differences are anticipated in the safety of sevabertinib in the US vs. non-US NSCLC patients with *HER2* activating mutations,

and overall, the safety profile of sevabertinib supports its applicability to the US patient population.

The FDA’s Assessment:

FDA generally agrees with the Applicant’s position. FDA conducted an analysis of TEAEs by demographic subgroup in the primary and pooled safety populations. Within these populations, there were no clear differences in the safety profile based on age, race, or sex. In the primary safety population, however, there were very few Black or African American patients; 3.7 and 2.2% of patients in the combined Group D + E and the pooled 20 mg population were Black or African American. Because of this, there is insufficient data to determine whether any differences in the safety profile exist for this population. Overall, no clear AE trends were observed among the different populations based on prior treatment, although data is limited by small cohort numbers and differences in time of exposure to sevabertinib.

FDA also conducted an independent analysis of TEAEs by age. In the combined Group D + E population, 40% of patients were 65 years of age and older and 11% were 75 years of age and older. Of the patients aged 65 years and older, 44% experienced Grade 3 or 4 TEAEs and 33% experienced SAEs. Of the patients less than 65 years of age, 41% experienced Grade 3 or 4 TEAEs and 29% experienced SAEs. Of the 268 patients in the pooled 20 mg population, 43% were 65 years of age and older and 13% were 75 years and older. The safety results in the pooled population subgroups by age were similar, though of note, Grade 3 diarrhea was observed in 23% of patients age ≥ 75 years and 14% of patients < 75 years old. Analysis is limited by the small number of patients 65 years of age and older; however, there is no suggestion of an overall difference in safety by age based on the data available.

8.2.7. Specific Safety Studies/Clinical Trials

Data and the Applicant’s Position:

No studies were performed to address specific safety concerns.

The FDA’s Assessment:

Not applicable.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

Please see The Applicant’s Position below.

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The Applicant’s Position:

Carcinogenicity studies have not been conducted. Consistent with the guideline ICH S9, carcinogenicity studies are not warranted to support clinical trials for therapeutics intended to treat patients with advanced cancer.

The FDA’s Assessment:

FDA agrees that carcinogenicity studies have not been conducted and limited long-term data preclude definitive evaluation of carcinogenicity.

Human Reproduction and Pregnancy

Data:

Please see The Applicant’s Position below.

The Applicant’s Position:

There are no human data available on the effect of sevabertinib on fertility or on the use of sevabertinib in pregnant women.

Available animal studies do not provide sufficient information regarding reproductive toxicity (Module 2.6.6, Section 6). The absence of HER2 and/or EGFR signaling has been shown to result in impairment of embryo-fetal development, and embryoletality, as well as post-natal death in animals (46). Based on its mechanism of action and findings in animal models (Module 2.6.6, Section 9), sevabertinib may cause fetal harm when administered during pregnancy.

Sevabertinib should not be given during pregnancy, unless the benefit of treatment of the woman is considered to outweigh the potential risks to the fetus. Female patients taking sevabertinib during pregnancy or who become pregnant while taking sevabertinib should be advised of the potential hazard to the fetus.

There is no data on the presence of sevabertinib or its metabolites in human milk. In rats, sevabertinib or its metabolites are excreted in milk. A risk to the breast-fed child cannot be excluded. Breastfeeding should be discontinued during treatment with sevabertinib and for 1 week following the final dose. The elimination half-life of sevabertinib is approximately ^{(b) (4)} hours. The recommended post-dose period of 1 week is based on 5 half-lives after completion of treatment, along with an additional buffer period.

The FDA’s Assessment:

FDA agrees with the Applicant’s position. Refer to Section 5 for FDA’s review of data to support recommendations for males and females of reproductive potential, lactation and pregnancy.

Pediatrics and Assessment of Effects on Growth

Data:

Please see The Applicant’s Position below.

The Applicant’s Position:

Sevabertinib has not been studied in a pediatric population. The Sponsor plans to request a full waiver for sevabertinib for pediatric patients. On 26 NOV 2024, the FDA agreed with the Agreed iPSP that was submitted on 24 OCT 2024 (Reference ID 5486478).

The FDA’s Assessment:

FDA agrees with the Applicant’s position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Please see The Applicant’s Position below.

The Applicant’s Position:

The highest dose of sevabertinib studied clinically was 40 mg BID, equivalent to a TDD of 80 mg. At this dose, the DLTs observed were stomatitis, vomiting, and diarrhea. There is no specific antidote for sevabertinib overdose. In the event of an overdose, the patient should be closely monitored, and general supportive treatment should be considered based on signs and symptoms.

No data are available on the drug abuse or dependency potential for sevabertinib. Withdrawal effects were not evaluated upon discontinuation of treatment.

The FDA’s Assessment:

FDA agrees with the Applicant’s assessment.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data and the Applicant’s Position:

Not applicable as sevabertinib is not yet marketed in any region.

The FDA’s Assessment:

Not applicable

Expectations on Safety in the Postmarket Setting

Data:

Please see The Applicant's Position below.

The Applicant's Position:

Sevabertinib belongs to the class of HER2/EGFR TKIs, which are typically associated with gastrointestinal toxicity, dermatologic toxicity, ILD, ocular toxicity, and cardiotoxicity. Overall, the data shows that sevabertinib was generally well tolerated at 20 mg BID and the most common study drug-related TEAEs were of low grade, reversible, monitorable, and manageable. The most common TEAEs and study drug-related TEAEs were mostly gastrointestinal toxicities (diarrhea, nausea, vomiting, and stomatitis) or skin-related toxicities (rash, paronychia, dry skin, and pruritus), consistent with the class toxicities of EGFR/HER2 TKIs. These risks are manageable by recommendations included in the proposed labeling. The safety of sevabertinib will be continuously monitored in the ongoing and planned studies, as well as in the postmarket setting.

The FDA's Assessment:

No major differences in the overall safety profile are expected in the post marketing setting.

8.2.10. Integrated Assessment of Safety

Data:

Safety data presented in this NDA are derived from the pivotal Study 21607 and results are presented in Section 8.2.3. An integrated analysis of safety was not performed since no data from other clinical studies in cancer patients are available for this NDA submission.

The Applicant's Position:

The primary safety population was comprised of 81 participants who qualified for Group D i.e. they had advanced NSCLC harboring *HER2* activating mutation, received prior systemic therapy but were naïve to HER2 ex20ins-targeted therapy, and were treated with sevabertinib at 20 mg BID (RP2D). In addition, safety data are provided from 268 participants receiving sevabertinib at a dose level of 20 mg BID and from 357 participants who received at least 1 dose of sevabertinib in Study 21607.

Sevabertinib was generally well tolerated at 20 mg BID. The most common TEAEs and study drug-related TEAEs were mostly gastrointestinal toxicities or skin-related toxicities consistent with the class toxicities of EGFR/HER2 TKIs. Overall, the TEAEs were manageable with standard of care in conjunction with dose modifications, resulting in very few (<5%) patients

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discontinuing study treatment. None of the events leading to treatment discontinuation occurred in >1 participant. The safety data in participants receiving 20 mg BID dose and in participants who received at least one dose of sevabertinib in Study 21607 were overall consistent with the safety data of the primary safety population.

With these data, the Applicant considers the safety profile of sevabertinib to be appropriately characterized. The proposed USPI provides guidance to physicians regarding the identification and management of risks associated with sevabertinib treatment.

The FDA's Assessment:

FDA agrees with the overall position of the Applicant that the safety profile for sevabertinib appears acceptable in the context of this severe and life-threatening disease. FDA disagrees with assigning definitive attribution to adverse drug events in a single-arm trial and has thus identified additional adverse drug reactions. The most common TEAEs of any Grade (occurring in $\geq 20\%$ of patients in either population) were diarrhea, stomatitis, nausea, and rash. The most common Grade 3-4 TEAEs (occurring in $\geq 2\%$ in either population) were diarrhea, nausea, vomiting, pneumonia, and decreased appetite. TEAE frequency was generally consistent among both the combined Group D + E and pooled 20 mg safety populations. FDA identified important safety risks of hepatotoxicity, elevated pancreatic enzymes, ocular toxicity, and interstitial lung disease/pneumonitis. FDA considers current product labeling adequate to address these safety concerns.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues in the review of this application which is based on results from SOHO-01, a non-randomized, open-label, multi-cohort, single-arm trial. The primary efficacy evaluation included patients who were naïve to HER2-targeted therapy (Group D) and patients who progressed on prior HER2-targeted ADCs (Group E).

Based on the limited evidence of effectiveness in patients with squamous histology and patients with non-TKD mutations, the primary efficacy population was limited to include only patients with both TKD mutations and non-squamous histology, which reduced the number of patients in the primary efficacy population from 81 to 70 patients in Group D and from 55 to 52 patients in Group E. This population revision was necessary to ensure that the indication accurately reflected the patient population most likely to benefit from treatment.

The confirmed ORR per RECIST by BICR was 71% (95% CI: 59, 82) in Group D and 38% (95% CI: 25, 53) in Group E. The median DOR by BICR was 9.2 months (95% CI: 6.3, 15.0) in Group D and 7.0 months (95% CI: 5.6, NR) in Group E. Multiple sensitivity analyses were conducted to assess the robustness of DOR estimates in Group D, indicating that the estimated median DOR may be sensitive to additional events or censoring. Nevertheless, even under the most conservative scenarios, the results continued to support a durable response with median DOR ranging from 6.8 to 8.8 months. Additional follow-up will help enhance the precision of estimate and confirm the durability of response. Response was maintained for at least 6 months in 54% of the responders in Group D and 60% of the responders in Group E.

Time-to-event endpoints such as PFS and OS in non-comparative trials are not interpretable to assess efficacy and are considered descriptive only. The evidence of efficacy based on ORR was consistent across subgroups; however, due to limited number of patients and responses, subgroup analyses yielded wide confidence intervals. These results are less precise and should be interpreted with caution.

A data quality issue in reported patient TKD mutation status was identified during the review process affecting the ability to reproduce the updated analysis population in Group D. The Applicant documented this issue in a cover letter submitted to the FDA and subsequently formally corrected the discrepancy in response documents and updated prescribing information through regulatory submissions.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The recommendation for accelerated approval is primarily supported by the results from Study 21607 (SOHO-01), a non-randomized, open-label, single-arm, multi-center, multi-cohort trial. The primary efficacy outcome measure for SOHO-01 is confirmed ORR according to RECIST v1.1 as assessed by BICR, with DOR by BICR as an additional efficacy outcome measure. The primary efficacy populations considered in FDA’s review included 70 patients with locally advanced or metastatic, non-squamous NSCLC with HER2 (ERBB2) TKD mutations who had received at least one line of prior systemic therapy, and 52 patients with unresectable or metastatic, non-squamous NSCLC with HER2 TKD mutations who had received prior platinum-based chemotherapy and a prior HER2 ADC. All patients received sevabertinib 20 mg orally BID in SOHO-01. Among the 70 patients who were naïve to HER2-targeted therapy, 94% had received prior platinum-based chemotherapy and 69% had received previous treatment with an anti-PD-1/anti-PD-L1 antibody. The confirmed ORR for this group per BICR was 71% (95% CI: 59, 82); 54% of responders had an observed DOR $\geq$ 6 months and 18% had a DOR $\geq$ 12 months. Responses were generally consistent across subgroups.

Among the 52 patients with locally advanced or metastatic, non-squamous NSCLC with HER2 TKD mutations who had received prior systemic treatment with platinum-based chemotherapy and a HER2-targeted ADC. The ORR was 38% (95% CI: 25, 53) was observed, with a median DOR of 7.0 months (95% CI: 5.6, NR) and 60% of responders having an observed DOR $\geq$ 6 months.

As HER2-mutated NSCLC tumors do not typically regress in the absence of therapy, ORR is attributable to an effect of the drug; for this disease setting, ORR is considered an intermediate endpoint reasonably likely to predict clinical benefit. A clinically meaningful ORR with relatively durable responses was observed in patients with non-squamous NSCLC with HER2 TKD activating mutations treated with sevabertinib. Based on magnitude and duration of responses observed in patients in SOHO-01 treated with prior platinum chemotherapy with or without prior HER2-targeted ADC, the treatment effect observed in patients treated with sevabertinib demonstrates a meaningful advantage over available therapies for this previously treated patient population.

The assessment of safety at the recommended dosage was based on data from patients with unresectable or metastatic non-squamous NSCLC who received sevabertinib 20 mg BID daily in SOHO-01. Sevabertinib demonstrated an acceptable safety profile when assessed in the context of a serious and life-threatening disease for the indicated population of patients. Significant and serious adverse reactions of diarrhea, hepatotoxicity, pancreatic enzyme elevation, ocular toxicity, and ILD/pneumonitis are sufficiently addressed in product labeling.

The Applicant submitted data from patients with squamous NSCLC and those with HER2 non-TKD mutations; however, the sample sizes in these populations were very limited, and response rates were numerically lower. FDA considered that there was insufficient evidence of efficacy in this population, and the indication considered in FDA’s review was limited to the treatment of adult patients with locally advanced or metastatic non-squamous NSCLC whose tumors have HER2 TKD activating mutations and who have received prior systemic therapy.

Based on demonstration of substantial evidence of effectiveness and a favorable benefit: risk profile, sevabertinib will be granted accelerated approval for the following indication: “For the treatment of adult patients with locally advanced or metastatic, non-squamous non-small cell lung cancer (NSCLC) whose tumors have activating *HER2 (ERBB2)* tyrosine kinase domain activating mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.”

The trial intended to verify the clinical benefit of sevabertinib is Study 22615 (SOHO-02), an open-label, randomized, controlled, global study of sevabertinib versus standard of care pembrolizumab plus platinum-based doublet chemotherapy in patients with previously untreated, unresectable locally advanced or metastatic non-squamous NSCLC harboring HER2 TKD mutations. The primary efficacy endpoint is PFS per RECIST 1.1 by BICR; key secondary endpoints include ORR and OS. The Consolidated Appropriations Act (2023) provides FDA with the authority to require that confirmatory studies to verify clinical benefit be underway prior to accelerated approval. SOHO-02 is 60% enrolled as of October 2025, and topline data from the primary PFS analysis are expected Q1 2027. As such, the review division considers the confirmatory trial for this accelerated approval to be underway.

8.4.1. Approach to Substantial Evidence of Effectiveness

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant’s proposed indication if the application received a complete response*):
HYRNUO is indicated for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) whose tumors have *HER2 (ERBB2)* tyrosine kinase domain activating mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

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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 or seek input from other external consultants as no significant efficacy or safety issues were identified during the review that required external input and the application did not raise significant public health questions regarding the role of sevabertinib for the proposed indication.

