CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219839Orig1s000

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.

Application Type	NDA
Application Number	219839
Priority or Standard	Priority
Submit Dates	November 7, 2024
Received Dates	November 7, 2024
PDUFA Goal Date	July 7, 2025
Division/Office	Division of Oncology 2/ Office of Oncologic Diseases
Review Completion Date	July 2, 2025
Established Name	Sunvozertinib
(Proposed) Trade Name	ZEGFROVY
Pharmacologic Class	Kinase inhibitor
Code name	DZD9008
Applicant	Dizal (Jiangsu) Pharmaceutical Co Ltd.
Formulation	Tablets
Dosing Regimen	200 mg orally once daily with food
Applicant Proposed Indication/Population	For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication/Population (if applicable)	For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

Table of Contents

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LIST OF TABLES

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.

TABLE OF FIGURES

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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

Glossary

ADME	Absorption, Distribution, Metabolism, Excretion
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
ARA	Acid Reducing Agents
AST	Aspartate Aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the Plasma Concentration-time Curve
AUC_{ss}	Area Under the Plasma Concentration-time Curve at Steady State
$AUC_{0\text{-inf}}$	Area Under the Plasma Concentration-time Curve from Time 0 to Infinite Time
BBB	Blood-Brain Barrier
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BDC	Bile Duct Cannulation
BLA	Biologics License Application
BLRM	Bayesian Logistic Regression Model
BM	Brain Metastasis
BTB	Brain Tumor Barrier
BTD	Breakthrough Therapy Designation
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CDx	Companion Diagnostic
CFR	Code of Federal Regulations
CI	Confidence Interval
CLcr	Creatinine Clearance
C_{max}	Maximum Plasma Concentration
CMC	Chemistry, Manufacturing, and Controls
CNS	Central Nervous System
COA	Clinical Outcome Assessment
cORR	Confirmed Objective Response Rate
CPK	Creatine Phosphokinase
CQA	Critical Quality Attributes
C-QTc	Concentration QTc

CRO	Contract Research Organization
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CYP	Cytochrome P450
DCO	Data Cut-Off
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DoR	Duration of Response
DRF	Dose Range Finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOP1	End of Phase 1
E-R	Exposure-Response
Exon19del	Exon 19 Deletion
Exon20ins	Exon 20 Insertion Mutation
FACT	Functional Assessment of Cancer Therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI_{50}	Concentration for 50% growth inhibition
GLP	Good Laboratory Practice
GT	Grouped Term
HRQoL	Health Related Quality of Life
HER2	Human Epidermal Growth Factor Receptor 2
IC_{50}	Half Maximal Inhibitory Concentration
ICH	International Council for Harmonisation
ILD	Interstitial Lung Disease
IND	Investigational New Drug
INR	International Normalized Ratio
iPSP	Initial Pediatric Study Plan
IRC	Independent Review Committee
ISS	Integrated Summary of Safety
ITT	Intention to Treat
LVEF	Left Ventricular Ejection Fraction
MATE	Multidrug and Toxin Extrusion

MET	Mesenchymal–Epithelial Transition Factor
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NDA	New Drug Application
NE	Not Estimable
NOAEL	No Observed Adverse Effect Level
NMPA	National Medical Products Administration
NSCLC	Non-Small Cell Lung Cancer
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transport
OPQ	Office of Pharmaceutical Quality
ORR	Objective Response Rate
OS	Overall Survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	Physiological Based Pharmacokinetic
PFS	Progression Free Survival
P-gp	Permeability Glycoprotein
PK	Pharmacokinetics
PMA	Premarket Approval
PMC	Post Marketing Commitment
PMR	Post Marketing Requirement
PPI	Protein-pump Inhibitor
PR	Partial Response
PRO	Patient Reported Outcome
PT	Preferred Term
PXR	Pregnant X Receptor
QD	Quaque Die (Once Daily)
QTc	QT Interval Corrected for Heart Rate
QTcF	Fridericia Corrected QT Interval
QWBA	Quantitative Whole-Body Autography
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
RDI	Relative Dose Intensity
RP2D	Recommended Phase 2 Dose

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.

SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SoD	Sum of Diameters
SOP	Standard Operating Procedure
SRC	Safety Review Committee
$t_{1/2}$	Elimination Half-life
t_{max}	Time to Reach Maximum Plasma Concentration
TdP	Torsades de Pointes
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Events
TKI	Tyrosine Kinase Inhibitor
TRAE	Treatment-Related Adverse Events
ULN	Upper Limit of Normal (the high limit of a reference range)
UMVUE	Uniformly Minimum Variance Unbiased Estimator
U.S.	United States
USPI	United States Prescribing Information
WBDC	Web Based Data Capture

1. Executive Summary

1.1. Product Introduction

Sunvozertinib is an orally bioavailable kinase inhibitor that inhibits epidermal growth factor receptor (EGFR) that binds to and inhibits EGFR exon 20 insertion mutations. Sunvozertinib inhibits phosphorylation in cells expressing EGFR exon 20 insertion mutations. Sunvozertinib is not currently approved in the United States and is approved in China. Dizal's proposed indication for sunvozertinib is "for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.

The recommended indication for accelerated approval is:

For the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

The FDA recommended dosage regimen for the proposed indication is sunvozertinib 200 mg orally once daily (QD) with food until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Dizal (Applicant) has provided substantial evidence of effectiveness supporting the accelerated approval of sunvozertinib 200 mg orally QD under 21 CRF part 314 subpart H, for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as determined by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

The recommendation for accelerated approval of sunvozertinib 200 mg orally QD is based on results from the WU-KONG1B trial (NCT03974022), a multinational, open-label, dose randomization trial. Patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations with disease progression on or after platinum-based chemotherapy, and measurable disease at baseline, were randomized (1:1) to receive sunvozertinib 200 mg QD (N=85) or sunvozertinib 300 mg QD (N=89). An additional 18 patients were not randomized and received sunvozertinib 300 mg QD (N=107 total patients received sunvozertnib 300 mg QD). The overall response rate (ORR) was 46% (95% CI: 35, 57) for patients who received sunvozertinib 200 mg QD and the ORR was 46% (95% CI: 36, 56) for patients who received sunvozertinib 300 mg QD. Based on a data cutoff date of December 2, 2024, the median duration of response (DOR) was 11.1 months (95% CI: 8.3, NE) for patients who received sunvozertinib 200 mg QD and 9.8 months (95% CI: 8.3, 13.9) for patients who received sunvozertinib 300 mg QD.

While response rates were consistent across the 200 mg and 300 mg dose levels, a higher rate of adverse events were observed at the higher dose. In particular, compared to the 200 mg QD

dosage, the 300 mg QD dosage had more events of Grade ≥3 diarrhea (2.2% vs 21%) and elevated CPK levels (5% vs 15%). Compared to the 200 mg dose, the 300 mg dose also had higher rates of adverse events leading to dose interruptions (48% vs 59%), dose reductions (23% vs 42%), and permanent discontinuation of sunvozertinib (8% vs 13%). Based on comparable efficacy and reduced toxicity with the lower dose, the FDA review team recommends a treatment dose of sunvozertinib 200 mg daily.

The FDA review team notes that amivantamab-vmjw is an FDA-approved bispecific antibody targeting EGFR and MET, that has multiple approved indications including for the second-line treatment of patients with EGFR exon 20 insertion-mutated NSCLC after disease progression on platinum-based chemotherapy. In this patient population, amivantamab-vmjw demonstrated an ORR of 40% (95% CI: 29, 51). Although the 95% confidence interval overlaps with that for sunvozertinib 200 mg QD (i.e., ORR 46%; 95% CI: 35, 57), sunvozertinib provides an option for an oral therapy with differential toxicity compared to amivantamab-vmjw which is administered by intravenous infusion. Sunvozertinib 200 mg QD is associated with less rash and does not have any risk of infusion-related reactions, which both occur frequently with amivantamab-vmjw. Additionally, anti-tumor activity was observed for sunvozertinib 200 mg QD in a subset of patients in WU-KONG1B who previously had disease progression on amivantamab-vmjw; among 12 patients previously treated with amivantamab-vmjw, 3 patients (ORR 25%; 95% CI: 6, 57) had a response to sunvozertinib 200 mg QD.

The lower bound of the 95% confidence interval around the point estimate for ORR observed with sunvozertinib 200 mg QD from the WU-KONG1B study is greater than the point estimate for ORR observed with other FDA-approved available therapies for this refractory population (e.g., docetaxel, docetaxel in combination with ramucirumab).

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence. The submitted evidence meets the statutory evidentiary standard for accelerated approval based on an ORR of sufficient magnitude and duration that is reasonably likely to predict clinical benefit in patients with EGFR exon 20 insertion-mutated NSCLC.

This will be the only currently available, FDA-approved oral therapy for patients with EGFR exon 20 insertion-mutated NSCLC who have received prior systemic therapy. In the context of its safety profile, the ORR and durable response observed with sunvozertinib 200 mg QD are reasonably likely to predict clinical benefit and provide a meaningful advantage over available treatments for this disease.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

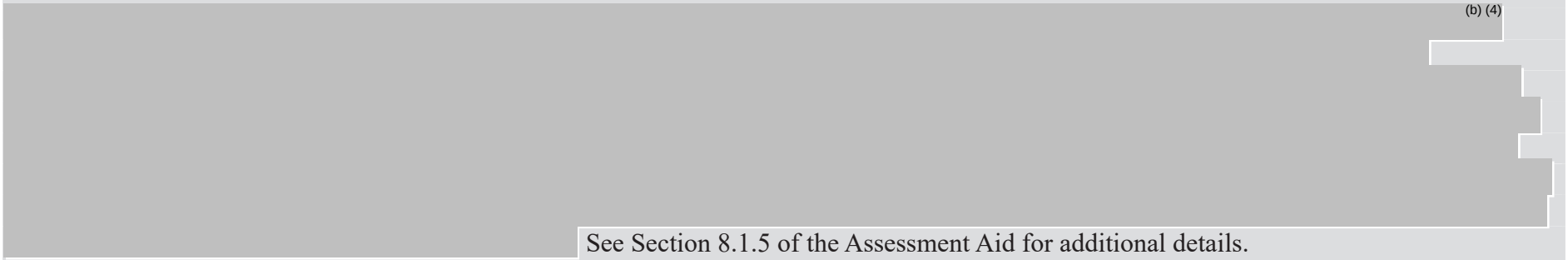
Lung cancer is the second most common cancer and the leading cause of cancer-related deaths in the U.S. (Siegel, 2024). Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases and approximately 40% to 50% of patients have metastatic disease at diagnosis (Ganti, 2021). In nearly 15% of patients diagnosed with metastatic NSCLC in the U.S., the tumor cells harbor oncogenic mutations involving the endothelial growth factor receptor (EGFR) gene. For 80% to 90% of the patients with metastatic EGFR mutated NSCLC, EGFR tyrosine kinase inhibitors (TKIs) are highly effective standard therapies; however, for the approximately 10% of patients with EGFR exon 20 insertion mutations, treatment with EGFR TKIs has thus far been less effective (Tan, 2022).

Mobocertinib was a TKI targeting EGFR exon 20 insertion mutations that was granted accelerated approval on September 15, 2021, for patients with previously treated EGFR exon 20 insertion mutated NSCLC; however, the confirmatory trial did not meet its prespecified primary endpoint of progression-free survival (PFS) and failed to verify the clinical benefit of mobocertinib. The sponsor (Takeda) subsequently voluntarily withdrew mobocertinib from the U.S. market and there are no other oral targeted therapies currently approved for EGFR exon 20 insertion mutated NSCLC. On March 1, 2024, FDA approved amivantamab, a bispecific EGFR and c-MET antibody which is administered as an intravenous infusion, in combination with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. FDA also granted traditional approval to amivantamab as a single agent for adult patients whose disease has progressed on or after platinum-based chemotherapy. However, amivantamab is associated with high rates and sometimes serious adverse reactions of rash, as well as high rates of infusion related reactions. Some patients may not tolerate amivantamab and nearly all patients will have disease progression on this available therapy. Available treatment options for patients who have progressed following amivantamab and platinum-based chemotherapy include docetaxel with or without ramucirumab; other single agent chemotherapy; or an anti-PD-(L)1 antibody as a single agent for patients who are anti-PD-(L)1 naïve, although the benefit of anti-PD-(L)1 antibodies in patients with EGFR exon 20 insertion mutated NSCLC is not well studied (Remon 2020, Remon 2021). An unmet medical need remains for more effective therapies for patients with metastatic NSCLC harboring EGFR exon 20 insertion mutations.

Sunvozertinib is an orally bioavailable kinase inhibitor that binds to and inhibits EGFR exon 20 insertion mutations. Support for this application is based on the efficacy and safety from Study DZ2019E0001 (WU-KONG1B). Study WU-KONG1B is a multinational, open-label, dose randomization trial. Patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, with disease progression on or after platinum-based chemotherapy, and measurable disease at baseline, were randomized (1:1) to receive sunvozertinib 200 mg QD (N=85) or

sunvozertinib 300 mg QD (N=89). An additional 18 patients were not randomized and received sunvozertinib 300 mg QD (N=107 total patients received sunvozertinib 300 mg QD). Patients with previously treated and stable intracranial metastases were eligible to enroll. All patients had received prior platinum-based chemotherapy, 42% had received prior anti-PD-(L)1 therapy, and 14% had received prior amivantamab. The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) as evaluated by a blinded independent review committee (BIRC). An additional efficacy outcome measure was duration of response (DoR) by BIRC.