10 Pediatrics

The Applicant’s Position:

The Applicant plans to request a full waiver of the pediatric study requirement for sevabertinib for all pediatric patients (i.e., neonates, infants and children aged 0 to <18 years) because studies are impossible or highly impractical to execute (because the number of pediatric patients is so small or geographically dispersed) (Section 505B(a)(4)(A)(i) of the Pediatric Research Equity Act).

Further reference is made to the FDA’s “Agreed Initial Pediatric Study Plan – Agreement” letter, dated 26 NOV 2024 (Reference ID 5486478), in which the FDA agreed with Bayer’s plan not to develop sevabertinib for the proposed indication in the pediatric population.

The FDA’s Assessment:

FDA agrees with the Applicant’s position. The approval letter will state that the requirements of PREA will be waived.

11 Labeling Recommendations

Data:

This is an original application. Please see annotated label in Module 1.14.1.2 for the proposed USPI.

The Applicant’s Position:

Not applicable.

The FDA’s Assessment

Summary of Significant Labeling Changes (High level changes and not direct quotations)

Table 75: Key Labeling Changes

Section	Applicant’s Proposed Labeling	FDA’s Proposed Labeling
1 INDICATIONS AND USAGE		FDA revised the indication statement to include the descriptors “locally” advanced and “metastatic non-squamous” and added “tyrosine kinase domain activating” to reflect the population studied.
2 DOSAGE AND ADMINISTRATION 2.1 Patient Selection		FDA revised the text to specify the patient selection to include “locally” advanced and “metastatic non-squamous” and added “tyrosine kinase domain activating” to
2.2 Recommended Dosage 2.3 Dosage Modifications for Adverse Reactions		FDA provided minor editorial revisions for clarity and brevity.
Table 2: Recommended HYRNUO Dosage Modifications for Adverse Reactions		FDA revised the proposed dosage modification for adverse reactions table to specify instructions for each adverse reaction in the WARNINGS AND PRECAUTIONS section; we added diarrhea, hepatotoxicity, interstitial lung disease / pneumonitis, pancreatic enzyme elevation and other adverse reactions.
2.4 Dosage Modifications for Strong CYP3A4 Inhibitors		FDA provided minor editorial revisions for clarity and brevity.

3 DOSAGE FORMS AND STRENGTHS		FDA provided minor editorial revisions for clarity and brevity.
5 WARNINGS AND PRECAUTIONS 5.1 Diarrhea 5.2 Hepatotoxicity 5.3 Interstitial Lung Disease/Pneumonitis 5.4 Ocular Toxicity 5.5 Pancreatic Enzyme Elevation		FDA added new warnings for consistency with the guidance <i>Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format (October 2011)</i> . Adverse reactions occurring at a very high rate, or those that are severe or life threatening were added to ensure safe use of HYRNUO. Appropriate monitoring, mitigation strategies and dosage modification were added.
5.6 Embryo-fetal toxicity		FDA revised the text for consistency with the guidance <i>Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format (July 2020)</i> .
6 ADVERSE REACTIONS 6.1 Clinical Trial Experience		FDA provided minor editorial revisions to the description of the pooled safety population. FDA revised the safety description of the SOHO-01 study for consistency across oncology labeling. All numbers in this section were adjudicated by FDA.
7 DRUG INTERACTIONS		FDA revised the text for consistency with the guidance <i>Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products-Content and Format, Guidance for Industry Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (December 2016)</i> .
8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy 8.2 Lactation 8.3 Females and Males of Reproductive Potential		FDA revised the text for consistency with the guidance <i>Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format (July 2020)</i> .

8.4 Pediatric Use		FDA provided minor editorial revisions for clarity and brevity.
8.5 Geriatric Use		FDA revised Geriatric Use to reflect the pooled safety population (N=268), and for consistency with 21 CFR 201.57(c)(9)(v)(A).
8.6 Renal Impairment 8.7 Hepatic Impairment 10 OVERDOSE		These subsections were removed for consistency with 21 CFR 201.56(d)(4) that states to omit clearly inapplicable sections, subsections, or specific information.
11 DESCRIPTION		FDA provided minor editorial revisions for clarity and brevity.
12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action		FDA revised the text for clarity and brevity. Because HYRNUO also has activity against epidermal growth factor receptor (EGFR), and this produces specific adverse reactions and embryo-fetal toxicity, EGFR is presented.
12.2 Pharmacodynamics		Text revised for consistency with 21 CFR 201.57(c)(13)(i)(B) requirements.
12.3 Pharmacokinetics		Text revised for consistency with 21 CFR 201.57(c)(13)(i)(C) requirements.
13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility		Subheadings inserted and statement regarding genotoxicity was included.
14 CLINICAL STUDIES 14.1 Locally Advanced or Metastatic Non-squamous NSCLC with HER2 TKD Activating Mutations		The text describing the efficacy of SOHO-01 was revised for clarity and brevity. Responses were separated by “previously treated, naïve to HER2-targeted therapy” and “previously treated including prior HER2 targeted antibody drug conjugates (ADCs)”.
16 HOW SUPPLIED/STORAGE AND HANDLING		FDA provided minor editorial revisions.
17 PATIENT COUNSELING INFORMATION		Section revised to reflect the contents of WARNINGS AND PRECAUTIONS.

The Patient Information document was reviewed and revised by the Patient Labeling Team, Office of Prescription Drug Promotion and the Division of Medication Error Prevention and Analysis.

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

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. Sevabertinib will be prescribed by oncologists who are trained in monitoring, diagnosing, and managing serious toxicities caused by antineoplastic drugs, including tyrosine kinase inhibitors. 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 will be included in the approval letter:

PMR 1

Complete the ongoing multicenter, randomized clinical trial, Study SOHO-02, intended to verify and describe the clinical benefit of sevabertinib in adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer whose tumors have HER2 (ERBB2) tyrosine kinase domain activating mutations and who have not received prior therapy for advanced disease.

Trial Completion: 04/2029

Final Report Submission: 10/2029

PMR 2

Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dosage of sevabertinib in patients with moderate 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.”

Trial Completion: 01/2026

Final Report Submission: 07/2026

PMR 3

Conduct a clinical drug interaction study to evaluate the effect of sevabertinib on the pharmacokinetics of sensitive substrates of MATE1 and MATE2-K in healthy subjects to assess the magnitude of exposure change of these substrates and serious potential risk of increased drug toxicity and inform an appropriate drug interaction management strategy for coadministration of sevabertinib with these transporter substrates. This study should be designed and conducted in accordance with “M12 Drug Interaction Studies”.

NDA/BLA Multi-disciplinary Review and Evaluation – NDA 219972

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Draft Protocol Submission: 02/2026
 Final Protocol Submission: 06/2026
 Trial Completion: 03/2027
 Final Report Submission: 09/2027

The majority of patients in the primary efficacy and safety populations are White or Asian and non-Hispanic/non-Latino, and the racial and ethnic demographics are not representative of the racial and ethnic composition of the U.S. population; however, based on the expectation that additional data will be obtained from the ongoing confirmatory trial, FDA does not plan to issue a PMC/PMR related to adequate representation of racial or ethnic groups at the time of this approval.

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? No
☐ 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 __ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant’s Position:

All investigators participating in Study 21607 were assessed for equity interest, significant payments, proprietary interests, and other compensation. Only 1 of the 904 total investigators had financial interests to disclose.

Covered Clinical Study (Name and/or Number):* 21607

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>904</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
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: _____		
Significant payments of other sorts: <u>1</u>		
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): 0		
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 submitted by the Applicant in Module 1.3 of this NDA were reviewed and no major concerns were noted.

Financial disclosure information was submitted for 904 investigators for Study 21607 (SOHO-01). Financial due diligence could not be completed for three sub-investigators due to financial disclosure forms not being submitted. In two of these three cases a Clinical Research Associate confirmed there were no financial interests per the Sponsor. No investigators were trial Sponsor employees. One sub-investigator involved in trial consent had disclosable financial interests or arrangements concerning a biomarker as part of a Sponsor funded project. However, per the Sponsor the payments were minimal (less than \$25000), made entirely to the sub-investigator’s institution, and payments concluded before the start of Study 21607. Hence the Sponsor concluded the potential for bias to be very limited.

19.3. Nonclinical Pharmacology/Toxicology

Data and the Applicant’s Position:

Not applicable

The FDA’s Assessment:

Refer to Section 5.

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19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Sevabertinib (BAY 2927088) in human plasma was analyzed by liquid chromatograph with tandem mass spectrometry. The primary assay method and validation parameters are indicated in **Table 76**. Method validation and in-use performance were adequate to support the assessment of sevabertinib systemic exposure in studies 21607, 22249, 22250, 22251, 22252, and 22253.

Table 76. Summary of the Bioanalytical Method Validation and In-Study Performance for Measurement of Sevabertinib (BAY 2927088) Using Method (b) (4) BIO-23-167

Bioanalytical method validation report name, amendments, and hyperlinks	Development and full validation of an LC-MS/MS method for the determination of BAY 2927088 in human K-EDTA plasma: Report ID B002973	
Method description	Agilent 1290 Infinity Bin Pump G4220A interfaced with a Sciex Triple Quadruple MS-Detector API5500	
Materials used for standard calibration curve and concentration	○ BAY 2927088 (biological matrix: human plasma K2- EDTA) ○ [¹³C₂ ²H₃ ¹⁵N] BAY 2927088 (biological matrix: human plasma K2- EDTA)	
Validated assay range	0.5 to 1500 ug/L	
Material used for quality controls (QCs) and concentration	○ BAY 2927088 (biological matrix: human plasma K2- EDTA) ○ [¹³C₂ ²H₃ ¹⁵N] BAY 2927088 (biological matrix: human plasma K2- EDTA) ○ QC concentrations: 0.5 ug/L (LLOQ), 1.5 ug/L (LQC), 30.0 ug/L (MQC), 750 ug/L (HQC), and 1200 ug/L (HLOQ)	
Source and lot of reagents	○ K2-EDTA human plasma from (b) (4) (MV-2023-0158j, rec'd 29-Jun-2023) ○ BAY 2927088 reference standard from Bayer AG, Germany (Lot BXRA27T, exp 31-Aug-2024) ○ [¹³C₂ ²H₃ ¹⁵N] BAY 2927088 ISTD from Bayer AG, Germany (Lot SXD 4226-1-01 A)	
Regression model and weighting	Linear regression model (weighted 1/X ²)	
Validation parameters	Method validation summary	Acceptability

Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative % bias from LLOQ to ULOQ	-4.9% to 4.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	2.0% to 7.2%	Yes
Performance of QCs during accuracy and precision runs	Cumulative % bias in QCs	-6.8% to 1.7% (inter-run)	Yes
	QCs for BAY 2927088: LLOQ, LQC, MQC, HQC, HLOQ		
Selectivity & matrix effect	Cumulative %CV in QCs	3.4% to 20.6% (inter-run)	Yes
	QCs for BAY 2927088: LLOQ, LQC, MQC, HQC, HLOQ		
Interference & specificity	Selectivity: Out of the 8 lots of matrix including 1 hemolytic and 1 hyperlipidemic, ≤20% interference for 7/8 samples and ≤5% for all 8 ISTD samples		Yes
	Matrix effect: No suppression or enhancement (CV ranged from 10.7% to 4.2%)		
Hemolysis effect	Signals observed in blank pooled and individual matrix were <20% of the LLOQ		Yes
Lipemic effect	Hemolysis effect was analyzed as part of selectivity and matrix effect with a hemolyzed matrix used (1 of 8 matrix lots). No influence of hemolytic plasma on BAY 2927088 (%bias and %CV <5%)		Yes
Dilution linearity	Lipemic effect was analyzed as part of selectivity and matrix effect with a lipemic matrix used (1 of 8 matrix lots). No influence of hyperlipidemic plasma on BAY 2927088 (%bias and %CV ≤5.1%)		Yes
Bench-top/process stability	10000 ug/L diluted by a factor of 10 for 6 replicates. Mean bias: -4.2% Precision (%CV): 3.4%		Yes
Freeze-Thaw stability	24 hours at ambient temperature		Yes
Long-term storage	4 cycles at -20 ± 5 °C		Yes
Method Performance in Study 21607 (Report Number: (b) (4) BIO-21-049C)	371 days at ≤-20°C.		Yes

Assay passing rate	0 of 9 runs were rejected (100% passing rate).	Yes
Standard curve performance	Cumulative % bias range: -2.3% to 1.7% Cumulative precision (%CV): ≤ 6.5%	Yes
QC performance	Cumulative % bias range: 0.8% to 5.6% Cumulative precision (%CV): ≤ 4.9%	Yes
Method reproducibility	98.7% of the sample results met acceptance criteria	Yes
Study sample analysis/stability	Calibration standards and QC samples were stored at -20°C ± 5°C. Stability was confirmed at 371 days. Samples were received and sample analysis was conducted within the validated storage duration (stability required up to 171 days at -20°C ± 5°C).	Yes
Method Performance in Study 22249 (Report Number: BAY22269-22269X-J)		
Assay passing rate	0 of 3 runs were rejected (100% passing rate).	Yes
Standard curve performance	Cumulative % bias range: -3.1% to 4.0% Cumulative precision (%CV): ≤ 4.6%	Yes
QC performance	Cumulative % bias range: -7.4% to 6.5% Cumulative precision (%CV): ≤ 3.1%	Yes
Study sample analysis/stability	Calibration standards were prepared and stored at -20°C ± 5°C. QCs were stored at the same temperature throughout the project. Stability was confirmed at 120 days. Samples were received and sample analysis was conducted within the validated storage duration (stability required up to 34 days at -20°C ± 5°C).	Yes
Method Performance in Study 22250 (Report Number: ^{(b) (4)}-BIO-24-037)		
Assay passing rate	0 of 7 runs were rejected (100% passing rate).	Yes
Standard curve performance	Cumulative % bias range: -0.7% to 2.8% Cumulative precision (%CV): ≤ 5.7%	Yes
QC performance	Cumulative % bias range: 1.7% to 3.5% Cumulative precision (%CV): ≤ 5.7%	Yes
Method reproducibility	100% of the sample results met acceptance criteria	Yes
Study sample analysis/stability	Calibration standards and QC samples were stored at -20°C ± 5°C. Stability was confirmed at 371 days. Samples were received and sample analysis was conducted within the validated storage duration (stability required up to 33 days at -20°C ± 5°C).	Yes
Method Performance in Study 22251 (Report Number: ^{(b) (4)}-BIO-24-036)		
Assay passing rate	0 of 2 runs were rejected (100% passing rate).	Yes

Standard curve performance	Cumulative % bias range: -3.1% to 4.3% Cumulative precision (%CV): ≤ 3.0%	Yes
QC performance	Cumulative % bias range: 1.5% to 5.0% Cumulative precision (%CV): ≤ 6.1%	Yes
Study sample analysis/stability	Calibration standards and QC samples were stored at -20°C ± 5°C. Stability was confirmed at 371 days. Samples were received and sample analysis was conducted within the validated storage duration (stability required up to 32 days at -20°C ± 5°C).	Yes
Method Performance in Study 22252 (Report Number: 247014BGAN)		
Assay passing rate	0 of 1 run were rejected (100% passing rate).	Yes
Standard curve performance	Cumulative % bias range: -4.6% to 6.6% Cumulative precision (%CV): ≤ 5.15%	Yes
QC performance	Cumulative % bias range: -0.6% to 8.8% Cumulative precision (%CV): ≤ 5.44%	Yes
Method reproducibility	100% of the sample results met acceptance criteria	Yes
Study sample analysis/stability	Calibration standards were prepared freshly throughout the project, with 224 days (high concentration) and 850 days (low concentration) stability at -20°C. QC samples were prepared and stored at -20°C throughout the project, with stability confirmed at 384 days (unfortified) and 357 days (with lactones). Samples were received and sample analysis was conducted within the validated storage duration (stability required up to 41 days at -20°C).	Yes
Method Performance in Study 22253 (Report Number: ^{(b) (4)}-BIO-24-038)		
Assay passing rate	1 of 9 runs were rejected for (88.8% passing rate).	Yes
Standard curve performance	Cumulative % bias range: -1.1% to 0.7% Cumulative precision (%CV): ≤ 6.6%	Yes
QC performance	Cumulative % bias range: 1.1% to 4.7% Cumulative precision (%CV): ≤ 5.9%	Yes
Method reproducibility	95% of the sample results met acceptance criteria	Yes
Study sample analysis/stability	Calibration standards and QC samples were stored at -20°C ± 5°C. Stability was confirmed at 371 days. Samples were received and sample analysis was conducted within the validated storage duration (stability required up to 39 days at -20°C ± 5°C).	Yes

19.4.2. **FDA Assessment of Model Risk**

The pharmacometrics analyses were focused on assessment of population PK and ER of efficacy and safety endpoints, shown in **Table** .

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** .

Table 77. FDA – Assessment of Model Risk

Elements	Details
Question of Interest	Is the proposed recommended dosage appropriate (b) (4) therapy? (b) (4)
Context of Use	- PopPK models were used to evaluate the patient factors on exposure and generate individual exposure for E-R analysis. - E-R analyses were conducted to understand exposure dependent changes in efficacy and safety in patients.
Decision Consequence	Median. The proposed recommended dosage of 20 mg BID is associated with a high % of diarrhea that remains clinically manageable.
Model Influence	Low. Dosage is determined by clinical observation with E-R analyses used as supportive evidence.
Model Risk	Median

Source: FDA reviewer analysis

Table 78. FDA - Model Evaluation

Methodology	Objective	Model evaluation	Section
PopPK	- Characterize PK profile - Evaluate patient factors substantially impact PK - Predict individual exposure for subsequent E-R analysis	Standard model evaluation	19.4.3
Exposure-efficacy	- Characterize E-R relationship - Evaluate if 20 mg BID is appropriate to be proposed dosage	Standard model evaluation for ORR and BTR with logistic regression model and Emax model	19.4.4.1-19.4.4.2
Exposure-safety	Characterize E-R relationship for safety endpoints	Standard model evaluation for general AEs (SAE, Gr $\geq$ 3 TEAEs, dose modifications),	19.4.4.3-19.4.4.4

Methodology	Objective	Model evaluation	Section
	Evaluate risk in subgroup (age$\geq$75 vs ag$<$75)	and AEs of interest (diarrhea) with Cox model	

Source: FDA reviewer analysis

19.4.3. Population PK Analysis

19.4.3.1. Executive Summary

The FDA's Assessment:

The Applicant is seeking approval for sevabertinib, an oral, reversible human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR) inhibitor, for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) whose tumors have HER2 activating mutations, and who have received a prior systemic therapy. The key pharmacometrics findings are summarized below:

- Sevabertinib PK was adequately characterized using a 2-compartment model with transit first-order absorption and first-order elimination.
- Administration of liquid service formulation is found to increase absorption rate by 49% and reduces relative bioavailability by 36% compared to tablet administration, which is clinically significant. Tablet formulation is the to-be-marketed formulation.
- Increasing albumin (as a fraction of total protein) and increasing body weight are associated with lower relative bioavailability, or equivalently, higher adjusted apparent clearance and adjusted volume of distribution of the central compartment, which is not clinically significant.
- No significant impact on sevabertinib exposure was found for mild and moderate hepatic impairment or mild renal impairment.
- No conclusions on the impact of severe renal impairment or moderate or severe hepatic impairment could be drawn due to a no patient in these categories

19.4.3.2. PPK Assessment Summary

The Applicant's Position:

General Information

Objectives of PPK Analysis		- To characterize the variability in PK of sevabertinib by population PK modeling based on PK data from study 21607. - To evaluate if the PK of sevabertinib is linear over the evaluated dose range in Study 21607 (total daily dose of 10 – 80 mg). - To evaluate if the PK of sevabertinib is time dependent. - To evaluate the contribution of predefined covariates to the PK variability using a covariate analysis. - To estimate individual exposure after single dose and at steady state and estimate the effective half-life - To summarize pharmacokinetic data of the metabolite BAY 3306572 (M1) per sampling timepoint - To translate preclinical pEGFR reduction over time to patients using a previously developed (preclinical) PK-PD model and sevabertinib PK in patients
Study Included		21607 (n=335 participants with PK samples)
Dose(s) Included (Table 13-3 in Module 5.3.3.5, Report B003829)		10, 20, or 40 mg Liquid Service Formulation (LSF) QD, 40 or 60 mg tablet QD, 10, 20, 30, or 40 mg tablet BID
Population Included		Participants with locally advanced or metastatic NSCLC harboring activating mutations in HER2 and/or EGFR.
Population Characteristics (Table 13-5 and 13-6 in Module 5.3.3.5, Report B003829)	General	Age: 62 (18 -91) yr, 40.6% subj >=65 yr, 11.3% subj >=75 yr Weight: 61.3 (29.3 - 155) kg Male: n=120 (35.8%) American Indian or Alaska Native, n=1 (0.3%); Asian, n=216 (64.5%); Black or African American, n=9 (2.69%); Not reported, n=18 (5.37%); White, n=91 (27.2%)
	Organ Impairment	Hepatic function NCI: Normal, n=262 (78.2%); Mild, n=72 (21.8); Moderate, n=0 (0%); Severe, n=0 (0%) Renal function: Normal, n=164 (49%); Mild, n=146 (43.6%); Moderate, n=25 (7.46%); Severe, n=0 (0%)
	Pediatrics (if any)	Not applicable
No. of Patients, PK Samples, and BLQ (Table 8-2 Module 5.3.3.5, Report B003829)		n=335 participants with at least one valid PK concentration n = 5712 / n = 88 (1.52%) (PK samples above/below LLOQ)
Sampling Schedule (Table	Rich Sampling	C1D1: 0, 0.5, 1, 2, 3, 4, 6, 8, 12h. C1D2: 0h. C1D8: 0h. C1D15: as C1D1. C1D16: 0h. C2D1, C3D1 & C5D1: 0, 2h.

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5-1, Module 5.3.3.5, Report B003829)	Sparse Sampling	C1D1 & C1D15: 0, 1, 2-4, 6-12h. C2D1, C3D1 & C5D1: 0, 1-4h.
Covariates Evaluated (Table 6-1 Module 5.3.3.5, Report B003829)	Static	Body weight, Age, Sex, Race, Geographical region (Asia/North America/South America/Western Europe and Israel; China vs rest of the world; Japan vs rest of the world; Asia vs rest of the world), Serum creatinine, eGFR, renal function, Total bilirubin, AST, ALT, NCI-ODQG liver function, Number of liver metastases as assessed by local investigator, Albumin, Total protein, Albumin as fraction of total protein (Albumin fraction), Diarrhea adverse event in cycle 1, smoking status, Loperamide use prior to the first all grade diarrhea adverse event, Tablet size, Formulation Tablet manufacturing process, use (at any time during the study) of: weak or moderate CYP3A4 inhibitor(s), weak or moderate CYP3A4 inducer (s), P-gp inhibitor(s), P-gp inducer(s), BRCP inhibitor(s), BCRP inducer(s)
	Time-varying	Loperamide treatment
Final Model	Summary	Acceptability [FDA’s comments]
Software and Version	Model evaluation and all graphical displays and statistical summaries were performed using R software version 4.2.0. PK model building was conducted using nonlinear mixed-effects modeling using NONMEM software (ICON Development Solutions, version 7.4.3) Simulations for visual predictive checks (VPC) were executed using NONMEM. Exposure simulations utilizing selected popPK models were implemented in R using the “RxODE” library	Acceptable
Model Structure (Figure 8-3 Module 5.3.3.5, Report B003829)	A 2-compartmental model with delayed first order absorption described with 5 transit compartments between the dosing and central compartment	Acceptable
Model Parameter Estimates	Table 8-6 in Module 5.3.3.5, Report B003829	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All model parameters were estimated with acceptable standard errors (RSE<30%) and shrinkage (<30%)	Acceptable
BLQ for Parameter Accuracy	As only 1.52% of the available PK samples were below the lower limit of quantification, the possible impact of	Acceptable

GOF, VPC (final/refined popPK model)	<i>these samples on model development and parameter accuracy was considered to be (very) low and samples below the lower limit of quantification were excluded from the analysis</i> <i>GOF: 14-7 and 14-8 in Module 5.3.3.5, Report B003829</i> <i>VPC (prediction-corrected): Figures 16-11 and 16-13 (section 16.3) in Module 5.3.3.5, Report B003829</i>	Acceptable
Significant Covariates and Clinical Relevance	<i>Figures 8-4 and 8.5 (Module 5.3.3.5, Report B003829) show the forest plots of the intrinsic and extrinsic covariates, respectively.</i> <i>Two significant covariate influences were found: increasing body weight and albumin (as a fraction of total protein) were associated with a decrease in relative bioavailability. The two significant covariate influences therefore inversely influence the adjusted relative clearance and adjusted relative volume of distribution of the central compartment, such that both increasing body weight and albumin fraction are associated with increasing adjusted relative clearance and volume of distribution of the central compartment.</i> <i>The model derived effect of differences in body weight and albumin fraction on exposure is visualized in Figure 8-6 Module 5.3.3.5, Report B003829, showing the predicted exposure ratio in (virtual) subjects with either an albumin fraction or body weight fraction at the lower (10th percentile) and higher (90th percentile) ends of their distribution in Study 21607 compared to a reference subject with a median albumin fraction and body weight. This figure shows that the 90% CI of all ratios are within the bioequivalence limits of 0.8–1.25. In addition, the 27% and 31% difference in ratio between the 10th and 90th percentiles of the body weight and albumin fraction distribution,</i>	Acceptable These significant covariates are not expected to result in clinically meaningful difference.

Analysis Based on Simulation (optional)	<i>respectively, is also considered not clinically meaningful and no dosage adjustment is needed to obtain comparable exposures among patients</i> <i>Figure 9-1 (Module 5.3.3.5, Report B003829): translation preclinical pEGFR reduction over time to patients using a previously developed (preclinical) PK-PD model and sevabertinib PK in patients</i> <i>Figure 9-2 (Module 5.3.3.5, Report B003829): percentage of patients with sevabertinib steady state exposure below and above the efficacious exposure based on xenograft data</i>	Acceptable These models were used to predict percentage of exposure above preclinical efficacy endpoints of different dosage and indirectly supported the proposed dosage.
Labeling Language 12.3 PK	Description (b) (4)	Acceptability [FDA's comments] Acceptable



Table 79. Summary of Baseline Characteristics and Laboratory Values in the Dataset

Source: Tables 13-5 and 13-6 in Module 5.3.3.5, Report B003829

Table 13-5: Summary statistics from FPKAS of continuous covariates for all subjects with valid PK (n=335)

Covariate (unit)	Min.	Max.	Median	Arith. Mean	Arith. s.d.	Arith. CV (%)	Geometric mean	Geometric s.d.	Geometric CV (%)
BW0 (kg)	29.3	155	61.3	62.97	14.1	22.39	61.51	1.241	21.87
AGE (y)	18	91	62	60.91	11.22	18.41	59.76	1.226	20.55
EGFR0 (mL/min)	43.78	190.8	89.12	91.64	25.37	27.68	88.43	1.303	26.95
CREAT0 (mg/dL)	0.38	1.46	0.74	0.7586	0.1819	23.97	0.7379	1.265	23.85
AST0 (U/L)	8	127	26	29.89	15.63	52.27	26.97	1.547	45.76
ALT0 (U/L)	3	120	19	23.09	16.82	72.87	19.23	1.789	63.42
BILIO (mg/dL)	0	1.6	0.52	0.5838	0.2584	44.27	NC ^a	NC ^a	NC ^a
LMETNUMI (n) ^b	0	5	0	0.4328	0.8995	207.8	NC ^a	NC ^a	NC ^a
ALB0 (g/dL)	2.5	5.1	4	3.963	0.4379	11.05	3.938	1.122	11.55
PROT0 (g/dL)	5	8.8	7.1	7.097	0.6278	8.846	7.068	1.095	9.052

^a Not calculable due to presence of 0 in the data^b Missing LMETNUMI values set to zero.