The overall response rate (ORR) was 46% (95% CI: 35, 57) for patients who received sunvozertinib 200 mg QD while the ORR was 46% (95% CI: 36, 56) for patients who received sunvozertinib 300 mg QD. Based on a data cutoff date of December 2, 2024, the median DoR was 11.1 months (95% CI: 8.3, NE) for patients who received sunvozertinib 200 mg QD and 9.8 months (95% CI: 8.3, 13.9) for patients who received sunvozertinib 300 mg QD. In an exploratory subgroup analysis of patients who received prior amivantamab and platinum-based chemotherapy, the ORR was 25% (95% CI: 5, 57) in the 12 patients who received sunvozertinib 200 mg and 36% (95% CI: 13, 65) in the 14 patients who received sunvozertinib 300 mg.



See Section 8.1.5 of the Assessment Aid for additional details.

Sunvozertinib has a manageable safety profile when assessed in the context of a life-threatening disease. The primary safety population consisted of the 91 patients in the 200 mg QD cohort and the 111 patients in the sunvozertinib 300 mg QD cohort in WU-KONG1B who received at least one dose of study therapy. Pooled safety data from patients with locally advanced or metastatic NSCLC who received at least one dose of study therapy, which included the patients in the primary safety population, were supportive and consisted of 121 patients who received sunvozertinib 200 mg QD in WU-KONG1 and WU-KONG2 and 311 patients who received sunvozertinib 300 mg QD in WU-KONG1, WU-KONG2, and WU-KONG6. In the primary safety population from the WU-KONG1B dose-randomization trial (n=91 at 200 mg and n=111 at 300 mg), a higher rate of adverse reactions was observed at the 300 mg dose compared to the 200 mg dose. Compared to the 200 mg QD dosage, the 300 mg QD dosage

had more events of Grade ≥3 diarrhea (2.2% vs 21%) and elevated CPK levels (5% vs 15%). Compared to the 200 mg dose, the 300 mg dose also had higher rates of adverse reactions leading to dose interruptions (48% vs 59%), dose reductions (23% vs 42%), and permanent discontinuation of sunvozertinib (8% vs 13%). In the pooled safety populations (n=121 at 200 mg and n=311 at 300 mg), ILD/pneumonitis occurred in 1.7% with 0% Grade ≥3 events for the 200 mg group and 5.5% with 1.3% Grade 3 and 2.3% Grade 4 events for the 300 mg group.

Among the 121 patients who received sunvozertinib 200 mg QD in the pooled safety population, the most common (≥20%) adverse reactions were diarrhea, rash, decreased appetite, stomatitis, fatigue, nausea, paronychia, vomiting, constipation, musculoskeletal pain, pruritus, dry skin, urinary tract infection, abdominal pain and decreased weight. In the primary safety population of 91 patients who received sunvozertinib 200 mg QD, serious adverse reactions occurred in 41% of patients; the most common (≥2%) serious adverse reactions were pneumonia (9%); dyspnea (4.4%); and pancreatitis, device-related infection and rash (2.2% each). Permanent discontinuation of sunvozertinib 200 mg QD in the primary safety population (n=91) occurred in 8% of patients; the most frequent events leading to permanent discontinuation (≥2%) were pneumonia and rash (2.2% each). Fatal adverse reactions occurred in 2.2% of patients in the primary safety population who received sunvozertinib 200 mg QD (n=91), due to thrombosis (1.1%) and COVID-19 infection (1.1%). The safety of sunvozertinib is adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during the review of the application requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS) to ensure the safe use of sunvozertinib.

A pre-market approval (PMA) application for the Life Technologies Corporation OncomineTM Dx Express Test was submitted to the Center for Devices and Radiological Health (CDRH) for contemporaneous review with this NDA. CDRH determined that the data submitted in the PMA for a tissue-based companion diagnostic test are supportive of approval of the OncomineTM Dx Express Test as a companion diagnostic (CDx) device to identify patients with non-squamous NSCLC with an EGFR exon 20 insertion mutation who may be eligible for sunvozertinib, and the PMA will be approved contemporaneously with this NDA.

The submitted evidence meets the statutory evidentiary standard for accelerated approval for the treatment of patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, previously treated with platinum-based chemotherapy. The benefit-risk profile in the indicated population is considered favorable based on the observed response rate and durable responses in a patient population with a life-threatening disease. This application represents a new treatment option for an indication with unmet medical need. The Applicant used advice from the FDA Oncology Center of Excellence's Project Optimus to conduct a dose randomization study, which led to a lower dose being approved. **Due to comparable efficacy results and reduced toxicity observed with the 200 mg dose compared to the 300 mg dose, the FDA review team recommends a treatment dose of sunvozertinib 200 mg orally daily.**

Based on a favorable risk:benefit assessment for this population with a serious, life-threatening disease, accelerated approval is recommended for sunvozertinib 200 mg orally daily with food, for the following indication:

For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

The trial intended to verify the clinical benefit of sunvozertinib is Study DZ2022E0005 (WU-KONG28), an open-label, randomized controlled, multiregional clinical trial of sunvozertinib versus platinum-based chemotherapy in patients with EGFR exon 20 insertion mutations who are newly diagnosed or treatment-naïve. The Consolidated Appropriations Act (2023) provides the FDA with the authority to require that confirmatory studies to verify clinical benefit be underway prior to accelerated approval. Study WU-KONG28 is completely enrolled as of June 2025, (b) (4) As such, the review division considers the confirmatory trial for this accelerated approval to be underway.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer deaths accounting for almost 20% of all cancer deaths (Siegel, 2024). • Epidermal growth factor receptor (EGFR) exon 20 insertion mutations occur in approximately 2 to 3% of all non-small cell lung cancer (NSCLC) cases and their presence is generally associated with limited response to first- and second-generations EGFR kinase inhibitors (Remon 2020, Riess 2018, Oxnard 2013, Arcila 2013). • In the U.S., the 5-year relative survival rate for NSCLC with distant disease is 9% (American Cancer Society, 2025).	Locally advanced and metastatic NSCLC with EGFR exon 20 insertion mutations is a life-threatening disease with poor survival. NSCLC with EGFR exon 20 insertion mutations is a rare subset of NSCLC.
Current Treatment Options	• On March 1, 2024, FDA approved amivantamab, a bispecific EGFR and c-MET antibody, in combination with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. FDA also granted traditional approval to amivantamab as a single agent for adult patients whose disease has progressed on or after platinum-based chemotherapy. • For patients with EGFR exon 20 insertion mutated NSCLC with disease progressed on or after prior platinum-based chemotherapy, amivantamab demonstrated an ORR of 40% (95% CI: 29, 51) with a median DOR of 11.1 months (95% CI: 6.9, NE). Amivantamab is associated with high rates of rash and infusion related reactions. • For patients with progression of disease following platinum-based chemotherapy, and amivantamab, treatment options include chemotherapy (single agent or docetaxel in combination with ramucirumab) associated with overall response rates (ORRs) of 6 to 23% with median DORs in the range of 4 to 9 months. Single agent anti-PD-(L)1 antibodies may also be considered; however, the benefit of anti-PD-(L)1 antibodies in patients with EGFR exon 20 insertion mutated NSCLC is not well studied.	There is an unmet medical need for patients with previously treated NSCLC harboring EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. No FDA-approved, oral targeted therapies are currently available for EGFR exon 20 insertion mutated NSCLC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The primary efficacy data supporting this NDA are from patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy enrolled in WU-KONG1B, a multinational, open-label, dose randomization clinical trial in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations with disease progression on or after platinum-based chemotherapy. • Among the 85 patients in the primary efficacy population who received sunvozertinib 200 mg daily (QD), the confirmed ORR per RECIST v1.1 by blinded independent review committee (BIRC) was 46% (95% CI: 35, 57) with a median DoR of 11.1 months (95% CI: 8.2, NE) as of a data cutoff (DCO) date of December 2, 2024. Of the 39 responders, 72% of patients had a DOR ≥6 months. • In an exploratory subgroup analysis of the 12 patients who received sunvozertinib 200 mg QD, and prior amivantamab and platinum-based chemotherapy, the ORR was 25% (95% CI: 5, 57). • The response rates for the sunvozertinib 200 mg QD and sunvozertinib 300 mg QD dose levels were the same in WU-KONG1B. For the 107 patients who received sunvozertinib 300 mg QD in WU-KONG1B, the ORR was 46% (95% CI: 36, 56) and the DoR was 9.8 months (95% CI: 8.3, 13.9).	The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORR, along with the observed duration of responses, are clinically meaningful in the context of the poor prognosis of the disease. While the ORR observed in the primary efficacy population did not exceed the upper bound of the 95% CI for ORR observed with available therapy (i.e., amivantamab), the option for treatment with a single agent administered orally, and the differing safety profile are reasonably likely to provide a meaningful advantage over available therapy to patients with an unmet need. Additional data to verify the clinical benefit of sunvozertinib for patients with NSCLC harboring EGFR exon 20 insertion mutations will be obtained from a randomized clinical trial with a primary endpoint of progression-free survival (PFS) by BIRC, and OS as a key secondary endpoint The ORR in WU-KONG1B was consistent across the 200 mg and 300 mg dose levels; however, an improved safety profile was observed for the lower dose, supporting approval of the sunvozertinib 200 mg QD dose level in this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The primary safety population supporting this NDA included patients randomized to the 200 mg QD dose cohort in WU-KONG1B. • Supportive data were submitted from the 200 mg pooled safety population along with the 300 mg QD dose cohort in WU-KONG1B and the 300 mg pooled safety population. • In the primary safety population of 91 patients who received sunvozertinib 200 mg QD, serious adverse reactions occurred in 41% of patients; the most common (≥2%) serious adverse reactions were pneumonia (9%), dyspnea (4.4%), and pancreatitis, device-related infection and rash (2.2% each). • Permanent discontinuation of sunvozertinib 200 mg QD occurred in 8% of patients in the primary safety population; the most frequent events leading to permanent discontinuation (≥2%) were pneumonia and rash (2.2% each). • Fatal adverse reactions occurred in 2.2% of patients in the primary safety population, due to thrombosis (1.1%) and COVID-19 infection (1.1%). • Compared to the 200 mg QD dosage, the 300 mg QD dosage had more events of Grade ≥3 diarrhea (2.2% vs 21%) and elevated CPK levels (5% vs 15%). • Compared to the 200 mg dose, the 300 mg dose had higher rates of adverse reactions leading to dose interruptions (48% vs 59%), dose reductions (23% vs 42%), and permanent discontinuation of sunvozertinib (8% vs 13%). • In the pooled safety populations (n=121 at 200 mg and n=311 at 300 mg), ILD/pneumonitis occurred in 1.7% with 0% Grade ≥3 events for the 200 mg dose level and 5.5% with 1.3% Grade 3 and 2.3% Grade 4 events for the 300 mg dose level.	Sunvozertinib 200 mg QD demonstrated a better safety profile than sunvozertinib 300 mg QD in WU-KONG1B. The observed safety profile of suvozertinib is acceptable in the context of the treatment of a life-threatening disease. Although sunvozertinib can cause serious adverse reactions, these safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage Administration sections of the prescribing information. The risk mitigation strategies included in the label are considered sufficient and a REMS was not considered necessary for the safe use of sunvozertinib.

1.4. Patient Experience Data

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

X	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	Section 8.1
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that was not submitted in the application, but was considered in this review.			

X

Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Lung cancer is one of the most common cancer types and the leading cause of cancer-related death globally, representing 11.7% of all cancer diagnosed and 20.4% of total cancer deaths worldwide (Bazhenova L, et al., 2021). In the United States, an estimated 234,580 new cases of lung cancer will be diagnosed in 2024 (Siegel RL, et al., 2024).

Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer (Bauml JM, et al., 2021). The majority of patients with NSCLC are diagnosed with advanced stage, with 70% to 80% of patients inoperable. Their prognosis are poor, with 5-year overall survival (OS) rate of approximately 15% to 17% (Wu L, et al., 2020; Zappa C, et al., 2016).

Oncogenic driver mutations in epidermal growth factor receptor (EGFR) have been identified in more than 15% of patients with NSCLC in western countries, and up to 50% of the corresponding Asian population (Wu L, et al., 2020). EGFR exon 19 deletion (exon19del) and L858R mutation are the two most common driver mutations. EGFR exon 20 insertion mutations (exon20ins) are the third most frequent mutations, which represent approximately 12% of all EGFR mutations in advanced NSCLC, and EGFR exon20ins are molecularly heterogeneous, with > 100 variants identified by next generation sequencing (Arcila ME, et al., 2013; Bauml JM, et al., 2021).

Expression of EGFR exon20ins in transgenic mice induce spontaneous development of tumor lesions in lung tissues (Wang M, et al., 2022; Riess JW, et al., 2018; Robichaux JP, et al., 2018; Siegel RL, et al., 2024), which suggest that EGFR exon20ins drive oncogenesis. Subsequent clinical studies demonstrated that blocking signaling through EGFR exon20ins could indeed bring clinical benefits to patients.

The FDA's Assessment:

FDA agrees with the Applicant's position.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

The insertional mutations at EGFR exon 20 cause steric hindrance and block access to the receptor active site by approved EGFR Tyrosine Kinase Inhibitors (TKIs). Clinically, NSCLC arising from EGFR exon20ins is distinguished by *de novo* resistance to currently approved EGFR TKIs, such as osimertinib (Wu L, et al., 2020).

On March 1, 2024, FDA approved amivantamab-vmjw (hereafter referred to as amivantamab), a bi-specific EGFR and c-MET antibody, with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon20ins. The efficacy evaluation for the first-line approval was based on the PAPILLON (NCT04538664) study,

comparing amivantamab with carboplatin and pemetrexed against carboplatin and pemetrexed. The amivantamab with carboplatin and pemetrexed arm showed statistically significant improvement of median progression free survival (PFS) over carboplatin and pemetrexed arm, 11.4 months vs. 6.7 months (Zhao W, et al., 2022). Consequently, FDA also granted traditional approval to amivantamab as a single agent for adult patients whose disease has progressed on or after platinum-based chemotherapy. FDA previously granted accelerated approval for this indication with efficacy evaluation of 40% confirmed objective response rate (cORR) (Park K, et al., 2021). Amivantamab is administered through intravenous infusion. On top of doublet chemo related adverse effects, infusion-related reactions are among the most frequent ≥ grade 3 treatment emergent adverse events (TEAEs). Infusion is obviously not patient-friendly. Furthermore, with amivantamab's first-line approval, more patients will need an effective treatment option after their disease progresses on or after amivantamab and doublet chemo treatment.