Table 13-6: Counts of time-invariant categorical covariates for all subjects in FPKAS (n=335)

Covariate	Category	Number of subjects	% of subjects
AGECAT	<65 years	199	59.4
	≥65 years	136	40.6
SEX	Female	215	64.2
	Male	120	35.8
RACE	American Indian or Alaska Native	1	0.3
	Asian	216	64.5
	Black or African American	9	2.69
	Not reported	18	5.37
	White	91	27.2
REGION1	Asia	214	63.9
	North America	29	8.66
	South America	1	0.3
	Western Europe & Israel	91	27.2
REGION2	China	83	24.8
	Non-China	252	75.2
REGION3	Japan	36	10.8
	Non-Japan	299	89.2
REGION4	Asia	214	63.9
	Non-Asia	121	36.1
RENALCAT	Mild	146	43.6
	Moderate	25	7.46
	Severe	0	0.00
	Normal	164	49.0
HEPACCAT	Mild	73	21.8
	Moderate	0	0.00
	Severe	0	0.00
	Normal	262	78.2
PROLOUSE	No	321	95.8
	Yes	14	4.18
DIACY1	No	96	28.7
	Yes	239	71.3
LMETCAT ^a	No	257	76.7
	Yes	78	23.3
SMOKE	Current	8	2.39
	Former	103	30.8
	Never	224	66.9
CYP1HMOD	No	206	61.5
	Yes	129	38.5
CYP1DMOD	No	223	66.6
	Yes	112	33.4
PGPINH	No	181	54.0
	Yes	154	46.0
PGPIND	No	156	46.6
	Yes	179	53.4
BCRPINH	No	123	36.7
	Yes	212	63.3
BCRPIND	No	331	98.8
	Yes	4	1.19
CYINHC1	Missing	144	43
	No	108	32.2
	Unclassified	13	3.88
	Weak	61	18.2
	Moderate	9	2.69

Table 13-6: Counts of time-invariant categorical covariates for all subjects in FPKAS (n=335)

Covariate	Category	Number of subjects	% of subjects
CYINDC1	Missing	144	43
	No	143	42.7
	Unclassified	6	1.79
	Weak	5	1.49
	Moderate	37	11
PGPINHC1	No	244	72.8
	Yes	91	27.2
PGPINDC1	No	273	81.5
	Yes	62	18.5
BCRINHC1	No	215	64.2
	Yes	120	35.8
BCRINDC1	No	332	99.1
	Yes	3	0.9

^a Missing LMETCATI values set to zero.

Table 80. Parameter Estimates and SE From Final Population PK Model

Source: Table 8-6 in Module 5.3.3.5, Report B003829

Table 8-6: Parameter estimates of the refined popPK model (runR323b)

Parameter	Unit	Estimate	RSE [%] ^a	LLCI ^b	ULCI ^c	Description
<i>Fixed effects (THETA)</i>						
KA _{pop}	1/h	7.90	3.29	7.39	8.41	Absorption rate (tablet)
CL _{pop} /F	L/h	3.09	2.59	2.94	3.25	Apparent clearance
VC/F	L	30.0	2.13	28.8	31.3	Apparent volume of distribution (central)
Q/F	L/h	0.634	14.9	0.449	0.819	Apparent inter-compartmental clearance
VP/F	L	20.4	19.8	12.5	28.3	Apparent volume of distribution (peripheral)

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Table 8-6: Parameter estimates of the refined popPK model (runR323b)

Parameter	Unit	Estimate	RSE [%] ^a	LLCI ^b	ULCI ^c	Description
CF1 _{LSF}	-	-0.361	18.1	-0.489	-0.233	Rel. Bioavailability for all LSFs compared to tablet (absolute change)
CKA _{LSF}	-	0.491	22.7	0.272	0.709	Proportional increase in KA for LSFs compared to tablet
CF1 _{ALBF}	-	-1.22	14.3	-1.56	-0.880	Exponent for ALB0/PROT0 influence on F1
CF1 _{BW0}	-	-0.517	18.5	-0.704	-0.330	Exponent for BW0 influence on F1
<i>Random effects: Inter-individual variability (OMEGA)</i>						
KA (ω^2)	-	0.330	10.9	0.259	0.401	Variance of exponential IIV on KA
KA (CV ^d)	%	62.6		54.4	70.2	
KA (Shrinkage)	%	8.58				
CL/F (ω^2)	-	0.135	10.5	0.107	0.162	Variance of exponential IIV on CL
CL/F (CV ^d)	%	38.0		33.6	42.0	
CL/F (Shrinkage)	%	8.63				
F1 (ω^2)	-	0.0936	11.2	0.0730	0.114	Variance of exponential IIV on F1
F1 (CV ^d)	%	31.3		27.5	34.8	
F1 (Shrinkage)	%	9.96				
<i>Residual error (SIGMA)</i>						
EPS(1,1) (σ^2)	-	0.250	4.44	0.228	0.271	Variance of proportional residual error for observations with TAD < 1.167 h or STIM=0
CV ^e	%	50.0		47.7	52.1	
EPS(2,2) (σ^2)	-	0.110	5.08	0.0994	0.121	Variance of proportional residual error for observations with TAD ≥ 1.167 h and STIM ≠ 0
CV ^e	%	33.2		31.5	34.8	

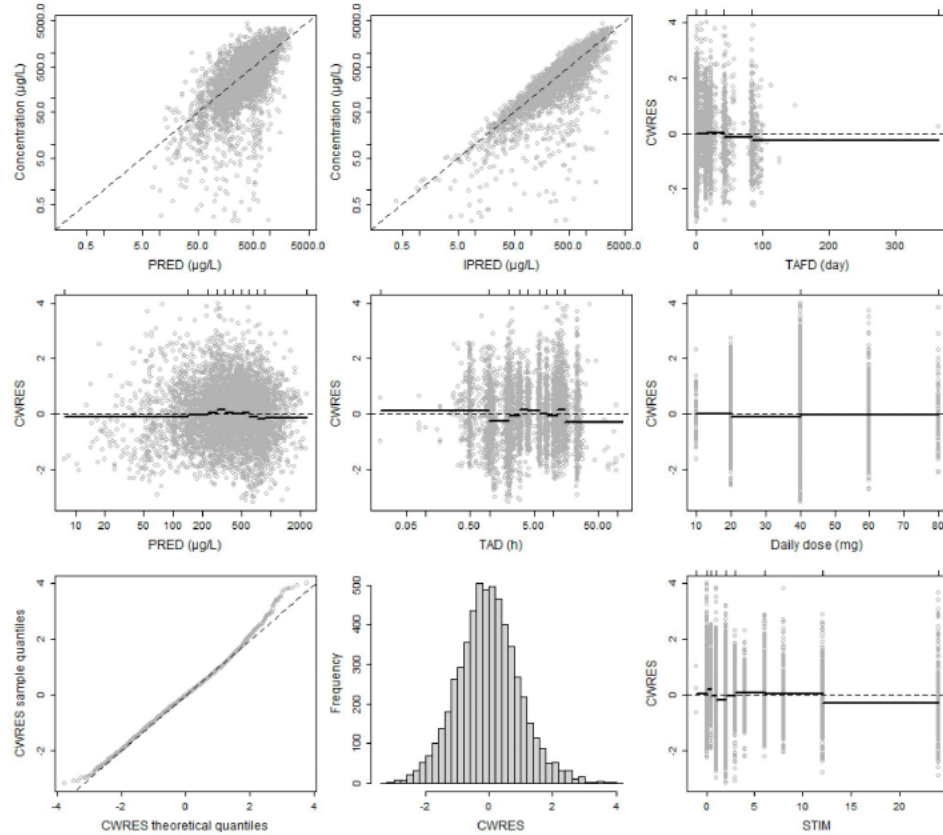
^a RSE = relative standard error (100·SE/estimate)^b LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)^c ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)^d Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2 .^e Coefficient of variation (CV) calculated as 100·SQRT(σ^2). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2 .

Table 81. Goodness-of-Fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)

Source: Figure 14-7 in Module 5.3.3.5, Report B003829

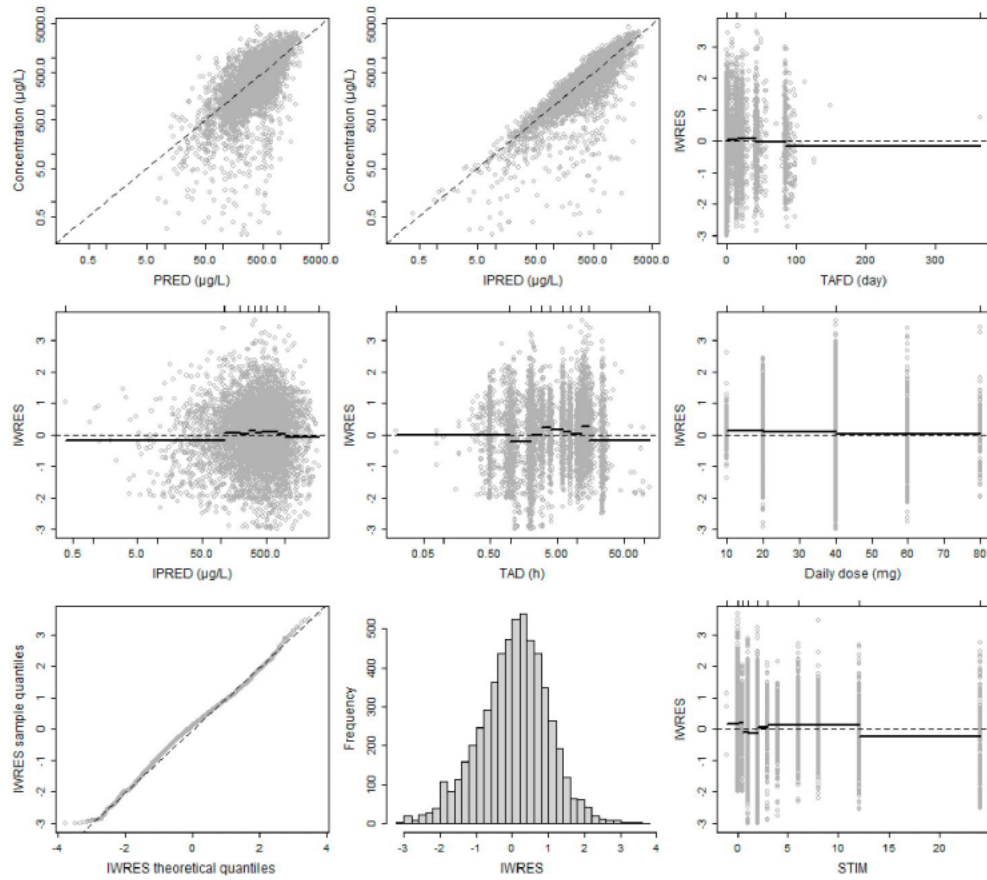
M&S Report BAY 2927088 / (b) (4) 50245 / B003829

14.3 Refined popPK model



Bold horizontal lines show arithmetic mean CWRES within each bin of independent variables. Bin limits are displayed as tick marks along the top of each plot.

Figure 14-7: CWRES GoF plots from the refined popPK covariate model for observations in FPKAS.



Bold horizontal lines show arithmetic mean IWRES within each bin of independent variables. Bin limits are displayed as tick marks along the top of each plot.

Figure 14-8: IWRES GoF plots from the refined popPK model for observations in FPKAS.

Table 82. VPC of Final Population PK Model, Prediction Corrected

Source: Figures 16-11 and 16-13 in Module 5.3.3.5, Report B003829

M&S Report BAY 2927088 / (b) (4) 50245 / B003829

16.3 Refined popPK model (runR323b)

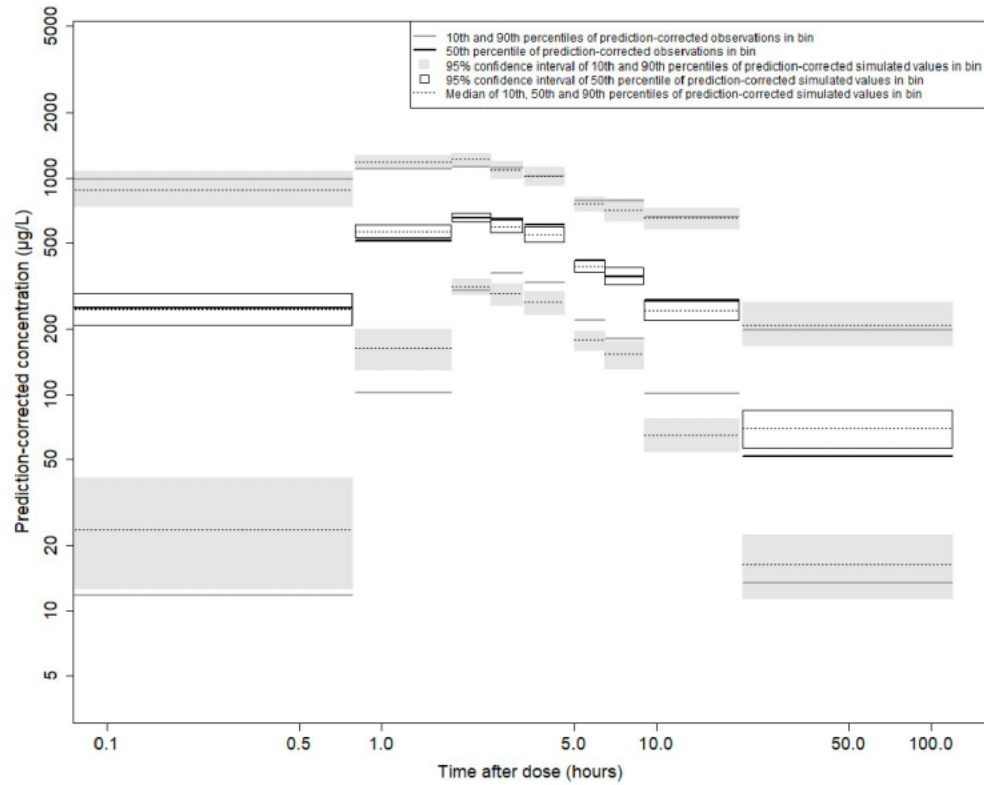


Figure 16-11: Percentile style VPC for observations in FPKAS from refined popPK model with log axes.