In addition to amivantamab, platinum-based chemotherapy with/without immunotherapy is also commonly used in the clinic, with marginal effectiveness. The ORRs in the first-line and ≥ second-line settings by chemotherapy-containing regimens were ~19% and ~14%, and median PFS were ~6.4 months and ~3.7 months, respectively (Yang G, et al., 2020; Bazhenova L, et al., 2021).

No EGFR TKI has been approved for the treatment of advanced NSCLC with EGFR exon20ins. Mobocertinib, an EGFR TKI, was previously granted accelerated approval by FDA, but it has been withdrawn from the market due to the failure of its phase 3 confirmatory study.

Therefore, a novel chemo-free treatment modality with convenient route of administration, e.g. oral, is needed to address the unmet medical needs of this serious disease, especially in patients who have failed from standard therapies.

Table 1 summarizes the clinical efficacy of current available therapies for previously treated NSCLC patients with EGFR exon20ins in ≥ second-line settings.

Table 1 Summary of Current Therapies and Anti-tumor Efficacy in Advanced NSCLC with EGFR Exon20ins in ≥ Second-line Settings

Treatment regimen	ORR, % (95% CI)	mPFS, months (95% CI)	mOS, months (95% CI)	References
Amivantamab (n = 81)*	40 (29, 51)	8.3 (6.5, 10.9)	NA	Park K, et al., 2021
Various therapies from real-world (n = 109)**	11.9 (5.8, 18.0)	3.3 (2.2, 7.3)	12.4 (7.1, 16.6)	Ou SH, et al., 2021 ESMO
Chemotherapy (n = 27~34)**	17.6	4 (3.2, 4.8)	14.2	Yang G, et al., 2020; Bazhenova L, et al., 2021
IO therapy (n = 20)**	5.0 (0.1, 24.9)	2.2 (1.7, 3.0)	7.1 (2.5, 10.1)	Ou SH, et al., 2021 ASCO
Other EGFR TKIs (n = 10)**	10.0 (0.3, 44.5)	3.4 (0.0, 5.9)	12.2 (1.3, 17.8)	Ou SH, et al., 2021 ASCO

Source: Applicant Table.
CI: confidence interval; EGFR: epidermal growth factor receptor; IO: immune-oncology, including anti-PD-1, PD-L1 and CTLA4, NA: not available; ORR: objective response rate; mOS: median overall survival; mPFS: median progression free survival; TKI:

tyrosine kinase inhibitor;
* FDA granted accelerated approval for amivantamab on May 21, 2021, and converted to traditional approval on March 1, 2024.
** Data are from real-world studies, including multiple treatment regimens in clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant with the exception that on September 15, 2021, mobocertinib was granted accelerated approval for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy. Mobocertinib is an EGFR TKI that was FDA approved; however, on October 2, 2023, the sponsor (Takeda) announced plans to voluntarily withdraw mobocertinib in the U.S. following the outcome of the randomized EXCLAIM-2 trial, which failed to meet its primary endpoint of PFS and verify the clinical benefit of mobocertinib.

3. Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Sunvozertinib (DZD9008, also named as DZ00000586 in some reports) is not currently approved in the U.S.

The FDA's Assessment:

FDA agrees with the Applicant's position. For completeness regarding the marketing history, since August 2023, sunvozertinib is approved for marketing in China for the treatment of advanced NSCLC with EGFR exon 20 insertion mutations after platinum-based chemotherapy.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Throughout the clinical development of sunvozertinib, the applicant has kept close engagement with FDA and benefited from meetings and discussions from these interactions. Dizal participated the Oncology Center of Excellence (OCE) Oncology Dosing Toolkit pilot project, sought and accepted FDA's advice for the overall product development strategies and requirements for New Drug Application (NDA) submission. The key FDA interactions are summarized in Table 2.

Table 2 Overview of Key FDA Interactions

Events/Date	Description
Study May Proceed Letter April 4, 2019	Study May Proceed Letter (IND 142003) was received for WU-KONG1 (DZ2019E0001).
Type B End of Phase 1 (EOP1) Meeting for Chemistry, Manufacture and Control (CMC) January 13, 2021	CMC topics for subsequent pivotal study, including proposed specifications for the drug substance and drug product, proposed regulatory starting materials of drug substance, formulation and dosage plan of drug product and overall CMC program development were discussed.

Events/Date	Description
Type B EOP1 Meeting February 5, 2021	Phase 2 study design, clinical development plan and the development plan for in vitro companion diagnostics was discussed.
Breakthrough Therapy Designation Granted January 26, 2022	BTD was granted for the treatment of patients with locally advanced or metastatic NSCLC with EGFR exon20ins whose disease has progressed on or after platinum-based chemotherapy.
Type B BTD Meeting for Clinical and Nonclinical March 31, 2022	Clinical development plan, phase 3 study design, drug supply, nonclinical toxicity study for human metabolites, and overall communication plan were discussed.
Type B BTD Meeting for CMC June 2, 2022	CMC development plan for further NDA filing, including the proposed regulatory starting materials for drug substance, the proposed commercial manufacturing process and stability study plan for drug product, and the proposed specifications for drug substance and drug product, including the control strategy of mutagenic impurities, (b) (4) impurities and dissolution were discussed.
Type B Meeting for Clinical Pharmacology (Written Responses Only) July 1, 2022	The FDA generally agreed the clinical pharmacology package plan.
Oncology Center of Excellence (OCE) Oncology Dosing Toolkit pilot project January 12, 2023	Dizal participated FDA Oncology Center of Excellence (OCE) Oncology Dosing Toolkit pilot project.
Type D Meeting (Written Responses Only) July 17, 2023	Dizal sought the FDA 's agreement on protocol amendment of WU-KONG1 Part B study.
Agreed Initial Pediatric Study Plan (iPSP) Submission February 14, 2024	The FDA agreed with the applicant's plan to submit a request for a full waiver for sunvozertinib for all pediatric age groups.
Pre-NDA Type B Meeting April 1, 2024	The FDA agreed with the applicant's plan on NDA submission for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon20ins, whose disease has progressed on or after platinum-based chemotherapy.
Breakthrough Therapy Designation Granted April 5, 2024	BTD was granted for first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon20ins.
Type B BTD Meeting June 24, 2024	Clinical and CMC questions related to NDA submission were discussed.

Source: Applicant Table.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. For clarification, FDA has interpreted the Applicant's text "… has kept close engagement with FDA and benefited from meetings and discussions from these interactions" to reflect that the Applicant requested specific meetings, as listed in the table, with the FDA to discuss the development plans for sunvozertinib.

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

4.1 Office of Scientific Investigations (OSI)

For Study DZ2019E0002, two clinical investigators (CIs), Drs. Dongqing Lv (Site #328) and James Yang (Site #501); the Contract Research Organization (CRO), (b) (4)., and the imaging CRO, (b) (4) were inspected. Inspections of Drs. Yang and Lv, and the imaging CRO, (b) (4) did not identify significant concerns regarding the study conduct, data discrepancies or integrity, Good Clinical Practice (GCP), or regulatory compliance.

Inspection of CRO (b) (4) observed delays in data query resolution and issues with investigational drug accountability record keeping. These deficiencies are unlikely to affect the overall reliability of the data generated from the sites. (b) (4) provided a corrective and preventive action (CAPA) plan that was reviewed and found to be acceptable.

Based on these inspections, Study DZ2019E0001 appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

For additional details, refer to the Clinical Inspection Summary by Dr. Lee Pai-Scherf, uploaded to DARRTS on May 21, 2025.

4.2 Product Quality

The drug product is an oral immediate release tablet containing 150 mg or 200 mg of sunvozertinib. The Office of Pharmaceutical Quality (OPQ) assessed NDA 219839 with respect to Chemistry, Manufacturing, and Controls (CMC) and determined that it meets all applicable standards to support the identity, strength, quality, and purity. As such, OPQ recommends approval of this NDA from a quality perspective. An expiration dating period of 36 months is granted for the drug product when stored at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).

For additional details, see the CMC Executive Summary by Dr. Shalini Anand, uploaded to DARRTS on June 3, 2025.

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

A Premarket Approval (PMA) application (P240040) for the Oncomine Dx Express Test (ODxET) was submitted to the Center for Devices and Radiological Health (CDRH). The ODxET is a qualitative *in vitro* diagnostic test that utilizes targeted next-generation sequencing (NGS) technology to detect epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations in DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor specimens from patients with non-small cell lung cancer (NSCLC), using the Genexus Dx Integrated Sequencer.

It was determined that the data submitted in the PMA are supportive of approval of the ODxET as a companion diagnostic device to identify patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy, and who may be eligible for treatment with ZEGFROVY (sunvozertinib).

The following information regarding testing for *EGFR* exon 20 insertions will be included in the sunvozertinib USPI: "All 85 patients in the efficacy population had *EGFR* exon 20 insertion mutations in tumor based on prospective local testing or central laboratory testing. Tumor samples from patients were tested retrospectively using Life Technologies Corporation Oncomine Dx Express Test. In these tumor samples, 68% (58/85) were positive for EGFR exon 20 insertion mutations, 2.4% (2/85) did not have an *EGFR* exon 20 insertion mutation identified, and 29% (25/85) did not generate reportable results."

5. Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Sunvozertinib (DZ9008) is an oral small molecule inhibitor of epidermal growth factor receptor (EGFR) that demonstrates activity against EGFR exon 20 insertion (exon20ins) mutations. Genetic alterations such as EGFR exon20ins lead to ligand-independent activation of the receptor which can contribute not only to cancer cell growth and proliferation, but also resistance to early-generation EGFR tyrosine kinase inhibitors (TKIs) (Seo and Lim, 2024). The established pharmacologic class for sunvozertinib is a kinase inhibitor.

In an in vitro biochemical assay, sunvozertinib exhibited comparable low nanomolar inhibitory activity against exon20ins mutation EGFR D770_N771insNPG (IC_{50} = 2.1 nM) and wild type (WT) EGFR (IC_{50} = 2.4 nM). In another biochemical screening assay, activity of sunvozertinib was evaluated against a panel of 117 kinases. Sunvozertinib exhibited an ~17-fold selectivity for EGFR L858R/T790M compared to WT EGFR and a >20-fold selectivity for EGFR L858R/T790M compared to HER2 and HER4. Inhibition of HER3 and EGFR exon 20 insertion mutations were not assessed.

In cellular assays, sunvozertinib inhibited phosphorylation of EGFR (pEGFR) in 12 cell lines expressing different exon20ins mutant variants at 2.2 to 9.7-fold lower IC_{50} values than pEGFR inhibition in WT EGFR expressing cells. The effect of sunvozertinib on cell proliferation was evaluated in the same 12 cell lines expressing different exon20ins mutant variants. Sunvozertinib inhibited cell proliferation in most of the exon20ins mutant cell lines at 1.2 to 8.4-fold lower GI_{50} values than in WT EGFR expressing cells. In two of the exon20ins mutation variant cell lines (H733_V774insNPH and V769_D770insASV) GI_{50} values were comparable to that of WT EGFR.

The in vivo activity of sunvozertinib was evaluated in immunocompromised mice bearing subcutaneous (SC) non-small cell lung cancer (NSCLC) xenograft models carrying EGFR exon20ins mutations (LU0387 and LU3075) or a squamous cell carcinoma cell line carrying WT EGFR (A431). In both EGFR exon20ins mutant patient-derived xenograft (PDX) models, anti-tumor activity was observed at doses of ≥ 25 mg/kg sunvozertinib twice daily (BID). Anti-tumor activity was also observed in cell line-derived xenografts expressing WT EGFR, though a 2-fold higher dose of sunvozertinib (50 mg/kg BID) was needed to cause tumor shrinkage in this model. In a study evaluating the in vivo pharmacokinetic (PK) and pharmacodynamic (PD) relationship of sunvozertinib, higher doses of sunvozertinib resulted in higher drug concentrations in the plasma and greater modulation of PD markers, pEGFR and phosphorylated extracellular signal-related kinase (pERK).

Secondary pharmacology studies evaluated the activity of sunvozertinib against 101 molecular targets which included different types of receptors, ion channels, transporters, and enzymes.

Sunvozertinib did not exhibit substantial off-target activity against other targets at clinically relevant concentrations (free C_{max} of approximately 60 nM at the highest recommended dose of 200 mg), although sunvozertinib inhibited ALK4 with IC_{50} values as low as 150 nM.

Sunvozertinib inhibited human ether-a-go-go related gene (hERG) current at a concentration of 1.21 μM, which corresponds to a ~20-fold exposure margin from the unbound C_{max} of sunvozertinib (~60 nM), thereby suggesting low potential for QT prolongation. Additionally, the toxicology studies in dogs did not show QT prolongation or any other cardiac electrophysiologic effects. Sunvozertinib had no effect on the respiratory system or central nervous system (CNS) of rats receiving a single oral dose at levels up to 100 mg/kg.

Sunvozertinib bound to plasma protein of various species in a concentration-dependent manner. In human plasma, 91.46% of sunvozertinib was bound to plasma protein at the 1 μM concentration. Following a single dose of radiolabeled sunvozertinib in pigmented rats, a wide distribution of sunvozertinib was observed with the highest radioactivity found in the cecum and small intestine contents, adrenal gland, pituitary gland, spleen, and uveal tract. Distribution of sunvozertinib-derived radioactivity in the uveal tract, meninges, and pigmented fur indicated melanin binding. Radioactivity in the brain and spinal cord remained below the limit of quantification, indicating that sunvozertinib has a low tendency to cross the blood-brain barrier. There were no major (>10%) human metabolites identified. Elimination studies showed that sunvozertinib administered orally or intravenously was primarily excreted via the fecal route in rats (88.7% and 85.3%, respectively) with minimal excretion via the urinary route (1.3% and 3.8%, respectively). Animal to human exposure multiples were calculated using the area under the curve (AUC) of 8,060 hr*ng/mL in patients at the highest recommended clinical dose of 200 mg/day.