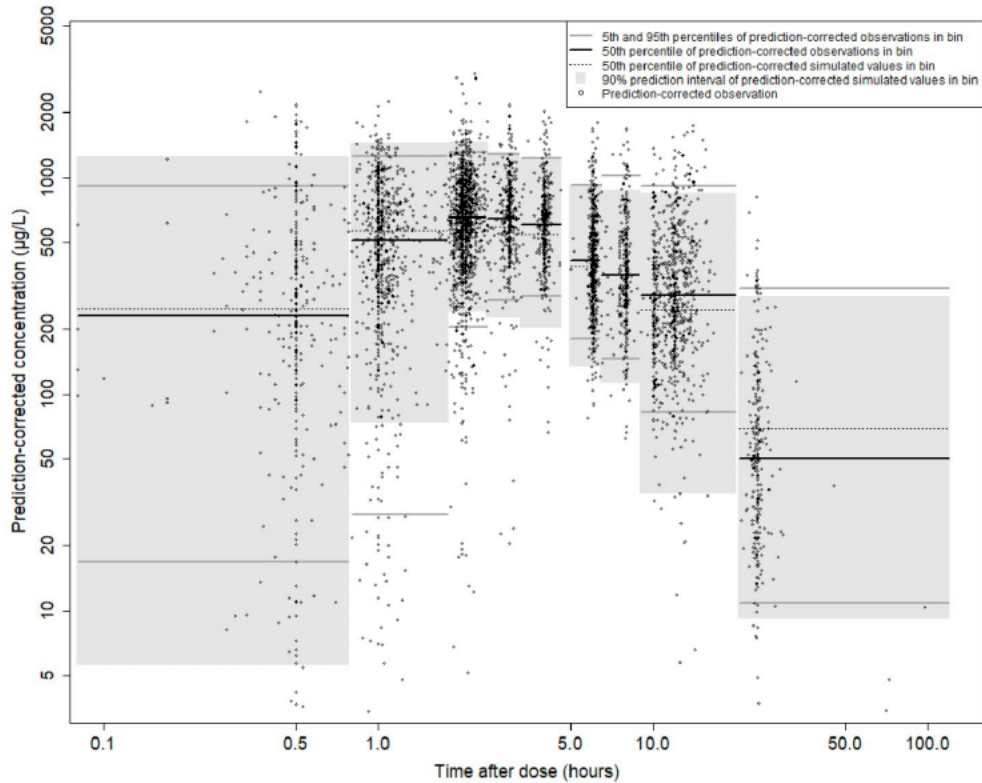
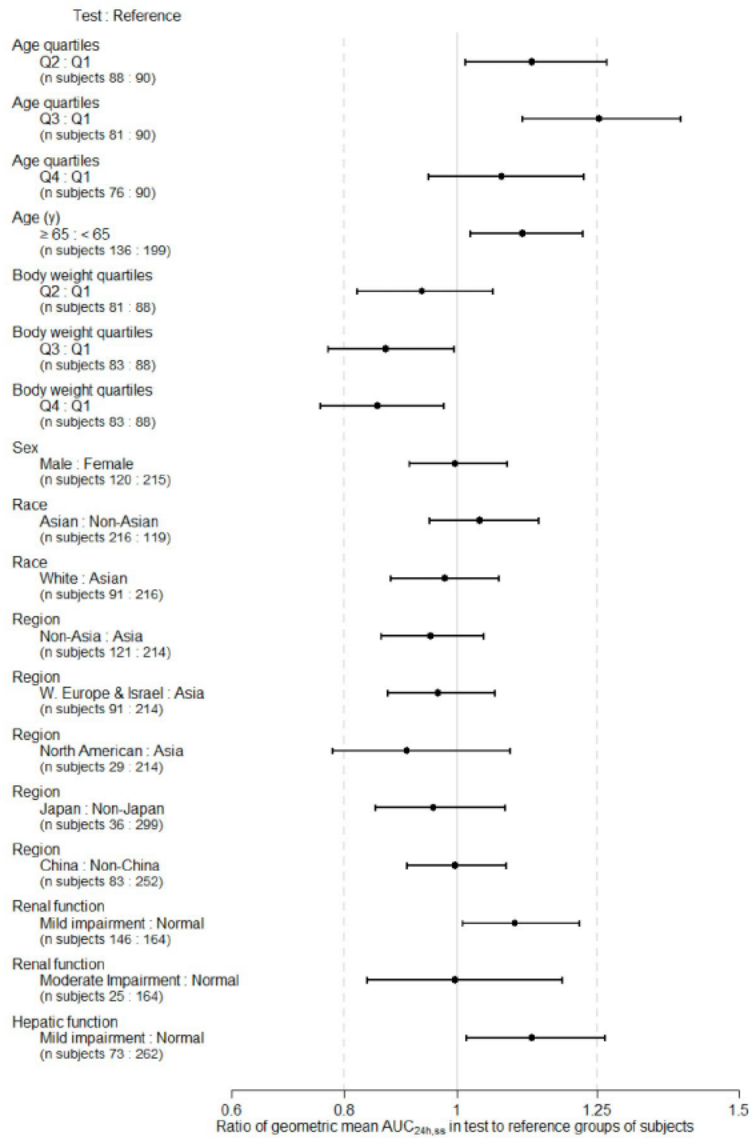


Figure 16-13: Range style VPC for observations in FPKAS from refined popPK model with log axes.

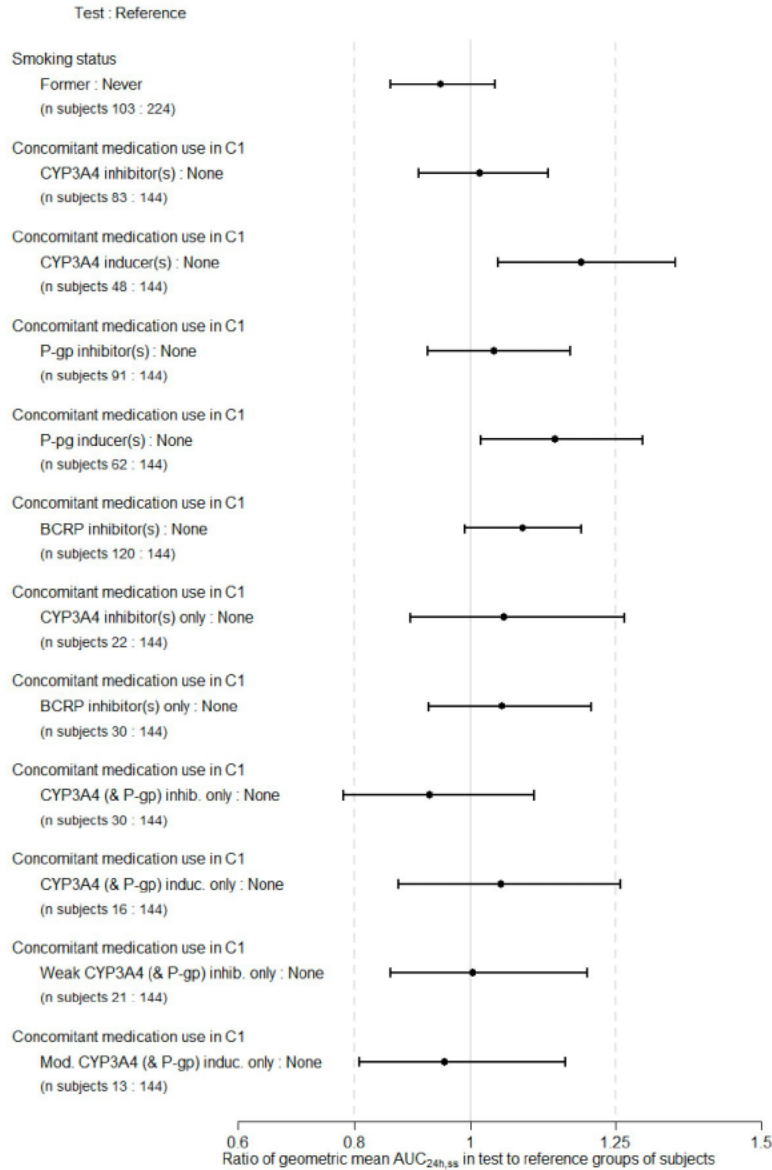
Table 83. Impact of Significant Covariates on Exposure

Source: Figure 8-4 (Module 5.3.3.5, Report B003829) forest plots of the intrinsic covariates



The horizontal black bars indicate the 90% CI of the ratio (test to reference covariate categories) of geometric means of AUC_{24h,ss}. Ratios are not displayed if the number of subjects in one category is <10. Age quartiles (years): Q1≤54, 54<Q2≤62, 62<Q3≤69, Q4>69. BW0 quartiles (kg): Q1≤54, 54<Q2≤61.3, 61.3<Q3≤70, Q4>70.

Figure 8-4: Plot of geometric mean AUC_{24h,ss} ratios for subgroups of subjects according to intrinsic covariates in FPKAS.



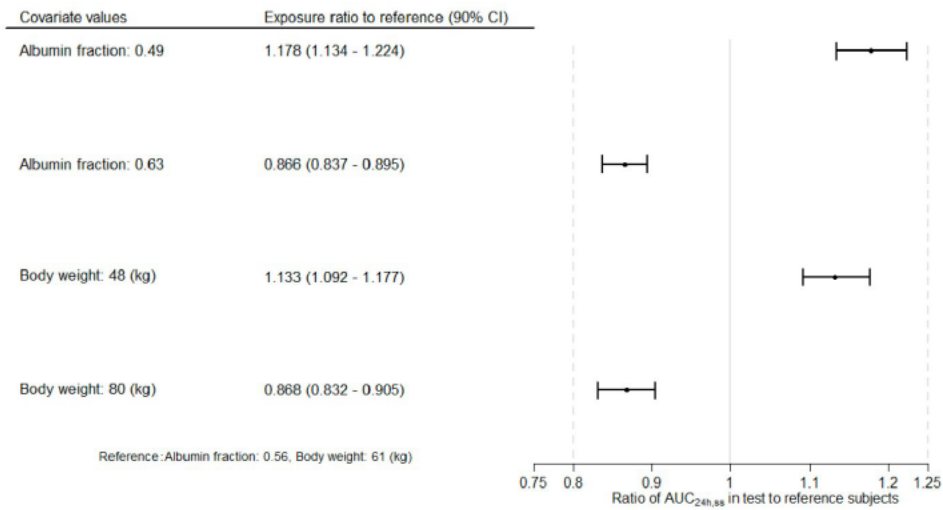
The horizontal black bars indicate the 90% CI of the ratio (test to reference covariate categories) of geometric means of AUC_{24h,ss}.

Figure 8-5: Plot of geometric mean AUC_{24h,ss} ratios for subgroups of subjects according to extrinsic covariates in FPKAS.

Source: Figure 8-6 (Module 5.3.3.5, Report B003829) predicted exposure ratio in (virtual) subjects based on differences in body weight and albumin fraction

8.4.2.2 Univariate method

Geometric mean ratios of $AUC_{24h,ss}$ in four test subjects (at combinations of 10th, 50th and 90th percentiles of ALBF and BW0) to a reference subject (ALBF 0.56, BW0 61 kg) were calculated according to the methodology in Section 6.5.2.2. The results are listed and visualized in Figure 8-6.

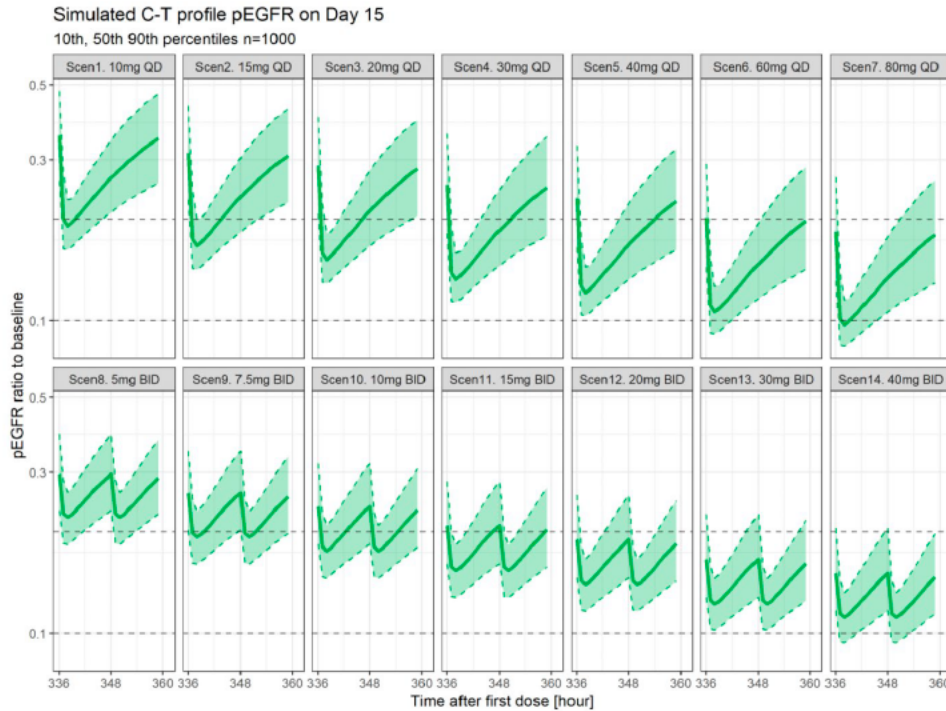


The horizontal black bars indicate the 90% CI of the ratio (to reference subject with albumin fraction of 0.56 and body weight of 61 kg) of $AUC_{24h,ss}$.

Figure 8-6: Plot of $AUC_{24h,ss}$ ratios according to the univariate method.

Figure 18. Simulation Results

Source: Figure 9-1 (Module 5.3.3.5, Report B003829): translation preclinical pEGFR reduction over time to patients using a previously developed (preclinical) PK-PD model and sevabertinib PK in patients



Simulated change in pEGFR for a typical patient is shown by the solid line. The shaded area show the simulated variability for 80% of the population. The dashed black line show a pEGFR reduction of 80 or 90% respectively.

Figure 9-1: Simulated change in pEGFR in patients for different doses and dosing frequencies of sevabertinib using the translational PK-PD model for pEGFR reduction.

Source: Figure 9.2 (Module 5.3.3.5, Report B003829): percentage of patients with sevabertinib steady state exposure below and above the efficacious exposure based on xenograft data

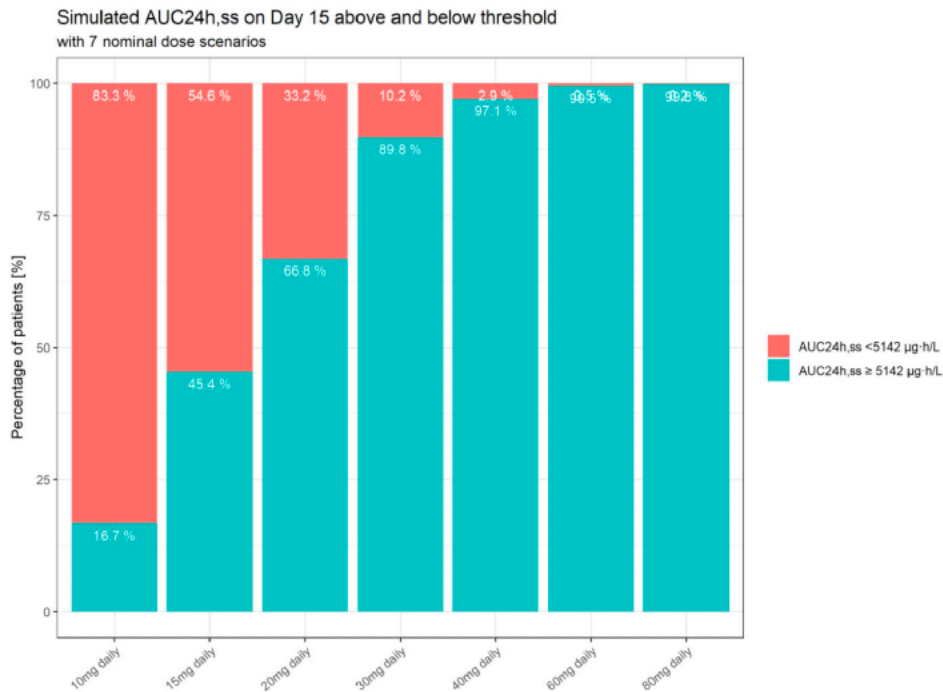


Figure 9-2: Simulated percentage of patients with sevabertinib steady state exposure (AUC_{24h,ss}) below or above the efficacious exposure estimated from preclinical exposure-efficacy relationship.

The FDA’s Assessment:

The population PK analysis is considered adequate. The intrinsic factors evaluated are not expected to result in clinically meaningful change in exposure.

19.4.3.3. PPK Review Issues

None.

19.4.3.4. Reviewer’s Independent Analysis

None.

19.4.4. **Exposure-Response Analysis**

19.4.4.1. **ER (Efficacy) Executive Summary**

The FDA’s Assessment:

- There are two dosage (10 mg and 20 mg QD) in the D/D1 subset (105 patients) in the efficacy ER assessment, in which there are limited data for the lower dosage and large between-cohort variability under the same dosage. No positive exposure-response relationship was observed for objective response rate (ORR).
- Participants with the HER2 activating mutations were more likely to have an objective response, which is exposure independent.

19.4.4.2. **ER (Efficacy) Assessment Summary**

The Applicant’s Position:

General Information		
Goal of ER analysis	<i>To evaluate the association between sevabertinib exposure and the primary (objective response rate) and exploratory (best tumor response) efficacy endpoints using a multivariate exposure-response analysis with predefined covariates</i>	
Study Included	<i>Study 21607</i>	
Endpoints	<i>Primary: Objective Response Rate (ORR) based on Blinded independent committee review (BICR) where possible in study groups D and D1 with second line (2L) participants harboring HER2 activating mutations (D/D1 subset)</i> <i>Exploratory: Maximal change in tumor size from baseline (best tumor response, BTR) in study groups D and D1 with second line (2L) participants harboring HER2 activating mutations (D/D1 subset)</i>	
No. of Patients (total, and with individual PK)	<i>n=115 participants in study groups D and D1 (D/D1 subset)</i>	
Population Characteristics (Module 5.3.3.5, Report B003834: Age: Tables 14-3, 14-20 and 14-21, Body weight: Table 14-10, Sex: Table 14-	General (D/D1 subset)	<i>Age: 62 (29 - 82) yr, 38.3% subj >=65 yr, 9.5% subj >=75 yr</i> <i>Weight: 61.3 (29.3 – 109) kg</i> <i>Male: n=39 (33.9%)</i> <i>American Indian or Alaska Native, n=0 (0%); Asian, n=72 (62.6%); Black or African American, n=2 (1.74%); Not reported, n=6 (5.22%); White, n=35 (30.4%)</i>

46, Race: Table 14-41)	Pediatrics (if any)	Not applicable	
Dose(s) Included		10 and 20 mg tablet BID (D/D1 subset)	
Exposure Metrics Explored (range) (Tables 14-50 – 14-55, Module 5.3.3.5, Report B003834)		$AUC_{24h,ss}$ (1750 – 95580 $\mu\text{g}\cdot\text{h/L}$), $C_{trough,ss}$ (18.3 - 3263 $\mu\text{g/L}$), $C_{max,ss}$ (171.6 – 4798 $\mu\text{g/L}$), $AUC_{24h,day1}$ (1560 – 39300 $\mu\text{g}\cdot\text{h/L}$), $C_{trough,day1}$ (14.6 – 1554 $\mu\text{g/L}$), $C_{max,day1}$ (165.7 – 2617 $\mu\text{g/L}$)	
Covariates Evaluated		Body weight, Age, Sex, Race, Geographical region (Asia/North America/South America/Western Europe and Israel; China vs rest of the world; Japan vs rest of the world, Mutational status, Albumin, Smoking status, Time since diagnosis, ECOG performance, AJCC grading at initial diagnosis, Tumor stage, Baseline tumor size, Brain metastases, Liver metastases, Number of metastatic sites, Alkaline Phosphatase (ALP), Lactate dehydrogenase (LDH), Neutrophil to lymphocyte ratio (NL ratio), Previous lines of anti-cancer therapy, Prior platinum therapy, Prior immunotherapy, Prior HER2 Ex20ins-targeted Therapy, Prior EGFR Ex20ins-targeted Therapy	
Final Model Parameters		Summary	
		Acceptability [FDA's comments]	
Model Structure		ORR (D/D1 subset): logistic regression model with a non-linear/saturable/E_{max} type exposure-response relationship BTR (D/D1 subset): E_{max}-type relationship with a BTR of zero for an exposure level of zero	Acceptable for ORR Not acceptable for BTR
Model Parameter Estimates		ORR (D/D1 subset): Table 17-4 (Module 5.3.3.5, Report B003834) BTR (D/D1 subset): Table 17-8 (Module 5.3.3.5, Report B003834)	Acceptable for ORR Not acceptable for BTR
Model Evaluation		ORR (D/D1 subset): Figure 10-10 (Module 5.3.3.5, Report B003834) BTR (D/D1 subset): Figure 10-20 (Module 5.3.3.5, Report B003834)	Acceptable for ORR Not acceptable for BTR
Covariates and Clinical Relevance		None of the baseline covariates has a statistically significant effect on either ORR or BTR in the D/D1 subset	Acceptable for ORR Not acceptable for BTR
Simulation for Specific Population		Not applicable	
Visualization of E-R relationships		Figure 3-7 (Module 5.3.3.5, Report B003834) for both ORR and BTR	Acceptable for ORR Not acceptable for BTR

Overall Clinical Relevance for ER	ORR (D/D1 subset): non-significant trends indicated potential increased objective response with higher exposure BTR (D/D1 subset): statistically significant ($p < 0.01$) exposure response relationship, with higher exposure being related to a larger decrease in tumor size	Acceptable for ORR Not acceptable for BTR
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	(b) (4)	No, the estimates were not robust to support a definitive positive E-R relationship (b) (4) (d) (4) refer to 19.4.4.6 for details.

Table 84. Summary of Baseline Characteristics and Laboratory Values in the Dataset

Age:

Source: Table 14-3, Module 5.3.3.5, Report B003834

Table 14-3: Summary statistics of AGE by analysis dataset

Dataset	N	Min.	Max.	Median	Arith. Mean	Arith. s.d.	Arith. CV (%)	Geometric mean	Geometric s.d.	Geometric CV (%)
PMx_SAF	335	18	91	62	60.9	11.2	18.4	59.8	1.23	20.6
PMx_ORs	326	18	91	62	60.9	11.1	18.2	59.8	1.22	20.4
PMx_ORs (D/D1 subset) ^a	115	29	82	62	60	11.2	18.6	58.8	1.23	20.6

Source: Table 14-20 and 14-21, Module 5.3.3.5, Report B003834

Table 14-20: Counts of AGECAT for all participants stratified by data set

Data set	Participant counts	
	< 65	≥ 65
PMx_SAF	199	136
PMx_ORs	194	132
PMx_ORs D/D1 subset	71	44

Table 14-21: Counts of AGECAT2 for all participants stratified by data set

Data set	Participant counts	
	< 75	≥ 75
PMx_SAF	297	38
PMx_ORs	289	37
PMx_ORs D/D1 subset	104	11

Body weight:

Source: Table 14-10, Module 5.3.3.5, Report B003834

Table 14-10: Summary statistics of BW0 by analysis dataset

Dataset	N	Min.	Max.	Median	Arith. Mean	Arith. s.d.	Arith. CV (%)	Geometric mean	Geometric s.d.	Geometric CV (%)
PMx_SAF	335	29.3	155	61.3	63	14.1	22.4	61.5	1.24	21.9
PMx_ORs	326	29.3	155	62	63.3	14.1	22.2	61.8	1.24	21.7
PMx_ORs (D/D1 subset) ^a	115	29.3	109	61.3	62.7	14.1	22.4	61.2	1.25	22.6

^a The D/D1 subset is defined as participants that were assigned to groups D and D1 within Study 21607 contained within the PMx_ORs dataset

Sex:

Source: Table 14-46, Module 5.3.3.5, Report B003834

Table 14-46: Counts of SEX for all participants stratified by data set

Data set	Participant counts	
	Male	Female
PMx_SAF	120	215
PMx_ORs	117	209
PMx_ORs D/D1 subset	39	76

Race:

Source: Table 14-41, Module 5.3.3.5, Report B003834

Table 14-41: Counts of RACE for all participants stratified by data set

Data set	Participant counts				
	White	Black/African American	Asian	American Indian/Alaska Native	Not reported
PMx_SAF	91	9	216	1	18
PMx_ORs	89	9	210	1	17
PMx_ORs D/D1 subset	35	2	72	0	6

Table 85. Parameter Estimates from Final ER Model of (endpoint)

ORR (D/D1 subset)

Source: Table 17-4, Module 5.3.3.5, Report B003834

Table 17-4: Final logistic regression model of objective response rate in the PMx_ORs D/D1 subset based on BICR tumor assessments where possible

Parameter	Estimate (95% CI)	Wald p-value	p-value ^a
Intercept	0.35018 (-0.066867 -- 0.76723)	0.0998	0.1257
Coefficient for transformed ^b AUC _{24h,ss}	57770000 (-1163900 -- 116700000)	0.0547	

^a Based on OFV compared to RCM

^b Transformation done using function $f(\text{AUC}_{24h,ss}) = \text{AUC}_{24h,ss} / (\text{IC}_{50} + \text{AUC}_{24h,ss})$ where $\text{IC}_{50} = 0.00008$ and the value of IC_{50} was established using a algorithmic approach

BTR (D/D1 subset)

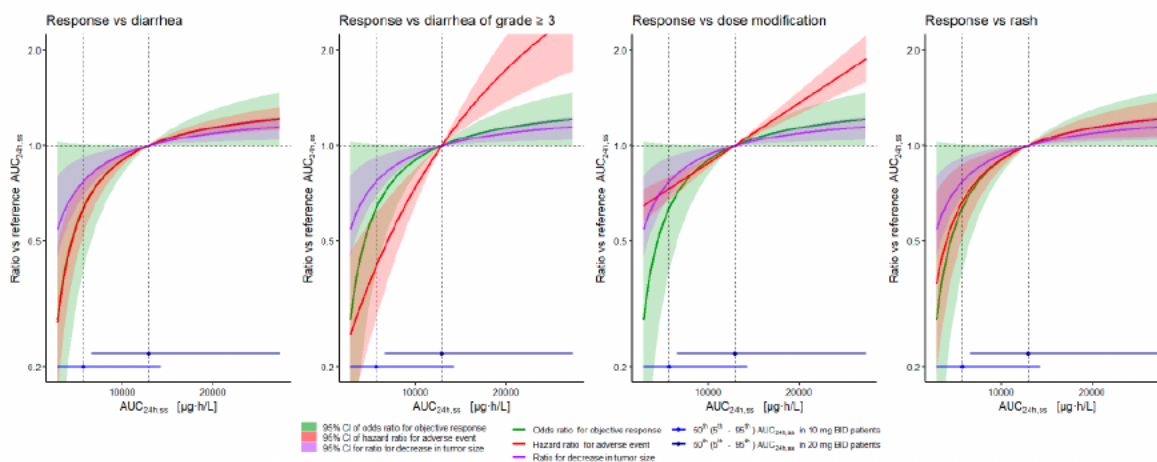
Source: Table 17-8, Module 5.3.3.5, Report B003834

Table 17-8: Final model for best tumor response in the PMx_ORs D/D1 subset based on BICR tumor assessments where possible

Parameter	Estimate (95% CI)
IC ₅₀	4000 (1000 -- 7025)
E _{max}	-58.635 (-74.463 -- -47.231)

Figure 19. ER Curves

Source: Figure 3-7, Module 5.3.3.5, Report B003834



Solid red line (shaded region): hazard ratio (95% CI) for, left to right plot, diarrhea, diarrhea with grade ≥ 3 , dose modification due to TEAE and rash. All plots - solid green line (shaded region) odds ratio (95% CI) for ORR for the objective response set D/D1 subset based on BICR tumor assessment where possible. All plots - solid purple line (shaded region): the ratio for BTR for the objective response set D/D1 subset based on BICR tumor assessment where possible. Ratio reference is based on the median $AUC_{24h,15}$ from all participants dosed 20 mg BID. Dark blue and blue horizontal lines: 5th – 95th percentile ranges of $AUC_{24h,15}$ from participants dosed 20 mg BID and 10 mg BID with central dot dissected by the vertical dashed lines giving the respective medians.

Figure 3-7: Benefit-risk plot comparing safety endpoints against efficacy endpoints for the objective response set D/D1 subset based on BICR tumor assessment where possible.

19.4.4.3. ER (Safety) Executive Summary

The FDA's Assessment:

- Sevabertinib exposure is associated with increased risk of all-Grade diarrhea, Grade 3 or worse diarrhea, all-Grade rash, and TEAEs leading to dose modification ($p < 0.01$).
- The following patient factors were identified as significant covariates (p value < 0.01) in the multivariate E-R analysis for respective endpoints.
 - Participants from Japan were found to have an increased risk of diarrhea as did those who had previously undergone HER2 targeted therapy.
 - For diarrhea of grade ≥ 3 , older participants were found to be at increased risk whilst participants with an Eastern Cooperative Oncology Group score greater than 0 were at decreased risk at baseline.
 - For dose modifications due to treatment emergent adverse events, participants taking drugs for treating constipation, White participants, and participants with weight at baseline ≤ 54 kg were found to be at increased risk at baseline.
 - For rash, participants with higher levels of bilirubin at baseline were at higher risk whilst participants from Japan were at decreased risk.