The Applicant conducted 13-week repeat-dose toxicology studies in rats and dogs with a recovery period of 4 weeks. At the high dose of 35 mg/kg, findings in rats included increased incidence of flaky tails, tail ridging, and head scabbing that was associated with folliculitis and inflammation of the tail. Additionally, increased sinusoidal macrophages in the lymph nodes were observed at 35 mg/kg. At doses ≥15 mg/kg accumulation of foamy macrophages in the lung, erythrophagocytosis in the mesenteric lymph nodes, and atrophy of the mammary glands that occurred only in males (approximately ≥0.3 times the clinical AUC at the 200 mg human dose) were observed in rats. These findings were generally reversible. Ocular toxicities (hemorrhage of the anterior chamber of the eye) were observed in rats at 35 mg/kg (approximately 0.8 times the clinical AUC at the 200 mg human dose) and persisted through the recovery period. Hematologic toxicities in rats included reversible decreased red blood cell parameters and increased white blood cells. In dogs, increased instances of loose or liquid feces and hyperplasia in the lungs and liver were observed at doses ≥3 mg/kg. At doses ≥1 mg/kg in dogs, inflammation in the lungs and liver, and erythrophagocytosis in the lymph nodes were observed. These findings in dogs were generally reversible. Of note, a single male dog at 6 mg/kg exhibited moderate alveolar flooding/hemorrhage in the lung that was associated with

moderate broncho-alveolar inflammation, minimal granulomatous inflammation, and epithelial hyperplasia in the bronchioles. Hematologic toxicities in dogs included reversible decreases in red blood cell parameters.

Findings observed in one or both species consistent with clinical experience included effects on the gastrointestinal tract, skin, lung, eyes, and decreased red blood cell parameters.

Sunvozertinib was not mutagenic in an in vitro bacterial reverse mutation assay. Additionally, sunvozertinib did not cause chromosomal aberrations in an in vitro chromosome aberration assay in Chinese hamster ovary (CHO) cells. Sunvozertinib was not clastogenic in an in vivo bone marrow micronucleus test in rats and did not demonstrate phototoxic potential in a GLP-compliant in vitro assay with mouse fibroblasts.

The Applicant did not conduct a carcinogenicity study with sunvozertinib; consistent with ICH S9, these studies are not warranted for the development of a drug intended for the treatment of patients with advanced cancer. Dedicated fertility studies with sunvozertinib were also not conducted; however, histopathology findings in the GLP 4-week repeat-dose toxicology study in dogs showed that male animals exhibited slight to moderate degeneration of the seminiferous tubules in the testes at 12/8 mg/kg (approximately 0.2 times the clinical AUC at the 200 mg human dose). Additionally, findings in a 14-day dose-range finding study in dogs showed that female animals exhibited slight atrophy of the vaginal epithelium at ≥50 mg/kg (approximately 1.4 times the clinical AUC at the 200 mg human dose).

To address the potential reproductive effects of sunvozertinib, the Applicant conducted a GLP-compliant embryo-fetal development study in Wistar Han rats. Once daily oral administration of sunvozertinib to pregnant rats during the period of organogenesis (Gestation Day [GD] 6 to 17) did not affect embryo-fetal survival at doses up to 40 mg/kg/day (0.6 times the clinical AUC at the 200 mg human dose); however, treatment with 40 mg/kg resulted in an increased incidence of misaligned sternebra (skeletal variation) noted in fetuses as compared to controls. Maternal toxicity was characterized by a decrease in body weight at 40 mg/kg sunvozertinib which correlated with decreased food consumption at ≥20 mg/kg sunvozertinib (≥0.5 times the clinical AUC at the 200 mg human dose) compared to controls.

A GLP-compliant embryo-fetal development study in rabbits was also performed. Once daily oral administration of sunvozertinib to pregnant rabbits during the period of organogenesis (GD 6 to 19) resulted in a dose-dependent decrease in maternal weight gain starting at 0.5 mg/kg (approximately 0.02 times the clinical AUC at the 200 mg human dose). Fetal toxicities included visceral malformations of the heart (dilation of the aorta and aortic arch) at ≥0.5 mg/kg in addition to narrow pulmonary arteries and absent median lobes in the lung at ≥1.5 mg/kg (approximately ≥0.07 times the clinical AUC at the 200 mg human dose) and ≥0.5 mg/kg, respectively. Skeletal variations included increases in instances of supernumerary bone of the fontanellar and shortened 13th right ribs at ≥1.5 mg/kg.

Overall, given the nonclinical data, the pharmacology/toxicology team recommends a warning for embryo-fetal toxicity in the label for ZEGFROVY (sunvozertinib). Consistent with the recommendations for embryotoxic and non-genotoxic drugs described in the FDA Guidance for Industry Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations, and considering the sunvozertinib terminal half-life of 47 hours, FDA recommends advising males to use effective contraception during treatment with sunvozertinib and for 2 weeks after the last dose. Given that the FDA clinical pharmacology team identified sunvozertinib to be a weak inducer of CYP3A, which may compromise the efficacy of hormonal contraception, the FDA recommends advising females of reproductive potential to use effective non-hormonal contraception during treatment with sunvozertinib and for 2 weeks after the last dose. The Applicant did not evaluate the presence of sunvozertinib in milk; however, because of potential adverse effects of sunvozertinib on a breastfeeding child, the review team recommends advising patients not to breastfeed during treatment with sunvozertinib and for 2 weeks after the last dose.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of sunvozertinib for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

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

5.3 Pharmacology

The Applicant's Position:

Primary pharmacology

The enzymatic and cellular activity, selectivity over wild-type EGFR, irreversibility, and anti-tumor activity of sunvozertinib against various EGFR exon20ins subtypes, have been evaluated through *in vitro* and *in vivo* studies.

In Vitro

The enzymatic potency of sunvozertinib, as well as its active metabolite DZ0753, against various mutant and wild-type EGFR was studied at 2 mM adenosine triphosphate (ATP), which is used to normalize the effect of ATP competition due to intrinsic difference in Km for ATP substrate on the inhibition potency. As shown in Table 3, both sunvozertinib and DZ0753 demonstrated potent enzymatic activities against various EGFR mutations, with relatively weaker activity against wild-type EGFR (Pharmacology report 02).

Table 3 Summary of Enzymatic Potency IC_{50} of Sunvozertinib and its Metabolite DZ0753 Against Mutant and Wild-Type EGFR Enzymes

Genes	IC_{50} (nM)[#] (n = 3)	
	Sunvozertinib	DZ0753
EGFR L858R	0.44 ± 0.02	0.60 ± 0.1
EGFR L858R/T790M	0.46 ± 0.19	0.13 ± 0.02*
EGFR Exon19del/T790M	0.76 ± 0.09	0.75 ± 0.06
EGFR L861Q	1.0 ± 0.43	0.84 ± 0.28
EGFR Exon19del	1.9 ± 0.36	1.7 ± 0.17
EGFR D770_N771insNPG	2.1 ± 0.45	1.8 ± 0.24
Wild-type EGFR	2.4 ± 1.4	2.1 ± 0.91

Source: Applicant Table.
[#]IC_{50} was expressed as mean ± standard deviation (SD). *n = 2. n = number of replicates.

Kinome-wide selectivity was evaluated in a kinase panel of 117 kinases at 1 μM of sunvozertinib and DZ0753, respectively. The results showed that besides EGFR L858R/T790M, which was potently inhibited (99%), 14 other kinases were inhibited > 50% (51% to 96%). The IC_{50} values for these 14 kinases were subsequently measured. The results are shown in Table 4. Taken together, these data showed that sunvozertinib and DZ0753 had strong enzymatic selectivity against other kinases (Pharmacology report 01).

Table 4 IC_{50} of Sunvozertinib and Its Metabolite DZ0753 on Kinases with Inhibition > 50% at 1 μM Concentration in Eurofins Kinase Panel

Kinase (Human)	IC_{50} (nM)	
	Sunvozertinib	DZ0753
BTK	213	355
FAK	255	226
Txk	471	252
BRK	529	633
ERBB4	704	348
ALK4	705	433
Ros	937	795
Mnk2	1032	1502
BLK	1036	516
ALK	1172	986
Fes	1764	3294
BMX	2289	1485
Yes	2895	3929
TrkA	>10,000	>10,000

Source: Applicant Table.

The potencies of sunvozertinib and DZ0753 on EGFR phosphorylation inhibition, the

pharmacodynamic biomarker, were assessed in *in vitro* cellular assays on Ba/F3 cell lines engineered to express different mutant variants of EGFR, and A431 cells that overexpress wild-type EGFR. As shown in Table 5, sunvozertinib demonstrated potent pharmacodynamic effect against multiple EGFR mutants, with good selectivity margin over wild-type EGFR (Pharmacology report 03; Pharmacology report 14; Pharmacology report 17).

Table 5 Summary of Cellular pEGFR Inhibitory IC_{50} by Sunvozertinib and Its Metabolite DZ0753 Across Various Cell Lines

Gene	Mutation	Cell Line	Model Type	IC_{50} (nM)[#] (n = 3)	
				Sunvozertinib	DZ0753
EGFR	Exon19del/T790M	Ba/F3_19Del/T790M	Engineered Cell Line	0.95 ± 0.24	3.4 ± 0.99
	L858R/T790M	NCI-H1975	Cancer Cell Line	1.1 ± 0.31	1.4 ± 0.36
	L858R	NCI-H3255	Cancer Cell Line	1.2 ± 0.17	3.4 ± 2.5
	Exon19del	PC-9	Cancer Cell Line	1.2 ± 0.38	4.8 ± 1.3
	L861Q	Ba/F3_L861Q	Engineered Cell Line	11 ± 2.0	7.5 ± 3.2
	H773_V774insPHPH	Ba/F3_InsPHPH	Engineered Cell Line	6.0 ± 2.7	NA
	H773_V774insPH	Ba/F3_InsPH	Engineered Cell Line	6.9 ± 0.97	NA
	D770_N771insY	Ba/F3_InsY	Engineered Cell Line	8.3 ± 2.9	NA
	D770_N771insNPG	Ba/F3_NPG	Engineered Cell Line	11 ± 2.4	7.5 ± 1.2
	D770_N771insG	Ba/F3_InsG	Engineered Cell Line	14 ± 4.6	NA
	A763_Y764insFQEA	Ba/F3_InsFQEA	Engineered Cell Line	15 ± 1.5	NA
	V769_D770insGVV	Ba/F3_InsGVV	Engineered Cell Line	18 ± 2.4	NA
	D770_N771insSVD	Ba/F3_SVD	Engineered Cell Line	18 ± 1.3	NA
	H773_V774insNPH	Ba/F3_NPH	Engineered Cell Line	20 ± 3.3	25 ± 5.2
	V769_D770insASV	Ba/F3_ASV	Engineered Cell Line	23 ± 7.1	NA
	P772_H773insDNP	Ba/F3_DNP	Engineered Cell Line	24 ± 6.4	18 ± 6.2
	V769_D770insGSV	Ba/F3_InsGSV	Engineered Cell Line	26 ± 3.2	NA
	Wild-type	A431	Cancer Cell Line	58 ± 19	55 ± 15

Source: Applicant Table.
[#]IC_{50} was expressed as mean ± SD. n = number of replicates. NA= not available. EGFR exon20ins subtypes in this table are presented using common terms.

The time-course cellular potency of sunvozertinib in suppressing pEGFR was tested in PC-9 cells to determine its irreversibility. pEGFR IC_{50s} shifted from 7.5 nM to 2.3 nM with prolonged incubation time (1 hour to 8 hours) (Pharmacology report 03), suggesting an irreversible inhibition mode.

The effect of sunvozertinib and DZ0753 on cell proliferation after 3-day treatment was investigated by CellTiter–Glo assay. Both sunvozertinib and DZ0753 showed potent activities against EGFR mutant (EGFRm) cells, but weaker activities in wild-type EGFR cells. The GI_{50} in cell lines is shown in Table 6 (Pharmacology report 04, Pharmacology report 14, Pharmacology report 17).

Table 6 Summary of Anti-Proliferation GI_{50} for Sunvozertinib and Its Metabolite DZ0753

Gene	Mutation	Cell Line	Model Type	GI_{50} (nM)# (n =3)	
				Sunvozertinib	DZ0753
EGFR	L858R	NCI-H3255	Cancer Cell Line	1.7 ± 0.28	6.7 ± 1.3
	Exon19del/T790M	Ba/F3_19Del/T790M	Engineered Cell Line	3.5 ± 1.5	18 ± 8.5
	Exon19del	PC-9	Cancer Cell Line	4.1 ± 0.58	17 ± 3.2
	L858R/T790M	NCI-H1975	Cancer Cell Line	12 ± 6.4	47 ± 28
	L861Q	Ba/F3_L861Q	Engineered Cell Line	31 ± 1.6	108 ± 22
	H773_V774insPHPH	Ba/F3_InsPHPH	Engineered Cell Line	12 ± 3.8	NA
	H773_V774insPH	Ba/F3_InsPH	Engineered Cell Line	6.3 ± 2.9	NA
	D770_N771insY	Ba/F3_InsY	Engineered Cell Line	37 ± 9.6	NA
	D770_N771insNPG	Ba/F3_NPG	Engineered Cell Line	27 ± 6.1	84 ± 16
	D770_N771insG	Ba/F3 InsG	Engineered Cell Line	19 ± 1.5*	NA
	A763_Y764insFQEA	Ba/F3_InsFQEA	Engineered Cell Line	11 ± 1.5	NA
	V769_D770insGVV	Ba/F3_InsGVV	Engineered Cell Line	39 ± 7.7	NA
	D770_N771insSVD	Ba/F3_SVD	Engineered Cell Line	45 ± 18	NA
	H773_V774insNPH	Ba/F3_NPH	Engineered Cell Line	60 ± 8.4	196 ± 63
	V769_D770insASV	Ba/F3_ASV	Engineered Cell Line	80 ± 26	NA
	P772_H773insDNP	Ba/F3_DNP	Engineered Cell Line	38 ± 9.2	126 ± 23
	V769_D770insGSV	Ba/F3_InsGSV	Engineered Cell Line	25 ± 10	NA
	Wild-type	A431	Cancer Cell Line	53 ± 8.7	102 ± 20

Source: Applicant Table.

#IC_{50} was expressed as mean ± SD. *n = 2. n = number of replicates. NA = not available. EGFR exon20ins subtypes in this table are presented using common terms.

Sunvozertinib and DZ0753 showed greater than 100-fold selectivity between IGF1R and InsR versus mutant EGFR, as measured by enzyme and cellular IGF1R and InsR phosphorylation inhibition IC_{50} (Table 7, Pharmacology report 05).

Table 7 Enzyme IC_{50} and Cellular IC_{50} for Sunvozertinib and Its Metabolite DZ0753

	Enzyme IC_{50} (nM)# (n = 3)		Cellular IC_{50} (nM)# (n = 3)	
	IGF1R	**InsR**	**IGF1R**	**InsR**
Sunvozertinib	935 ± 296	101 ± 15	4884 ± 2337	5088 ± 3319
DZ0753	1720 ± 331	165 ± 18	4934 ± 1856	6431 ± 3686

Source: Applicant Table.
#IC_{50} was expressed as mean ± SD. n = number of replicates

In Vivo

Cell line or patient-derived xenograft models

The anti-tumor activity of sunvozertinib was evaluated in multiple subcutaneous cell line- and patient-derived xenograft models carrying EGFR exon20ins, exon19del, L858R/T790M, uncommon mutations or wild-type EGFR. When tumor volumes reached 150 to 250 mm^3, mice were randomly allocated to different treatment groups. The results showed that sunvozertinib induced dose-dependent tumor growth inhibition in these animal models. The tumor growth inhibition by sunvozertinib after the last dose in various xenograft models is summarized in Table 8 (Pharmacology Report 06).

Table 8 Summary of Tumor Growth Inhibition in Subcutaneous Xenograft Models at the End of Sunvozertinib Treatment

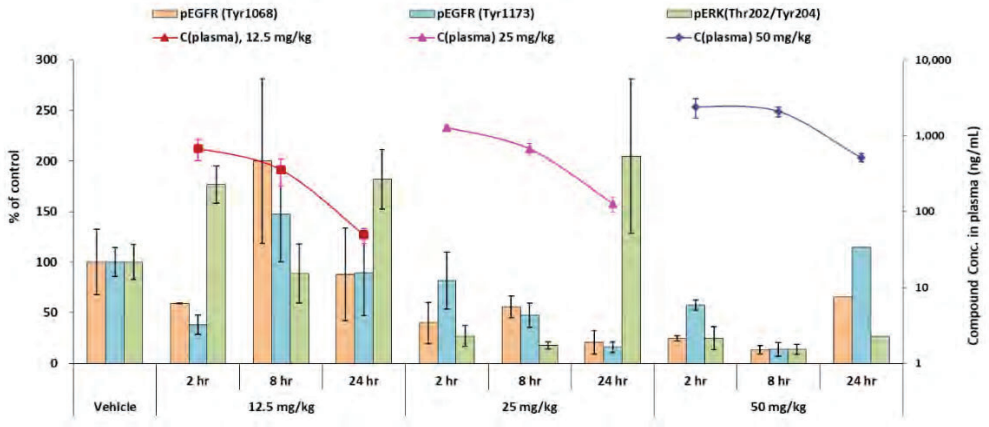
Study Number	Xenograft Model	Duration of Treatment (Days)	Dose Regimen (mg/kg, bid)	Tumor Growth Inhibition (%)
DZINVO-002	PC-9 (Exon19del), cell line-derived (n = 7)	14	4	120
			10	148
			30	154
			75	154
DZINVO-003	NCI-H1975 (L858R/T790M), cell line-derived (n = 7)	14	10	129
			30	130
			75	152
DZINVO-006	LC019 (G719S/L861Q), patient-derived (n = 6)	21	25	166
			50	166
DZINVO-019	A431 (wild-type EGFR), cell line-derived (n = 9)	16	12.5	68
			25	96

Study Number	Xenograft Model	Duration of Treatment (Days)	Dose Regimen (mg/kg, bid)	Tumor Growth Inhibition (%)
			50	109
DZINVO-040	LU0387 (H773_V774insNPH), patient-derived (n = 9)	28	12.5	48
			25	112
			50	113
DZINVO-041	LU3075 (P772_H773insDNP), patient-derived (n = 9)	28	12.5	55
			25	113
			50	117

Source: Applicant Table.
bid = twice daily. n = number of mice per group. Tumor growth inhibition > 100% indicates tumor regression. n = number of mice per group in the xenograft model.

The *in vivo* dose/pharmacokinetic (PK)/pharmacodynamic relationship of sunvozertinib in tumor xenograft model was conducted at the end of efficacy study in patient-derived xenograft model LU3075 carrying EGFR exon20ins P772_H773insDNP. Plasma and tumor tissue samples were collected at different time points post last dose of sunvozertinib on Day 28 to analyze the drug concentrations in plasma by liquid chromatography–mass spectrometry, and pEGFR and pERK expression in tumor tissues by immunohistochemistry (IHC) staining. The results showed positive dose/PK/pharmacodynamic relationship by sunvozertinib (Figure 1, Pharmacology Report 07).

Figure 1 Summary of PK/pharmacodynamic Relationship of Sunvozertinib in Patient-Derived Xenograft Model LU3075 (P772_H773insDNP)



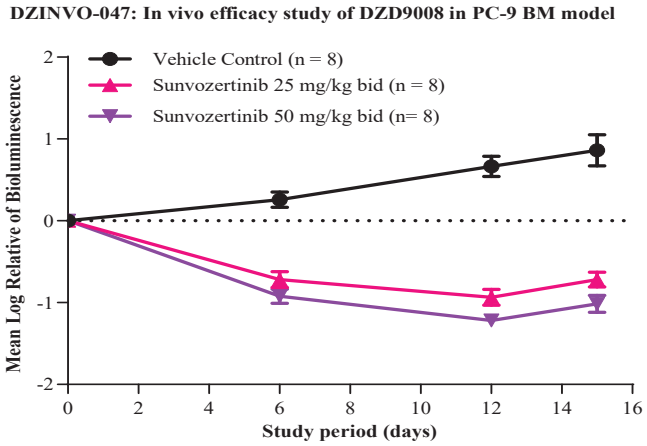
Source: Applicant Figure.
Note: Three mice per timepoint per group. C(plasma) = drug concentration in plasma. hr = hour. Thr = threonine. Tyr = tyrosine. 3 mice per timepoint.

Cell line-derived brain metastasis xenograft model

The therapeutic potential of sunvozertinib against brain tumors was evaluated in a mouse brain metastasis xenograft model carrying EGFR exon19del (PC-9 model). When bioluminescence signal reached approximately 10^7 photons/sec, the mice were assigned into different treatment

groups, and treated with either vehicle or sunvozertinib at different doses. The results showed a dose-dependent anti-tumor efficacy of sunvozertinib (Figure 2, Pharmacology Report 08).

Figure 2 *In Vivo* Anti-tumor Efficacy of Sunvozertinib in PC-9 Brain Metastasis Model



Source: Applicant Figure.
Note: Data in the figure were shown with mean log relative of bioluminescence and standard error (SE) of mean. bid = twice daily.

The FDA's Assessment:

The Applicant uses terminology such as "potency", "potently", "strong", and "good" to describe study results; such terms should be avoided as they are vague, subjective, and promotional.

FDA generally agrees with the Applicant's presentation of the pharmacology data with additional data and FDA's conclusions discussed below. Relevant to the proposed clinical indication, EGFR D770_N771insNPG is an exon 20 insertion mutation.

In Vitro Studies

The Applicant evaluated the activity of sunvozertinib and its active metabolite DZ0753 in biochemical and cellular assays. FDA notes that the activity of sunvozertinib and DZ0753 on exon 20 insertion mutation (EGFR D770_N771insNPG) was similar to wild-type EGFR (Applicant's Table 3). The other mutations in Applicant's Table 3 are not relevant to the proposed clinical indication.

The Applicant evaluated the activity of sunvozertinib and DZ0753 in a Eurofins kinase panel of 117 kinases (Pharmacology report 1; Applicant's Table 4). Activity against ErbB family member HER2 was included in the study but is not shown in Applicant's Table 4. Sunvozertinib exhibited an ~30-fold selectivity for EGFR L858R/T90M (IC_{50}= 13 nM) compared to HER2 (IC_{50} = 392 nM). Similarly, DZ0753 exhibited an ~21-fold selectivity for EGFR L858R/T790M compared to

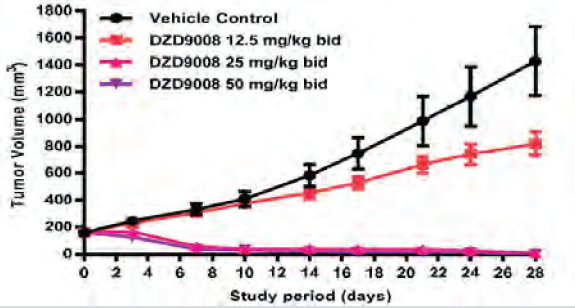
HER2 (IC_{50} = 271 nM). Inhibitory activity against HER3 and EGFR exon 20 insertion mutations were not assessed.

FDA did not review studies in Pharmacology Report 5 investigating the inhibitory effect of sunvozertinib and DZ0753 on insulin growth factor receptor 1 (IGF1R) and insulin receptor (InsR) as they were not relevant to the proposed clinical indication.

In Vivo Studies

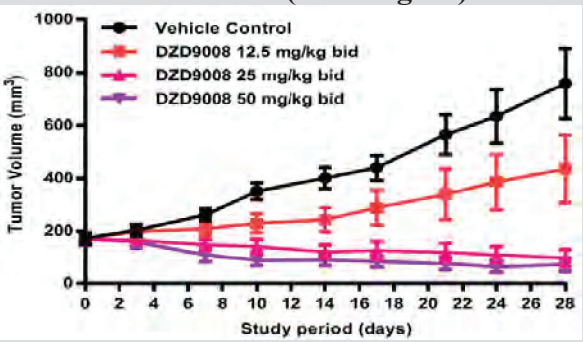
The Applicant investigated the in vivo anti-tumor activity of sunvozertinib in nude mice (6-9/group) implanted subcutaneously (SC) with a human squamous cell carcinoma cell line expressing WT EGFR (A431) or patient-derived NSCLC xenograft models carrying EGFR exon20ins mutations (LU0387 and LU3075). Tumor growth curves for LU0387 and LU3075 models are shown in Figures 2 and 3. In both PDX models, treatment with ≥25 mg/kg led to tumor growth inhibition of >100% (Applicant's Table 8). In contrast, a higher dose of sunvozertinib (50 mg/kg) was needed to cause tumor shrinkage in A431 xenografts expressing WT EGFR. The other xenograft models reported in Applicant's Table 8 are not relevant to the proposed clinical indication.

Figure 2. Anti-tumor Activity of Sunvozertinib (DZD9008) in a Subcutaneous LU0387 NSCLC PDX Model (FDA Figure)



(Excerpted from Applicant's Submission – Pharmacology Report 6)

Figure 3. Anti-tumor Activity of Sunvozertinib (DZD9008) in a Subcutaneous LU3075 NSCLC PDX Model (FDA Figure)



(Excerpted from Applicant's Submission – Pharmacology Report 6)

In the in vivo pharmacokinetic (PK) and pharmacodynamic (PD) relationship of sunvozertinib in xenograft models (Applicant's Figure 1; Pharmacology Report 07), FDA acknowledges that higher doses of sunvozertinib led to higher drug concentrations in the plasma and greater modulation of pEGFR (Tyr1068 and Tyr1173) and pERK (Thr202/Tyr204) relative to control (vehicle) group. FDA also notes that at low doses of sunvozertinib (12.5 mg/kg) pERK was not suppressed relative to control (vehicle) group whereas both pEGFR Tyr1068 and pEGFR Tyr1173 shows some suppression at 2 hours post-dose.

FDA did not review the studies in Pharmacology Report 8 investigating the anti-tumor activity of sunvozertinib in a mouse brain metastasis xenograft model carrying EGFR exon19del (PC-9 model) as it is not relevant to the proposed clinical indication.

Secondary Pharmacology

The Applicant's Position:

Sunvozertinib showed good selectivity in the secondary pharmacology research.

Sunvozertinib and DZ0753 were screened in diverse sets of *in vitro* radioligand binding, enzymatic and functional assays, which covered 101 distinct molecular targets, including different types of receptors, ion channels, transporters, and enzymes (100042609_ESP, 100042610_DSP, 100042828_ESP, 100042830_DSP). In these studies, sunvozertinib was active against 55 targets. The IC_{50} values for these targets were further determined and the results showed that they were 70-fold higher than that for EGFR exon20ins (2.1 nM, Module 2.6.2/Section 1.1). DZ0753 showed similar weak activities against 52 targets with 50-fold higher IC_{50}.

The FDA's Assessment:

The Applicant uses terminology such as "weak" and "good" to describe study results; such terms should be avoided as they are vague, subjective, and promotional.