19.4.4.4. ER (Safety) Assessment SummaryThe Applicant's Position:

General Information		
Goal of ER analysis	- To evaluate the association between sevabertinib exposure and all grade treatment emerging adverse events (TEAEs) for diarrhea and rash, diarrhea of grade ≥ 3 and all-type TEAEs leading to dose modifications using a multivariate exposure-response analysis. - To visualize the therapeutic window of sevabertinib for the treatment of second line participants harboring HER2 activating mutations to support the dose rationale.	
Study Included	21607	
Population Included	Participants with locally advanced or metastatic NSCLC harboring activating mutations in HER2 and/or EGFR with exposure estimates (n=335)	
Endpoints	Time to first event of TEAEs for (all grade) diarrhea and rash, Grade = 3 diarrhea and all-type TEAEs leading to dose modifications	
No. of Patients (total, and with individual PK)	n=335	
Population Characteristics (Table 14-2 and 14-19 in Module 5.3.3.5, Report B003834)	General	Age: 62 (18 -91) yr, 40.6% subj ≥ 65 yr, 11.3% subj ≥ 75 yr Weight: 61.3 (29.3 - 155) kg Male: n=120 (35.8%) American Indian or Alaska Native, n=1 (0.3%); Asian, n=216 (64.5%); Black or African American, n=9 (2.69%); Not reported, n=18 (5.37%); White, n=91 (27.2%)
	Organ impairment	Hepatic function NCI: Normal, n=262 (78.2%); Mild, n=72 (21.8); Moderate, n=0 (0%); Severe, n=0 (0%) Renal function: Normal, n=164 (49%); Mild, n=146 (43.6%); Moderate, n=25 (7.46%); Severe, n=0 (0%)
	Pediatrics (if any)	Not applicable
	Geriatrics (if any)	Age: 62 (18 -91) yr, 40.6% subj ≥ 65 yr, 11.3% subj ≥ 75 yr Male: n=120 (35.8%)
Dose(s) Included	10, 20, or 40 mg LSF QD, 40 or 60 mg tablet QD, 10, 20, 30, or 40 mg tablet BID	

Exposure Metrics Explored (range) <i>(Tables 14-50 – 14-55, Module 5.3.3.5, Report B003834)</i>	<i>AUC_{24h,ss} (1328 – 95580 µg·h/L), C_{trough,ss} (8.35- 3263 µg/L), C_{max,ss} (171.6– 4798 µg/L), AUC_{24h,day1} (1210 – 39300 µg·h/L), C_{trough,day1} (5.18– 1554 µg/L), C_{max,day1} (165.7– 2617 µg/L)</i>	
Covariates Evaluated <i>(Table 6-2, Module 5.3.3.5, Report B003834)</i>	<i>Body weight, Age, Sex, Race, Geographical region (Asia/North America/South America/Western Europe and Israel; China vs rest of the world; Japan vs rest of the world, Total bilirubin, AST, ALT, NCI-ODQG liver function, Loperamide use prior to the first all grade diarrhea adverse event, History of irritable bowel (IBS) and or inflammatory bowel syndrome (IBD), History diarrhea, Use of drugs for constipation at baseline, Prior antibiotic use, Previous lines of anti-cancer therapy, Prior platinum therapy, Prior immunotherapy, Immunotherapy as last systemic treatment prior to treatment start, Prior Enhertu, Prior HER2 Ex20ins-targeted therapy, Prior EGFR Ex20ins-targeted therapy, Liver metastases, ECOG performance, Baseline tumor size, AJCC grading at initial diagnosis, Tumor stage</i>	
Final Model Parameters	Summary	Acceptability [FDA’s comments]
Model Structure	<i>Cox proportional hazards (Cox-PH) model with non-linear/saturable/Emax type exposure-response relationship for all grade diarrhea, diarrhea of grade ≥ 3 and all grade rash and linear exposure-response relationship for all-type TEAEs leading to dose modifications</i>	Acceptable
Model Parameter Estimates <i>(located in Module 5.3.3.5, Report B003834)</i>	<i>all grade diarrhea: Table 17-9 diarrhea of grade ≥ 3: 17-10 all-type TEAEs leading to dose modifications: 17-11 all grade rash: 17-12</i>	Acceptable
Model Evaluation <i>(located in Module 5.3.3.5, Report B003834)</i>	<i>all grade diarrhea: section 16-5 diarrhea of grade ≥ 3: section 16-6 all-type TEAEs leading to dose modifications: section 16-7 all grade rash: section 16-8</i>	Acceptable
Covariates and Clinical Relevance	<i>Participants from Japan had a significantly higher baseline risk of all grade diarrhea compared to the rest of the participants. Younger participants and participants with ECOG=1 had a lower risk of diarrhea Grade ≥3 at baseline</i>	Acceptable

	<i>compared to older participants and participants with ECOG=0, respectively</i> <i>Participants from Japan showed a lower risk of all grade rash compared to participants who were not from Japan, while participants with higher bilirubin concentration at baseline had a higher risk compared to participants with lower bilirubin levels.</i> <i>White participants, participants who used medication for the treatment of constipation, and participants with a body weight ≤54 kg showed a higher baseline probability for dose modifications due to TEAEs</i> <i>Of note, none of the statistically significant covariate effects on the risk of selected AEs (diarrhea and rash) were found to have an effect on dose modifications due to TEAEs also. Hence, a statistically significant baseline covariate effect on AE risk does not necessarily indicate that a higher AE risk in a specific sub-population, e.g. elderly, can be mitigated by dose modifications. For instance, the incidence of all grade diarrhea grouped by exposure quartile was similar in elderly (≥65 years) compared to participants <65 years, i.e. in both age groups the incidence of all grade diarrhea was lower for subjects with the lowest exposure (Q1) vs participants with higher exposures (Q2–Q4) (See Figure 15-1 in Module 5.3.3.5, Report B003834).</i>	
Simulation for Specific Population		
Visualization of E-R relationships	<i>Figure 3-7 (Module 5.3.3.5, Report B003834) for ORR, BTR and selected AEs</i>	Acceptable
Overall Clinical Relevance for ER	<i>A statistically significant increase in probability for all grade diarrhea with increasing exposure was identified. Participants from Japan had a significantly higher baseline risk compared to the rest of the participants</i>	Acceptable

	<i>Exposure showed a statistically significant association with diarrhea Grade ≥ 3. Younger participants and participants with ECOG=1 had a lower risk of diarrhea Grade ≥ 3 at baseline compared to older participants and participants with ECOG=0, respectively</i> <i>A statistically significant association between exposure and all grade rash was observed. At baseline, participants from Japan showed a lower risk of all grade rash compared to participants who were not from Japan, while participants with higher bilirubin concentration at baseline had a higher risk compared to participants with lower bilirubin levels</i> <i>There was a significantly increased probability for dose modifications due to TEAEs with increasing exposure. White participants, participants who used medication for the treatment of constipation, and participants with a body weight ≤ 54 kg showed a higher baseline probability for dose modifications due to TEAEs</i>	
Labeling Language	Description	Acceptability [FDA’s comments]
12.2 Pharmacodynamics	<i>Higher sevabertinib exposure, across the dose range of 10 to 80 mg total daily dose (0.25 times to 2 times the recommended dose), was associated with an increased probability of diarrhea (including Grade 3) and rash</i>	Acceptable

Table 86. Summary of Baseline Characteristics and Laboratory Values in the Dataset*Source: Tables 14-2 and 14-19 in Module 5.3.3.5, Report B003834***Table 14-2: Summary statistics of continuous covariates for all participants**

Covariate (unit)	N ^a	Min.	Max.	Median	Arith. Mean	Arith. s.d.	Arith. CV (%)	Geometric mean	Geometric s.d.	Geometric CV (%)
AGE (y)	335	18	91	62	60.9	11.2	18.4	59.8	1.23	20.6
ALB0 (g/dL) ^{b,c}	335	2.5	5.1	4	3.96	0.439	11.1	3.94	1.12	11.6
ALP0 (U/L)	335	30	570	92	117.9	80.1	67.9	102.7	1.62	51
ALTO (U/L)	335	3	120	19	23.1	16.8	72.9	19.2	1.79	63.4
AST0 (U/L)	335	8	127	26	29.9	15.6	52.3	27	1.55	45.8
BASETSI (mm) ^{b,c}	335	10	312	48	58.8	41.2	70	47	1.98	77.5
BILI0 (mg/dL)	335	0	1.6	0.52	0.584	0.258	44.3	NC ^e	NC ^e	NC ^e
BW0 (kg)	335	29.3	155	61.3	63	14.1	22.4	61.5	1.24	21.9
LDH0 (U/L)	335	2.5	2282	255	321	229.5	71.5	274.3	1.75	60.3
NL0 (U/L)	335	0.62	37.1	3.7	4.39	3.38	77	3.68	1.77	61.8
NMSI (n) ^{b,c}	335	1	13	5	4.98	1.99	40	4.58	1.53	44.7
PACTNUM (n) ^{b,d}	335	1	10	2	2.33	1.64	70.5	1.9	1.87	68.9
PBMSBLI (n) ^{b,c}	335	0	3	0	0.332	0.615	185.2	NC ^e	NC ^e	NC ^e
PLMSBLI (n)	335	0	3	0	0.388	0.825	212.7	NC ^e	NC ^e	NC ^e
TSIDIAGM (months)	335	0.066	248.3	16.4	24.9	28.7	115.3	13.6	3.52	196.7

^a Includes participants with missing value for covariate^b Statistics (excluding N) calculated using only participants with covariate value^c 1 participant has value missing^d 50 participants have value missing^e Not calculated due to presence of 0 in the data

14.2.1 Counts of categorical covariates

Table 14-19: Counts of categorical covariates for all participants

Covariate	Category	Number of participants	% of participants
AGECAT	< 65	199	59.4
	≥ 65	136	40.6
AGECAT2	< 75	297	88.66
	≥ 75	38	11.34
AJCC	G1	13	3.88
	G2	35	10.45
	G3	29	8.66
	G4	4	1.19
	GX	233	69.55
	Missing	21	6.27
COMEDDIA	No/missing	213	63.58
	Yes	122	36.42
ECOG	0	114	34.03
	1	221	65.97
EEX20I	Yes	11	3.28
	No	324	96.72
HDIRR	No/missing	324	96.72
	Yes	11	3.28
HEPACCAT	Normal	262	78.21
	Mild	73	21.79
HEX20I	Yes	77	22.98
	No	258	77.02
HIRBS	No/missing	334	99.7
	Yes	1	0.3
IMMULAST	No	263	78.51
	Yes	72	21.49
MUTAT1	EGFR classical +C797X	12	3.58
	EGFR exon 20	48	14.33
	HER2 exon 20	219	65.37
	HER2 point	26	7.76
	EGFR atypical	1	0.3
	EGFR classical	25	7.46
	N/A	2	0.6
	Missing	2	0.6
PACTGR1N	0	50	14.93
	1	117	34.92
	2	72	21.49
	≥ 3	96	28.66
PACTGR2N	< 2	167	49.85
	≥ 2	168	50.15
PANUSE	No/missing	335	100
PBMSBLCI	No	246	73.43
	Yes	88	26.27
	Missing	1	0.3
PENHERT	Yes	56	16.72
	No	279	83.28
PIMMUN	Yes	178	53.13
	No	157	46.87
PLMSBLCI	No	261	77.91
	Yes	74	22.09
PPLAT	Yes	242	72.24
	No	93	27.76
PROLOUSE	No	321	95.82

Table 14-19: Counts of categorical covariates for all participants

Covariate	Category	Number of participants	% of participants
	Yes	14	4.18
RACE	White	91	27.16
	Black/ African American	9	2.69
	Asian	216	64.48
	American Indian/ Alaska Native	1	0.3
	Not reported	18	5.37
	REGION1	Asia	214
	North America	29	8.66
	South America	1	0.3
	Western Europe and Israel	91	27.16
REGION2	China	83	24.78
	Non-China	252	75.22
REGION3	Japan	36	10.75
	Non-Japan	299	89.25
REGION4	Asia	214	63.88
	Non-Asia	121	36.12
SEX	M	120	35.82
	F	215	64.18
SMOKE	Never	224	66.87
	Former	102	30.45
	Current	8	2.39
	Missing	1	0.3
TUMORST	Stage III A	6	1.79
	Stage III B	3	0.9
	Stage IV A	108	32.24
	Stage IV B	191	57.02
	Missing	27	8.06

Table 87. Parameter Estimates From Final ER Model of (Endpoint)

All grade diarrhea

Source: Table 17-9, Module 5.3.3.5, Report B003834

Table 17-9: Final Cox-PH model of diarrhea in PMx_SAF participants

Parameter	Estimate (95% CI)	Wald p-value	p-value ^a
Coefficient for participants from Japan	0.84822 (0.48315 -- 1.2133)	<0.0001	<0.0001
Coefficient for participants with prior HER2 Ex20ins-targeted therapy	0.31496 (0.037681 -- 0.59225)	0.026	
Coefficient for transformed AUC _{24h,ss}	586960 (335300 -- 838620)	<0.0001	

^a Based on OFV compared to RCM

^b Transformation done using function $f(AUC_{24h,ss}) = AUC_{24h,ss}/(IC50 + AUC_{24h,ss})$ where $IC50 = 0.00008$ and the value of $IC50$ was established using a algorithmic approach

Diarrhea of grade ≥ 3

Source: Table 17-10, Module 5.3.3.5, Report B003834

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Table 17-10: Final Cox-PH model of diarrhea with grade ≥ 3 in PMx_SAF participants

Parameter	Estimate (95% CI)	Wald p-value	p-value ^a
Coefficient for Age	0.03849 (0.0095555 -- 0.067425)	0.0091	<0.0001
Coefficient for ECOG = 0	0.91885 (0.34596 -- 1.4917)	0.0017	
Coefficient for transformed ^b AUC _{24h,ss}	0.051378 (0.02905 -- 0.073707)	<0.0001	

^a Based on OFV compared to RCM^b Transformation done using function $f(\text{AUC}_{24\text{h,ss}}) = \text{AUC}_{24\text{h,ss}} / (\text{IC}_{50} + \text{AUC}_{24\text{h,ss}})$ where $\text{IC}_{50} = 20000$ and the value of IC_{50} was established using a algorithmic approach*All-type TEAEs leading to dose modifications**Source: Table 17-11, Module 5.3.3.5, Report B003834*

Table 17-11: Final Cox-PH model of dose modification due to TEAE in PMx_SAF participants

Parameter	Estimate (95% CI)	Wald p-value	p-value ^a
Coefficient for participants taking comedication for treating diarrhea	0.68547 (0.38156 -- 0.98938)	<0.0001	<0.0001
Coefficient for participants whose race is listed as white	0.67962 (0.35619 -- 1.003)	<0.0001	
Coefficient for Weight – Quartile 1: ≤ 54 kg	0.48402 (0.15175 -- 0.81628)	0.0043	
Coefficient for AUC _{24h,ss}	0.00000043599 (0.00000031832 -- 0.00000055366)	<0.0001	

^a Based on OFV compared to RC*All grade rash**Source: Table 17-12, Module 5.3.3.5, Report B003834*