FDA generally agrees with the Applicant's summary of the secondary pharmacology data but does not agree with the calculations of fold difference between IC_{50} values of EGFR exon20ins and investigated molecular targets. See Tables 5 and 6 for updated fold changes. The unbound C_{max} of sunvozertinib at the recommended human dose of 200 mg calculated by the FDA nonclinical team is ~60 nM. Given the IC_{50} value for inhibition of ALK4 (IC_{50} = 150 nM) is greater than the free C_{max} (~60 nM) at the recommended 200 mg dose, this target is unlikely to be clinically significant for sunvozertinib.

Table 5. Inhibition or Stimulation Effects of Sunvozertinib in Cellular and Nuclear Receptor Functional Assays (FDA Table)

Assay	IC_{50} (M)	IC_{50} (uM)	Fold higher than sunvozertinib IC_{50} for EGFR exon20 ins (2.1 nM)	Fold higher than unbound C_{max} of sunvozertinib at the recommended human dose of 200 mg (60 nM)
EGFR kinase *(h)*	1.70E-08	0.017	8.1	-
ALK4 *(h)* (ACVR1B)	1.50E-07	0.15	71.4	2.50
IRK (*h*) (InsR)	5.10E-07	0.51	242.9	8.50
NK_1*(h)* (agonist radioligand)	9.20E-07	0.92	438.1	15.33
D_1(*h*) (antagonist radioligand)	1.10E-06	1.1	523.8	18.33

(Reviewer generated table from data in Study #100042609 ESP and Study #100042610_DSP)

Table 6. Inhibition or Stimulation Effects of DZ0753 in Cellular and Nuclear Receptor Functional Assays (FDA Table)

Assay	IC_{50} (M)	IC_{50} (uM)	Fold higher than DZ0753 IC50 for EGFR exon20 ins (1.8 nM = 0.0018 uM)
EGFR kinase (*h*)	2.20E-08	0.02	12.2
ALK4 *(h)* (ACVR1B)	1.10E-07	0.11	61.1
IRK *(h)* (InsR)	6.30E-07	0.63	350.0
Src kinase (*h*)	1.40E-06	1.40	777.8

(Reviewer generated table from data in Study #100042828_ESP and Study #100042830_DSP)

Safety Pharmacology

The Applicant's Position:

Safety pharmacology assessments included a hERG assay, evaluations of sunvozertinib's effect on the respiratory system and central nervous system (CNS) in rats at dose levels up to 100 mg/kg via single oral dose, and cardiovascular system in dogs at dose levels up to 30 mg/kg via single oral dose. In addition, cardiovascular system was evaluated in 4-week and 13-week repeated dose toxicity studies in dogs at doses up to 12 and 6 mg/kg/day, respectively (665-0003-EP, 78102-18-461, 78102-18-463, 78102-18-462, 78103-18-327, JXB0024).

Sunvozertinib inhibited the function of hERG channel with an IC_{50} value of 1.21 μM. In addition, sunvozertinib showed no effect on respiratory system, CNS or cardiovascular system in the above studies, indicating that it has a favourable safety profile.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of the safety pharmacology data with the additional pertinent details and notable finding. The unbound C_{max} of sunvozertinib at the recommended human dose of 200 mg calculated by the FDA nonclinical team is ~60 nM, thus the IC_{50} of 1.21 μM for hERG channel inhibition corresponds to a ~20-fold exposure margin. In

Study #78102-220836, the active metabolite DZ0753 inhibited the function of hERG channel with an IC_{50} of 8.18 μM, suggesting low potential for QT prolongation.

5.4 ADME/PK

Data:

Absorption

In vivo PK studies (78104-18-417, 78104-18-418), *in vitro* permeability study (ADME-DIH-220218-Caco-2 BCS), 4-week repeated dose toxicology studies (78103-18-326, 78103-18-327), 13-week repeated dose toxicology studies (JXB0023, JXB0024), reproductive and development toxicology studies (665-0081-DR, 78111-220447)

The absorption rate was moderate in rats, dogs and rabbits with time to reach maximum plasma concentration (t_{max}) between 0.5 and 4 hours. The extent of oral absorption was moderate in rats and dogs with bioavailability of 39.6% and 48.8%, respectively. Sunvozertinib exhibited high passive permeability in biopharmaceutics classification system (BCS) calibrated Caco-2 assay. Sunvozertinib exposure increased approximately in a dose-proportional manner in preclinical PK, general toxicology, and reproductive and development toxicity studies. There was no apparent sex difference in exposure for rats and dogs, and no marked accumulation was observed in these species, which is consistent with its half-life of ~7 hours in rats and 9 to 10 hours in dogs from PK studies.

Distribution

In vitro studies (ADME-DIH-180802-PPB, ADME-DIH-201112-1-Blood Partition), *in vivo* study (DZP/02), quantitative whole-body autography (QWBA) study (DZP/23)

In vitro, sunvozertinib was highly bound to plasma proteins in all species tested. Over the concentration range evaluated, there was a trend for increased unbound fraction of sunvozertinib in a concentration-dependent manner in mouse, rat, rabbit, dog, and human plasma (ranging from 2.18% to 13.3%). The mean blood-to-plasma ratio of sunvozertinib *in vitro* was 0.695, which was considered low partition of sunvozertinib to human blood cells. However, sunvozertinib-derived radioactivity was distributed more to blood cells than to plasma in rats *in vivo*.

The QWBA data indicated that [^{14}C]-sunvozertinib was widely distributed throughout the body in rats after a single oral dose, whereas distribution of radioactivity into CNS tissues was low. The elimination was slow for several tissues in partially pigmented rats (including uveal tract, meninges, eye, spleen, adrenal gland, thyroid gland, pituitary gland, bone marrow, ex-orbital lachrymal gland and thymus), and was not yet complete by 60 days post-dose. Results also suggested sunvozertinib-derived radioactivity had affinity to melanin in partially pigmented rats.

Metabolism

In vitro and *in vivo* metabolism studies (DZP/03, DZP/24)

Biotransformation of sunvozertinib has been examined in hepatocytes of rat and dog (the species used for nonclinical general toxicology studies) and human. The metabolism of sunvozertinib in hepatocytes was primarily to form oxidative and N-dealkylated products with direct

conjugation to a range of glutathione, cysteine-glycine, cysteine and glucuronide metabolites.

Metabolite profiling studies were performed to characterize circulating metabolites after multiple doses of sunvozertinib in rats, dogs, and human. Overall, the data indicated that unchanged sunvozertinib was the primary circulating entity in human, and two human metabolites, including demethylated metabolite DZ0753 and cysteine conjugate metabolite M704, were slightly greater than 10% of the total ultraviolet area. These two metabolites were detected in at least one species in toxicology studies.

Excretion

Rat mass balance studies (DZP/02)

In intact rats, fecal excretion was the major route of elimination of sunvozertinib and its metabolites, whereas urinary excretion was a minor route of elimination. In bile duct cannulation (BDC) rats, biliary excretion is an important route for the elimination of the radioactive dose. Further, *in vivo* metabolism data showed that unchanged sunvozertinib was excreted to a limited extent, indicating metabolism was the major route of elimination. Also, the metabolites of sunvozertinib were primarily excreted via bile in BDC rats.

PK Drug Interactions

In vitro metabolic studies (ADME-DIH-180802-CYP Phenotyping, DZP/25, XF2225), CYP inhibition studies (ADME-DIH-180802-CYP Inhibition, ADME-DIH-180802-CYP TDI, ADME-DIH-201112-CYP TDI, ADME-DIH-CYP K_I/k_{inact}, (b)(4)205087, (b)(4)225091), CYP induction studies (ADME-DIH-180802-CYP Induction, 21DIZAP1R1), transporter substrate studies (ADME-DIH-180802-P-gp Substrate, ADME-DIH-180802-BCRP Substrate, 20DIZAP2), transporter inhibition studies (ADME-DIH-180802-P-gp Inhibition, ADME-DIH-180802-BCRP inhibition, ADME-DIH-180802-SLC inhibition, CYP1958 R15)

CYP mediated drug interaction potential

In vitro, cytochrome P450 (CYP)3A4/5 were the principal CYP enzymes responsible for human metabolism of sunvozertinib. DZ0753 was formed via CYP3A enzyme. Moreover, DZ0753 was predominantly metabolized via glutathione conjugation with CYP metabolism being minimal.

Sunvozertinib was a reversible inhibitor of CYP2D6 and CYP3A4 *in vitro*, but not a time-dependent inhibitor of other CYP isoforms tested. Sunvozertinib induced CYP3A4 and CYP2C8 messenger ribonucleic acid (mRNA) in primary human hepatocytes, but not CYP1A2, CYP2B6, CYP2C9 and CYP2C19.

Transporter mediated drug interaction potential

In vitro, sunvozertinib was a substrate of permeability glycoprotein (P-gp) but not breast cancer resistant protein (BCRP) and organic anion transporting polypeptide (OATP)1B1/3.

Sunvozertinib showed inhibition of P-gp, BCRP, OATP1B1/3, organic cation transport (OCT)2, multidrug and toxin extrusion (MATE)1 and MATE2-K *in vitro*, with identification of potential for *in vivo* inhibition (by calculation/extrapolation) for OATP1B1, P-gp and BCRP using the approaches recommended by FDA *in vitro* drug-drug interaction (DDI) guidance.

The Applicant's Position:

Sunvozertinib has high *in vitro* Caco-2 permeability when active transport is saturated (≥ 30 μM), and an oral bioavailability estimated at 39.6% in rats and 48.8% in dogs, suggesting favorable absorption properties. Exposure generally increases in a dose-proportional manner. No obvious sex difference and marked accumulation were observed following repeated oral dosing.

Sunvozertinib is highly plasma protein bound across species, with a high volume of distribution in rat and dog, indicating extensive distribution outside of body water. In a QWBA study with albino and partially pigmented rats, [^{14}C]-sunvozertinib-derived radioactivity was widely distributed throughout the body, particularly with the tissues containing melanin.

All notable human metabolites identified were also found in rat and dog hepatocytes. DZ0753 was not considered as a major metabolite as it presented less than 10% of drug related materials in plasma from human mass balance study, as well as similar pharmacology activity and plasma binding as sunvozertinib.

Excretion of sunvozertinib was primarily as metabolites via the biliary/fecal route.

As a victim of DDI, sunvozertinib exposure may be affected by coadministration with CYP3A4/5 inhibitors or inducers.

As a perpetrator of DDI at clinically relevant doses, sunvozertinib induced CYP3A4 and CYP2C8 mRNA expression *in vitro*, possibly through pregnane X receptor (PXR). Activation of PXR may induce the expression of transporter such as P-gp. Sunvozertinib itself has the potential for hepatic OATP1B1, intestinal P-gp and BCRP inhibition.

The FDA's Assessment:

FDA generally agrees with the Applicant's summaries of the nonclinical ADME/PK data, with additional notable findings described below. All the in vitro PK drug-drug interaction studies (e.g., cytochrome P450 metabolism and transporter studies) were reviewed by FDA's clinical pharmacology team; see Section 6 for FDA's assessment of these studies.

Type of Study	Major Findings
Absorption	
Pharmacokinetic of DZD9008 in Wistar Han Rats Following Oral and Intravenous Administration at Different Dose Levels/ 78104-18-417	• No sex differences were observed. • Following a single oral administration at 3 mg/kg, the mean absolute bioavailability (F = PO AUC_{inf} / IV AUC_{inf}) was calculated by FDA to be 39.6%. • Following a 7-day repeated once daily oral dosing at 9 mg/kg, there is no marked accumulation for AUC_{0-t} and C_{max} after repeated dose.
Sunvozertinib Combined Male and Female PK Parameters Following Single or Multiple Dose to Rats	

Dose (mg/kg)	Route of administration	Dose frequency	t_{max} (hr)	C_{max} (μM)	AUC_{0-t} (μM·hr)	AUC_{inf} (μM·hr)	$t_{1/2}$ (hr)	CL (mL/min/kg)	V_{ss} (L/kg)
3	IV	Single	-	-	2.67	2.8	6.37	30.8	13.6
3	PO	Single	4	0.12	1.02	1.11	6.84	-	-
9	PO	Single	4	0.34	3.7	3.87	6.77	-	-
27	PO	Single	3	1.01	10.8	10.9	6.77	-	-
9 (D1)	PO	Single	4	0.34	2.91	NA[a]	NA[a]	-	-
9 (D7)	PO	Multiple	4	0.51	4.71	NA	NA	-	-

All results are average value from male and female rats; results are expressed as mean (n = 3/sex) except for t_{max} which is expressed as median (n =3/sex); NA: not applicable; D1= day 1; D7 = day 7; [a]: not calculated because only two PK points were detected after the C_{max}; IV Dosing Vehicle: 5% DMSO, 95% SBE-β-CD (30%, w/v) in water; PO Dosing Vehicle: 0.5% HPMC, 0.1% Tween 80 in water.

(Adapted from Applicant's Submission)

Pharmacokinetics of DZD9008 in Beagle Dogs Following Oral and Intravenous Administration at Different Dose Levels / 78104-18-418	• No sex differences were observed. • Following a single oral administration at 1 mg/kg, the mean absolute bioavailability (F = PO AUC_{inf} / IV AUC_{inf}) was calculated by FDA to be 51.1%. • Following a 7-day repeated once daily oral dosing at 9 mg/kg, there is no marked accumulation for AUC_{0-t} and C_{max} after repeated dose.

Sunvozertinib Combined Male and Female PK Parameters Following Single or Multiple Dose to Dogs

Dose (mg/kg)	Route of administration	Dose frequency	t_{max} (hr)	C_{max} (μM)	AUC_{0-t} (μM·hr)	AUC_{inf} (μM·hr)	$t_{1/2}$ (hr)	CL (mL/min/kg)	V_{ss} (L/kg)
1	IV	Single	-	-	0.75	0.94	13.9	30.9	29.5
1	PO	Single	2	0.05	0.37	0.48	9.07	-	-
3	PO	Single	2	0.18	1.15	1.40	10.5	-	-
9	PO	Single	1.5	0.42	3.18	3.39	8.72	-	-
3 (D1)	PO	Single	2	0.14	0.91	1.11	10.7	-	-
3 (D7)	PO	Multiple	3	0.09	0.94	NA	NA	-	-

All results are averaged value from male and female rats; results are expressed as mean (n = 3/sex) except for t_{max} which is expressed as median (n =3/sex); NA: not applicable; D1 = day 1; D7 = day 7; IV Dosing Vehicle: 5% DMSO, 95% SBE-β-CD (30%, w/v) in water; PO Dosing Vehicle: 0.5% HPMC, 0.1% Tween 80 in water.

(Adapted from Applicant's Submission)

Distribution

Determination of *in vitro* Binding of DZD9008 and DZ0753 to Plasma Proteins in the Mouse, Rat, Dog and Human, as well as Human Serum Albumin and Human α1-acid Glycoprotein Solutions / ADME-DIH-180802-PPB and ADME-DIH-211124-PPB	• Plasma protein binding of metabolite DZ0753 was concentration-dependent in mouse and rat plasma, but concentration-independent in rabbit, dog, and human plasma • Sunvozertinib and the metabolite DZ0753 were 91.46% and 91.62%, respectively, bound to human plasma protein at 1 μM, which is the more relevant concentration based on the mean C_{max} (412 ng/mL; ~0.71 μM) in patients given 200 mg sunvozertinib
Non-Clinical Metabolism Study (Absorption, Distribution, Metabolism and Excretion Studies Following a Single Oral or Intravenous Dose Administration of [^{14}C]-DZD9008 to Male and Female Rats) / DZP/02	• Wistar Han rats (n=3/sex) received a single oral administration of 10 mg/kg [^{14}C]-sunvozertinib • No sex difference in the exposure of both sunvozertinib or radioactivity was observed in male and female rats • Up to 6 hours post-dose, blood-to-plasma ratios ranged between 0.72 and 2.58, increasing up to 7.81 at 48 hours post-dose

Tissue Distribution Following a Single Oral Dose of [^{14}C]-DZD9008 to Male and Female Rats / DZP/23	• Single oral administration of 10 mg/kg [^{14}C]-sunvozertinib (target radioactivity of 100 µCi/kg) to albino Wistar Han rats (n=3/sex, n=1/timepoint) and partially pigmented male Lister Hooded rats (n=8) • In all studies, radioactivity in the brain and spinal cord remained below the limit of quantification, indicating that drug-related material has low tendency to cross the blood-brain barrier

Tissues With ≥ 10 µg · equivilants/g of Sunvozertinib at Peak Concentration Time Following a Single Oral Administration of [^{14}C]-Sunvozertinib to Non-Pigmented Rats

Tissue (Males)	TRA concentration (µg·equivalent/g)		
	2 hours	6 hours	24 hours
Small intestine contents	177#	132#	3.99
Stomach contents	137#	157#	BLQ
Caecum contents	64.1#	141#	13.5
Liver	15.8	9.75	3.95
Kidney: Medulla	12.5	7.80	3.83
Spleen	12.4	16.7	5.44
Small intestine mucosa	12.2	8.61	1.73
Kidney: Cortex	11.9	6.79	2.52
Kidney: Whole	11.8	7.30	3.17
Adrenal gland	11.4	6.20	2.53
Forestomach mucosa	10.9	4.14	1.14
Lung	10.9	7.70	1.44

Tissue (Females)	TRA concentration (µg·equivalent/g)		
	2 hours	6 hours	24 hours
Small intestine contents	191#	218#	9.56
Caecum contents	1.85	185#	33.1
Stomach contents	355#	183#	BLQ
Large intestine contents	BLQ	158#	82.2#
Spleen	8.76	26.7	8.90
Ex-orbital lachrymal gland	1.96	15.9	8.41
Lung	5.85	15.3	3.55
Pineal body	NS	14.3	4.86
Salivary gland	3.65	14.2	3.03
Thyroid gland	3.94	12.9	3.49
Liver	13.5	12.5	5.11
Pituitary gland	4.50	11.4	8.54
Adrenal gland	7.12	10.6	3.95
Bone marrow	2.63	10.6	4.90
Kidney: Medulla	5.15	10.5	3.83

Peak concentration time was 2-6 hours for males and 6 hours for females; TRA: Total radioactivity; # : Above upper limit of accurate quantification (>53.5 µg equivalents/g); BLQ: Below lower limit of accurate quantification (<0.073 µg equivalents/g); NS: No sample- tissue not sectioned

(Adapted from Applicant's Submission)

Tissues with ≥ 5 µg · equivilants/g of Sunvozertinib at Peak Concentration Time Following a Single Oral Administration of [^{14}C]-Sunvozertinib to Pigmented Rats

Tissues	TRA concentration (µg·equivalent/g)		
	2 hours	6 hours	24 hours
Caecum contents	31.6	167#	21.3
Small intestine contents	201#	33.4	4.64
Adrenal gland	6.50	13.0	2.19
Pituitary gland	3.83	12.3	5.66
Spleen	8.06	12.0	3.10
Eye: uveal tract	2.64	10.6	20.2
Large intestine mucosa	1.03	9.66	5.04
Lung	6.25	9.56	0.711
Small intestine mucosa	18.8	7.40	1.28
Kidney: medulla	6.02	6.76	2.54
Pineal body	NS	6.52	2.15
Bone marrow	2.99	6.34	1.24
Kidney: whole	5.91	6.26	2.09
Kidney: cortex	6.12	5.99	1.55
Ex-orbital lachrymal gland	1.80	5.98	1.43
Thyroid gland	5.48	5.80	1.28
Salivary gland	4.04	5.48	0.922
Liver	9.56	5.41	1.81

Peak concentration time was 2-24 hours; TRA: Total Radioactivity; # : Above upper limit of accurate quantification (>53.5 µg equivalents/g); BLQ: Below lower limit of accurate quantification (<0.073 µg equivalents/g); NS: No sample- tissue not sectioned

(Adapted from Applicant's Submission)

Metabolism

Investigation of Hepatocyte Metabolism in Rat, Dog and Human / DZP/03	• Metabolism of sunvozertinib was evaluated after a 2-hour incubation of sunvozertinib with cryopreserved rat, dog, and human hepatocytes via HPLC and LC-MS/MS analyses ○ There was no unique human metabolite

Metabolism of Sunvozertinib (DZD9008) by Rat, Dog, and Human Hepatocytes

Component[a]	Rat	Dog	Human
DZD9008	✓	✓	✓
M888: Glutathione conjugate of DZD9008 (+ 305 amu)	✓	✓#	✓#
M748: Tentative cysteine-glycine conjugate of N-dealkylated, mono-hydroxy, keto metabolite of DZD9008	✓	✓#	✓#
M762: Tentative cysteine-glycine conjugate of N-dealkylated, O-methoxy keto metabolite of DZD9008	✓	✓#	×
M746: Tentative cysteine-glycine conjugate of N-dealkylated, mono-hydroxy, desaturated metabolite of DZD9008	✓	✓	×
M296: DZD9008 half molecule	✓	✓	✓
M759: Glucuronide conjugate of DZD9008	✓	✓	✓
M890: Glutathione conjugate of DZD9008 (+ 307 amu)[$]	✓	✓	✓
M486: N-dealkylated DZD9008	✓	✓	✓
M599: DZD9008 N-oxide	✓	✓	✓
M704: Cysteine conjugate of DZD9008	✓	✓	✓
M530: Tentative bis-N-dealkylated, oxidative deaminated, O-methyl catechol DZD9008	✓	✓	✓#
M569: N-demethylated DZD9008 (DZ0753)	✓	✓	✓
M525: Tentative N-dealkylated, bis-desaturated DZD9008	✓	✓	✓

as detected by LC-MS/MS; x not detected by LC-MS/MS

(Excerpted from Applicant's Submission)

Screening, semi-quantification and identification of metabolites of	• Plasma samples from humans (clinical study DZ2019E0001; dose = 300 mg), rats (13-week toxicology study JXB0023; dose = 35

DZD9008 in human, rat and dog plasma / DZP/24	mg/kg), and dogs (13-week toxicology study JXB0024; dose = 6 mg/kg) were evaluated semi-quantitatively via UV peak comparison and/or LC-MS/MS analyses • Two human metabolites were present at >10% by UV (DZ0753=10.3%; M704=12.2%). DZ0753 was also present in rat and dog plasma and M704 was also present in rat plasma. • M704 is not expected to be pharmacologically active due to conjugation of cysteine to the acrylamide moiety of sunvozertinib.
Absorption, Distribution, Metabolism and Excretion Studies Following a Single Oral or Intravenous Dose Administration of [^{14}C]-DZD9008 to Male and Female Rats / DZP/02	• Wistar Han rats (n=3/sex) received a single oral administration of 10 mg/kg [^{14}C]-sunvozertinib • No sex difference in the exposure of either sunvozertinib or radioactivity was observed in male and female rats; therefore, the below table represents the mean of male and female [^{14}C]-sunvozertinib recovery data

Excretion of Sunvozertinib (DZD9008) Following Single Oral or Intravenous Dose of [^{14}C]-Sunvozertinib

Route of Administration	[^{14}C]-DZD9008 Recovery (%)				
	Bile	Urine	Feces	Cage Wash	Carcass
Oral	-	1.3	88.7	0.4	1.4
Intravenous	-	3.8	85.3	0.6	3.0
Intravenous (bile duct-cannulated)	56.5	8.1	16.1	0.8	9.0

(Adapted from Applicant's Submission)

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

A series of general toxicology studies in compliance with GLP have been completed, including single-dose oral toxicity studies in Wistar Han rats and Beagle dogs, 4-week and 13-week repeated dose toxicity and toxicokinetics studies in Wistar Han rats and Beagle dogs with 4-week recovery. In addition, two non-GLP studies were completed, including a 4-week oral repeated dose range finding (DRF) study in Wistar Han rats, and a 14-day oral repeated dose range finding study in Beagle dogs.

Toxicities of sunvozertinib and their reversibilities were evaluated in rats and dogs. Changes observed in repeated-dose GLP studies showed that the toxicities were generally dose-related and reversible. Dose-limiting toxicity was gastrointestinal (GI) tract effects (including diarrhea, low food consumption and body weight loss), consistent with clinical symptoms in human. The main target organs were GI tract, eyes, skin, lungs, and immune organs, etc. The toxicological profile of chronic dosing (13 weeks) was similar to that of short-term dosing (4 weeks). Dogs were more sensitive to sunvozertinib than rats in terms of exposure and dose (converted by body surface area), but clinical symptoms were similar in both species (except that skin abnormality was only observed in rats).

The major abnormal changes of sunvozertinib in rats and dogs were consistent with consequences of the pharmacological inhibition of wild type EGFR by sunvozertinib or sequelae of primary effects.

5.5.1.1 Single Dose Toxicology

Study Title (Number): An Acute Toxicity Study of DZD9008 following Oral Gavage with a 14-Day Observation Period in Wistar Han Rats (78103-18-342)

Key Study Findings

- Male and female rats were oral administered once (gavage) with sunvozertinib at 100, 200 or 400 mg/kg. The maximum tolerated dose is 400 mg/kg.
- Transient gastrointestinal tract findings, including abnormal feces, body weight loss and inappetence, were noted at ≥ 200 mg/kg.
- Increases of reticulocyte count were noted at 400 mg/kg.
- Increased liver and spleen weights were noted in females at 400 mg/kg, but lack of correlated gross pathology and clinical pathology changes.

GLP compliance: Yes

Study Title (Number): An Acute Toxicity Study of DZD9008 following Oral Gavage with a 14-Day Observation Period in Beagle Dogs (78103-18-343)

Key Study Findings

- Male and female dogs were orally administered once (gavage) with sunvozertinib at 30, 75 or 150 mg/kg. The maximum tolerated dose is 150 mg/kg.
- Gastrointestinal tract findings, including emesis and low body weight gain, were noted at 150 mg/kg.
- Organ weight changes, including slight decreases in thymus weight and slight increases in thyroid weight, were noted in males ≥ 75 mg/kg. Gross pathology changes, including diffused dark red and focal yellowish in cecum mucosa, were noted in males at 75 mg/kg.

GLP compliance: Yes

5.5.1.2 Repeated Dose Toxicology

Study Title (Number): DZD9008 - 13 Week Oral (Gavage) Toxicity Study in the Rat with a 4 Week Treatment-Free Period (JXB0023)

Key Study Findings

- Male and female rats were orally administered (gavage) with sunvozertinib at 15, 25 or 35 mg/kg/day. The no observed adverse effect level (NOAEL) is 35 mg/kg/day.
- Microscopic findings were seen in the mesenteric lymph nodes (increased sinusoidal

macrophages and erythrophagocytosis), mammary gland (atrophy– male only) and lungs (accumulation of foamy macrophages).

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	15, 25 and 35 mg/kg/day, once daily for 13 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxypropyl methylcellulose (HPMC) (w/v) with 0.1% Tween 80 (v/v) in water
Species/Strain:	Crl:WI (Han) rat
Number/Sex/Group:	Main study: 10 rats/sex/group; recovery (control and high dose group only): 5 rats/sex/group; toxicokinetic: 3 rats/sex for control group, 5 rats/sex/group for sunvozertinib treated groups.
Age:	6-7 weeks
Satellite groups:	Toxicokinetic and metabolites in safety testing (MIST) assessment

Observations and Results: changes from control

Mortality	No sunvozertinib related mortality.
Clinical signs	Increased incidence of flaky tails, tail ridging and head scabbing at 35 mg/kg/day from Day 66 and persisted for most animals until the end of dosing or recovery phase.
Body weight	Reversible lower body weight gain than controls were observed in males (25 and 35 mg/kg/day) and females (all doses).
Food consumption	No drug related finding.
Ophthalmoscopy	No drug related finding.
Hematology	Slight decreases in red blood cell, haemoglobin and hematocrit were noted at the end of dosing phase. Besides, increases in white blood cell, neutrophil, reticulocyte and platelet were noted. Above changes were reversible.