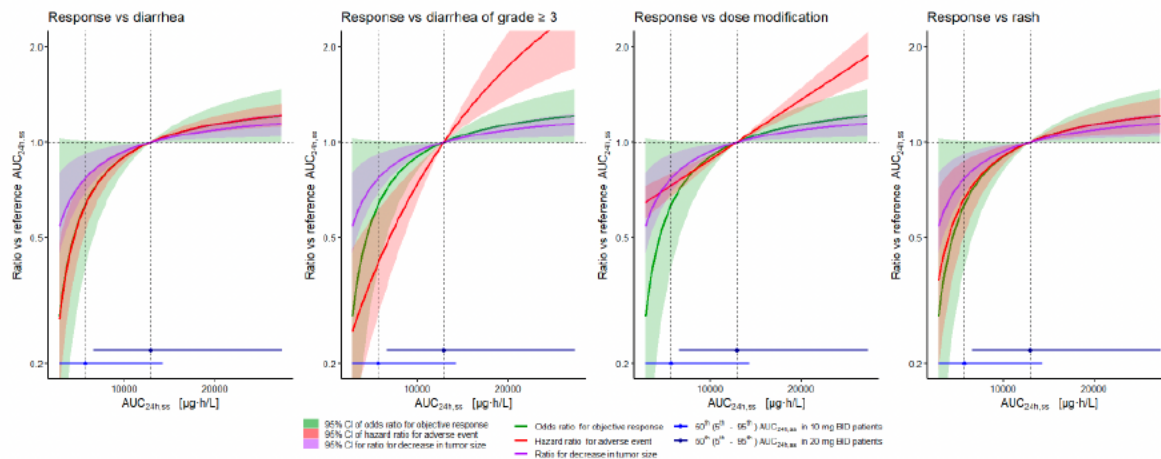
Table 17-12: Final Cox-PH model of rash in PMx_SAF participants

Parameter	Estimate (95% CI)	Wald p-value	p-value ^a
Coefficient for total bilirubin	1.0111 (0.45891 -- 1.5634)	0.0003	0.0047
Coefficient for participants from Japan	-0.77622 (-1.3504 -- -0.20203)	0.0081	
Coefficient for transformed ^b AUC _{24h,ss}	0.05723 (0.019529 -- 0.094931)	0.0029	

^a Based on OFV compared to RCM^b Transformation done using function $f(\text{AUC}_{24\text{h,ss}}) = \text{AUC}_{24\text{h,ss}} / (\text{IC}_{50} + \text{AUC}_{24\text{h,ss}})$ where $\text{IC}_{50} = 900$ and the value of IC_{50} was established using a algorithmic approach

Figure 20. ER Curves

Source: Figure 3-7, Module 5.3.3.5, Report B003834



Solid red line (shaded region): hazard ratio (95% CI) for, left to right plot, diarrhea, diarrhea with grade ≥ 3 , dose modification due to TEAE and rash. All plots - solid green line (shaded region) odds ratio (95% CI) for ORR for the objective response set D/D1 subset based on BICR tumor assessment where possible. All plots - solid purple line (shaded region) the ratio for BTR for the objective response set D/D1 subset based on BICR tumor assessment where possible. Ratio reference is based on the median $AUC_{24h,15}$ from all participants dosed 20 mg BID. Dark blue and blue horizontal lines: 5th - 95th percentile ranges of $AUC_{24h,15}$ from participants dosed 20 mg BID and 10 mg BID with central dot dissected by the vertical dashed lines giving the respective medians.

Figure 3-7: Benefit-risk plot comparing safety endpoints against efficacy endpoints for the objective response set D/D1 subset based on BICR tumor assessment where possible.

The FDA’s Assessment:

FDA generally agrees with Applicant’s conclusions. However, due to data limitations, the E-R analysis for BTR is inconclusive. Refer to 19.4.4.2 for details.

19.4.4.5. ER Review Issues

None.

19.4.4.6. Reviewer’s Independent Analysis

E-R analysis for BTR

The reviewer had concerns with the applicant’s E-R analysis using Emax model, e.g., E0 fixed to 0 and the approach to estimate EC50 that had inherent limitations (i.e., grid search to find EC50 value with smallest AIC). Therefore, the reviewer conducted independent Bayesian Emax model assessment. As shown in **Table**, the estimated EC50 had a large credible interval, suggesting that the data are not informative to robustly estimate EC50 and the efficacy is likely near plateau. While we agree that there is a positive E-R trend, the uncertainty precludes the conclusion (b) (4)

(D) (4)

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E-R analysis for diarrhea

Age was identified as a covariate in the ER analysis for diarrhea of grade ≥ 3 where a prominent increase in diarrhea event onset was observed in 4th quartile of age bin [69-91]. Therefore, geriatric subgroup with 65- and 75-year cutoff was evaluated. When age was subgroup to be groups of ≥ 75 and < 75 , the categorized age is also identified a covariate in Cox proportional hazard model with similar OFV value as that of age as a continuous covariate that produced comparable AIC. Furthermore, the Kaplan-Meier plot of diarrhea of grade ≥ 3 stratified by age groups showed a clear difference between two groups, shown in **Figure 21**. Based on CoxPH analysis, patients aged ≥ 75 years was associated with 2.32 folds risk of grade ≥ 3 diarrhea than those aged < 75 years. The wide CI reflects the limited subjects in this age subgroup.

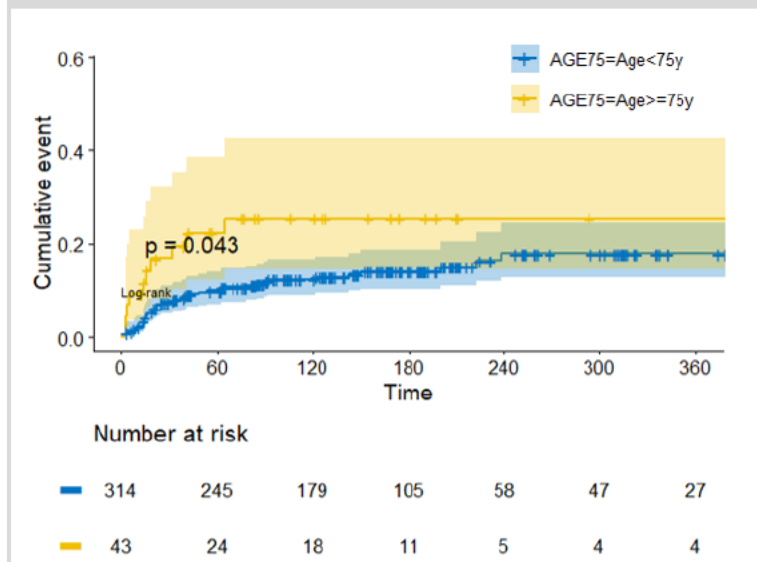
Table 88. BTR Bayesian Emax Model Assessment

	mean	SD	2.5% CR	97.5%CR
Emax	-7.12	1.48	-10	-4.13
EC0	-6.18	0.96	-8.1	-4.28
EC50	1273	946	49	3391
gamma	2.1	1.16	0.91	3.63

CR: credible interval

Source: reviewer independent assessment

Figure 21. Diarrhea Grade ≥ 3 Kaplan-Meier Plot Stratified by Age Groups



Source: reviewer independent assessment

19.4.4.7. Overall Benefit-Risk Evaluation Based on E-R Analyses

The Applicant's Position:

The identified exposure-response relationships for efficacy (ORR and BTR) and safety (incidence of all grade and Grade ≥ 3 diarrhea, dose modifications due to TEAEs and all grade rash) are shown in Figure 3-7 (Module 5.3.3.5, Report B003834). Since responses and outcomes were different, the efficacy and safety parameters were scaled to allow comparing the shapes of the different relationships. The responses at the median exposure after 20 mg BID were used as references and a scaled value < 1 shows a lower and a value > 1 a higher response compared to this reference.

Of note, information on the magnitude of the different responses cannot be obtained from this figure, as it shows the relative change compared to the reference (median exposure after 20 mg BID). As a result, a 50% reduction in, e.g., all grade diarrhea vs BTR will differ in absolute numbers.

The shapes of exposure-response relationships for all grade diarrhea and all grade rash are similar. Both show a more gradual increase in probability towards the upper/flat part of exposure-response relationship for exposures above *versus* below the median exposure after 20 mg BID. For exposures below the median, the probability decreases more rapidly with decreasing exposure.

For probability of diarrhea Grade ≥ 3 and dose modifications due to TEAEs, the exposure range reached for a dose range of 10–20 mg BID was in the steep phase of their exposure-response relationship, showing a more or less linear increase in probability with increasing exposure. This increase was steeper for diarrhea Grade ≥ 3 compared to dose modifications due to TEAEs. As a result, the decrease in probability for diarrhea Grade ≥ 3 and dose modifications due to TEAEs at exposures below the median exposure after 20 mg BID is as strong as the increase in probability at exposures above this median.

The shapes of the exposure-response for ORR and BTR are similar to those for all grade diarrhea and all grade rash. At exposures above the median exposure after 20 mg BID, the upper/flat part of the exposure-response relationship was reached, whereas ORR and BTR rapidly decreased at exposures below this median. These similar shapes for safety and efficacy indicate that the therapeutic window is small, i.e. a lower probability for safety events will coincide with lower efficacy and *vice versa*.

Within the exposure range between the median exposure after a dose of 10 and 20 mg BID respectively, the exposure response relationships for efficacy (ORR) and diarrhea Grade ≥ 3 were separated with (relative) ORR being above the diarrhea Grade ≥ 3 curve. This indicates that the relative decrease in probability of diarrhea Grade ≥ 3 was larger compared to the relative decrease in ORR with a 50% reduction in exposure by lowering the dose from 20 to 10 mg BID.

Based on the integrative analyses including PK-PD analyses/modeling, the clinical efficacy and safety data presented, and exposure-response evaluations, a dose of 20 mg BID was selected as

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the optimal dosage. While exposure of doses >20 mg BID was in the upper/flat part of the exposure-response curve for ORR and maximal change in tumor size, more participants are expected to reach >80% reduction in pEGFR over 24 hours with doses >20 mg BID and patients might further benefit from these higher doses. On the other hand, exposure of doses >20 mg BID showed a steep increase in incidence of diarrhea Grade ≥ 3 and TEAEs leading to dose modifications, which may limit the clinical application of these higher doses. While exposure of doses <20 mg BID showed a decrease in AE incidence, as exposure was in the steep phase of the exposure-response relationship, exposure was also in the steep phase of the exposure-response for efficacy suggesting lower probability of efficacy (ORR and maximal change in tumor size) compared to the 20 mg BID dose.

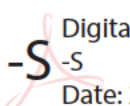
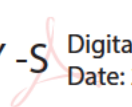
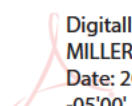
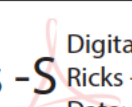
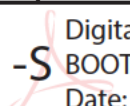
The FDA's Assessment:

The proposed recommended dosage of 20 mg BID is supported by the clinical efficacy and safety, numerically higher ORR compared to 10 mg BID, positive trends observed in exposure-efficacy and exposure-safety, and PK/PD analysis

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Refer to Section 8.2.

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Kelie Reece, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	Select one: ☒ Authored ☒ Approved
Signature:  Kelie M. Reece -S Digitally signed by Kelie M. Reece Date: 2025.11.10 17:40:52 -05'00'				
Nonclinical Reviewer	Liliya Tyutyunyik, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	Select one: ☒ Authored ☒ Approved
Signature:  LILIYA S. TYUTYUNYK-MASSEY -S Digitally signed by LILIYA S. TYUTYUNYK-MASSEY -S Date: 2025.11.10 19:39:31 -05'00'				
Nonclinical Supervisor	Claudia Miller, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	Select one: ☒ Authored ☒ Approved
Signature:  CLAUDIA MILLER -S Digitally signed by CLAUDIA MILLER -S Date: 2025.11.13 11:40:15 -05'00'				
Division of Hematology Oncology Toxicology (DHOT) Deputy Division Director	Tiffany Ricks, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5	Select one: ☐ Authored ☒ Approved
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Clinical Pharmacology Reviewer	Christopher Jay, Ph.D.	CDER/OTS/OCP/DCPI	Sections: 6, 19.4	Select one: ☐ Authored ☐ Approved
Signature:  BRIAN P. BOOTH -S Digitally signed by BRIAN P. BOOTH -S Date: 2025.11.12 15:02:46 -05'00'				
Clinical Pharmacology Acting Scientific Lead	Yixuan Dong, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
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Pharmacometrics Reviewer	Hezhen Wang, Ph.D.	CDER/OTS/OCP/DPM	Sections: 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Hezhen Wang -S Digitally signed by Hezhen Wang -S Date: 2025.11.12 13:34:43 -05'00'			
Pharmacometrics Acting Team Leader	Ye Xiong, Ph.D.	CDER/OTS/OCP/DPM	Sections: 19.4	Select one: ☒ Authored ☒ Approved
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Genomics Reviewer	Jielin (Jillian) Sun, Ph.D.	CDER/OTS/OCP/DTPM	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Jielin Sun -S Digitally signed by Jielin Sun -S Date: 2025.11.12 14:22:02 -05'00'			
Master Pharmacokineticist	Sarah Dorff, Ph.D.	CDER/OTS/OCP/DTPM	Sections: 6	Select one: ☐ Authored ☒ Approved
	Signature: SARAH E. DORFF -S Digitally signed by SARAH E. DORFF -S Date: 2025.11.12 14:38:35 -05'00'			
Division of Cancer Pharmacology II Division Director	Nam Atiqur Rahman, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: NAM A. RAHMAN -S Digitally signed by NAM A. RAHMAN -S Date: 2025.11.12 15:05:37 -05'00'			
Clinical Reviewer (Efficacy and Safety)	Kevin Breen, M.D.	CDER/OOD/DO2	Sections: 1,2,3,4,7,8.1, 8.2,8.4,9,10,12,13,19.1 and 19.2	Select one: ☒ Authored ☒ Approved
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Clinical Team Leader	Diana Bradford, M.D.	CDER/OOD/DO2	Sections: see CDTL	Select one: ☐ Authored ☐ Approved
	Signature: see CDTL signature			
Statistical Reviewer	Yi Ren, Ph.D.	CDER/OTS/DBV	Sections: 1, 8	Select one: ☒ Authored ☐ Approved
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Statistical Team Leader	Flora Mulkey, MS.	CDER/OTS/DBV	Sections: 1, 8	Select one: ☒ Authored ☒ Approved
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Division Director (OB/DBV)	Shenghui Tang, Ph.D.	CDER/OTS/DBV	Sections: 1, 8	Select one: ☐ Authored ☒ Approved
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Associate Director for Labeling (ADL)	Barbara Scepura, MSN, CRNP	CDER/OOD	Section: 11	Select one: ☒ Authored ☐ Approved
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Cross-Disciplinary Team Leader (CDTL)	Diana Bradford, M.D.	CDER/OOD/DO2	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature: See DARRTs signature			
Deputy Director	Nicole Drezner, M.D.	CDER/OOD/DO2	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: See DARRTs signature			

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