% difference compared to controls by end of dosing phase and recovery phase

Dose (mg/kg/day)		15		25		35	
Sex		M	F	M	F	M	F
White blood cell	Week 13[a]	+5%	+21%	+9%	+7%	+11%	+38%**
	Week 17[b]	-	-	-	-	+7%	-9%
Neutrophil	Week 13	+8%*	+62%*	+13%**	+105%**	+55%***	+226%***
	Week 17	-	-	-	-	+36%	+42%
Red blood cell	Week 13	-1%	-2%	-2%	-5%*	-1%	-3%*
	Week 17	-	-	-	-	-1%	-1%
Haemoglobin	Week 13	-	-4%**	-4%**	-7%***	-6%***	-5%***
	Week 17	-	-	-	-	-2%	-1%
Hematocrit	Week 13	-	-3%*	-3%**	-6%**	-4%**	-4%**
	Week 17	-	-	-	-	-2%	-1%
Reticulocyte	Week 13	-	-	-	-	+13%*	+7%
	Week 17	-	-	-	-	+7%	+11%
Platelet	Week 13	+15%*	+11%	+6%*	+17%	+19%**	+17%
	Week 17	-	-	-	-	+5%	+7%

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$ [a]: Week 13 is the end of dosing phase. [b]: Week 17 is the end of recovery phase.

Coagulation	No drug related finding.
Clinical	Slight increases in alanine aminotransferase (ALT), creatinine and urea were noted at the end

Chemistry

of dosing phase. These changes were reversible.

% difference compared to controls by end of dosing phase and recovery phase							
Dose (mg/kg/day)		15		25		35	
Sex		M	F	M	F	M	F
ALT	Week 13	+9%	+13%	+15%*	+27%**	+27%***	+40%***
	Week 17	-	-	-	-	+12%	-7%
Creatinine	Week 13	+13%*	+18%**	+20%*	+30%***	+7%*	+21%***
	Week 17	-	-	-	-	+11%	+2%
Urea	Week 13	-	+9%	+12%*	+14%**	+10%*	+16%**
	Week 17	-	-	-	-	+8%	+5%

*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$. Week 13 is the end of dosing phase; week 17 is the end of recovery phase.

Urinalysis

Reversible slight increases in specific gravity were noted in males at 35 mg/kg/day and females at 25 mg/kg/day at the end of dosing phase.

Dose (mg/kg/day)		15		25		35	
Sex		M	F	M	F	M	F
Specific gravity	Week 13	-	-	-	+0.8%*	+0.8%*	-
	Week 17	-	-	-	-	-	-

*: $p < 0.05$. Week 13 is the end of dosing phase; week 17 is the end of recovery phase.

Gross pathology

Ridged tail and abnormal coloration in mesenteric lymph nodes were noted in males and females at 35 mg/kg/day, and females at 25 mg/kg/day at the end of dosing phase. At the end of the recovery phase, the tail abnormalities persisted for those previously give sunvozertinib.

Organ weight

Decreased weights of liver and kidney were noted in males and females at all dose levels at the end of dosing phase. Decreased weights of spleen were noted in males at all dose levels at the end of dosing phase. Above changes were reversible.

Histopathology

Refer to Table 9 for histopathology findings. The main target organs included mesenteric lymph nodes (increased sinusoidal macrophages and erythrophagocytosis), mammary glands (atrophy, male only) and lungs (accumulation of foamy macrophages). The former finding was fully reversible, and the lung and male mammary gland findings showed partial reversibility, considered likely to become complete with a slightly longer recovery period.

Toxicokinetics

- Systemic exposure of sunvozertinib (C_{max} and AUC_{0-24}) increased in a broadly dose proportional manner.
- There was no sex difference or accumulation.

TK parameters refer to Table 10.

Table 9 Histopathology Findings in 13-Week Rat Toxicity Study

Dose (mg/kg/day)	0		15		25		35	
Sex	M	F	M	F	M	F	M	F
Animal Number Evaluated (End of Dosing Phase)	10	10	10	10	10	10	10	10
Mesenteric lymph nodes								
Erythrophagocytosis (Total)	(2)	(0)	(5)	(3)	(6)	(6)	(9)	(7)
Minimal	2	0	5	3	4	3	5	5
Slight	0	0	0	0	2	2	3	2
Moderate	0	0	0	0	0	1	1	0
Increased sinusoidal macrophages (Total)	(0)	(0)	(0)	(0)	(0)	(0)	(10)	(5)
Minimal	0	0	0	0	0	0	3	3
Slight	0	0	0	0	0	0	7	2

Dose (mg/kg/day)	0		15		25		35	
Sex	M	F	M	F	M	F	M	F
Mammary Gland								
Atrophy (Total)	(2)	(0)	(4)	-	(9)	-	(10)	(0)
Slight	1	0	1	-	2	-	0	0
Moderate	0	0	3	-	3	-	5	0
Marked	1	0	0	-	4	-	5	0
Lungs								
Accumulation of foamy macrophages (Total)	(0)	(1)	(4)	(5)	(2)	(6)	(2)	(8)
Minimal	0	1	4	4	1	5	0	5
Slight	0	0	0	1	1	1	2	2
Moderate	0	0	0	0	0	0	0	1
Animal Number Evaluated (End of Recovery Phase)	5	5	0	0	0	0	5	5
Lungs								
Accumulation of foamy macrophages (Total)	(1)	(0)	(0)	(0)	(0)	(0)	(3)	(2)
Minimal	1	0	0	0	0	0	2	1
Slight	0	0	0	0	0	0	1	1
Mammary Gland								
Atrophy (Total)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(2)
Slight	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	0	1

Source: Applicant Table.

Table 10 TK Parameters of Sunvozertinib in 13-Week Rat Toxicity Study

Dose Phase	Toxicokinetic Parameters [a]	Dose(mg/kg/day)					
		15	25	35	15	25	35
		Male	Male	Male	Female	Female	Female
Day 1	T_{max} (hr)	4.0	2.0	2.0	4.0	2.0	2.0
	C_{max} ± SE (μmol/L)	0.27±0.02	0.47±0.06	0.83±0.15	0.32±0.05	0.57±0.11	0.59±0.19
	AUC_{0-24} ± SE (hr*μmol/L)	3.15±0.30	5.53±0.39	9.01±0.30	3.29±0.62	5.82±0.27	7.86±0.99
Day 87	T_{max} (hr)	2.0	4.0	4.0	4.0	2.0	4.0
	C_{max} ± SE (μmol/L)	0.28±0.09	0.60±0.08	0.75±0.15	0.32±0.02	0.69±0.02	0.71±0.04
	AUC_{0-24} ± SE (hr*μmol/L)	3.89±0.30	9.02±0.93	10.9±1.05	3.84±0.37	7.91±0.69	9.81±0.51

Source: Applicant Table.
[a]:C_{max} (μmol/L) = ng/mL/(584.09 g/mol), AUC_{0-24} (μmol*h/L) =ng*h/mL/(584.09 g/mol).

Study Title (Number): A 28-Day Oral Toxicity and Toxicokinetic Study of DZD9008 with a

28-Day Recovery Period in Wistar Han Rats (78103-18-326)

Key Study Findings

- Male and female rats were orally administered (gavage) with sunvozertinib at 25, 50/15 or 65/35 mg/kg/day. The NOAEL is 35 mg/kg/day. Animals were dosed at 25, 50 or 65 mg/kg/day at the beginning. The dose level of 50 and 65 mg/kg/day were paused due to inappetence and body weight loss, and then reduced to 15 and 35 mg/kg/day from Day 15, respectively. Dose levels of 15 and 35 mg/kg/day were dosed for 28 consecutive days then followed with a 28-day recovery period.
- Reversible and dose dependent abnormal stool, body weight loss and low food intake were noted at 25, 50 and 65 mg/kg/day.
- Microscopic findings were seen in the lungs (infiltration of macrophages) and pancreas (fibrosis and infiltration of pigment-laden macrophages).

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	25, 50/15 and 65/35 mg/kg/day, once daily for 28 days (42 days for 25 mg/kg/day, 28 days for 15 and 35 mg/kg/day, up to 6 days for 50 and 65 mg/kg/day).
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxypropyl methylcellulose (HPMC) (w/v) with 0.1% Tween 80 (v/v) in sterile water for injection
Species/Strain:	Wistar Han rat
Number/Sex/Group:	Main study: 10 sex/group; recovery: 5 sex/group; toxicokinetics: 8 sex/group for sunvozertinib treated groups and 4 sex/group for control group.
Age:	8-10 weeks
Satellite groups:	Toxicokinetic assessment

Observations and Results: changes from control

Mortality	No sunvozertinib related mortality.
Clinical signs	Reversible and dosage related abnormal stool was noted in both sexes, including soft stool at 25, 50 and 65 mg/kg/day, loose feces at 50 and 65 mg/kg/day, and yellow staining at ≥ 25 mg/kg/day.
Body weight	Reversible body weight loss was noted at 25, 50 and 65 mg/kg/day in both sexes mainly in the first week of dosing phase.
Food consumption	Reversible lower food consumption than concurrent controls was noted at 25, 50 and 65 mg/kg/day in both sexes at first week of dosing phase.
Ophthalmoscopy	Persistent pupillary membrane, iris synechia and pinpoint multifocal opacity of anterior lens capsule were noted at the end of dosing phase. Above changes were not persisted at the end of recovery phase.

Dose (mg/kg/day)	25		50/15		65/35	
Sex	M	F	M	F	M	F
Animal Evaluated (end of dosing phase)	10	10	10	10	10	10
Animal with findings						
Persistent pupillary membrane	-	-	-	2	2	-
Iris synechia	1	-	-	-	1	-
Pinpoint multifocal opacity of anterior lens capsule	-	-	-	-	1	-
Animal Evaluated (end of recovery phase)	5	5	5	5	5	5

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<tr><td>Animal with findings</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
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</td></tr>
<tr><td>Hematology</td><td>
Reversible decreases of red blood cell, hematocrit and hemoglobin were noted in both sexes in all treatment groups.
<table>
<tr><td>Dose (mg/kg/day)</td><td colspan="2">25</td><td colspan="2">50/15</td><td colspan="2">65/35</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>M</td><td>F</td><td>M</td></tr>
<tr><td>End of dosing phase</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Red blood cell</td><td>-4%</td><td>-4%</td><td>-4%</td><td>-2%</td><td>-8%**</td><td>-4%</td></tr>
<tr><td>Hematocrit</td><td>-3%</td><td>-5%</td><td>-3%</td><td>-1%</td><td>-7%**</td><td>-6%*</td></tr>
<tr><td>Hemoglobin</td><td>-4%</td><td>-6%*</td><td>-3%</td><td>-2%</td><td>-9%*</td><td>-6%*</td></tr>
<tr><td>End of Recovery Phase</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
*: $p < 0.05$, **: $p < 0.01$
</td></tr>
<tr><td>Coagulation</td><td>No drug related finding.</td></tr>
<tr><td>Clinical Chemistry</td><td>
Reversible decreases of albumin and total protein were noted in both sexes in all treatment groups.
<table>
<tr><td>Dose (mg/kg/day)</td><td colspan="2">25</td><td colspan="2">50/15</td><td colspan="2">65/35</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>M</td><td>F</td><td>M</td></tr>
<tr><td>End of dosing phase</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Albumin</td><td>-6%**</td><td>-10%**</td><td>-5%**</td><td>-6%</td><td>-9%**</td><td>-15%**</td></tr>
<tr><td>Total protein</td><td>-3%</td><td>-5%</td><td>-3%</td><td>-2%</td><td>-4%</td><td>-8%*</td></tr>
<tr><td>End of Recovery Phase</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
*: $p < 0.05$, **: $p < 0.01$
</td></tr>
<tr><td>Urinalysis</td><td>No drug related finding.</td></tr>
<tr><td>Gross pathology</td><td>No drug related finding.</td></tr>
<tr><td>Organ weight</td><td>No drug related finding.</td></tr>
<tr><td>Histopathology</td><td>
Histopathology changes were noted in lung and pancreas at the end of dosing phase. At the end of recovery phase, changes in lung fully recovered; however, changes in pancreas (fibrosis) still exist, besides, minimal or mild infiltration of pigment- laden macrophages were observed in pancreas of male animals at all dose levels.
<table>
<tr><td>Dose (mg/kg/day)</td><td colspan="2">0</td><td colspan="2">25</td><td colspan="2">50/15</td><td colspan="2">65/35</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>Animal Number Evaluated (End of Dosing Phase)</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>Lung with mainstem bronchi</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Infiltration, alveolar macrophages (Total)</td><td>(0)</td><td>(0)</td><td>(5)</td><td>(4)</td><td>(5)</td><td>(1)</td><td>(5)</td><td>(6)</td></tr>
<tr><td>Minimal</td><td>0</td><td>0</td><td>5</td><td>4</td><td>5</td><td>1</td><td>5</td><td>6</td></tr>
<tr><td>Pancreas</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Fibrosis (Total)</td><td>(0)</td><td>(0)</td><td>(2)</td><td>(0)</td><td>(1)</td><td>(0)</td><td>(4)</td><td>(0)</td></tr>
<tr><td>Minimal</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Mild</td><td>0</td><td>0</td><td>1</td><td>0</td><td>1</td><td>0</td><td>3</td><td>0</td></tr>
<tr><td>Number Evaluated (End of Recovery Phase)</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td><td>5</td></tr>
<tr><td>Pancreas</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Fibrosis (Total)</td><td>(0)</td><td>(0)</td><td>(2)</td><td>(0)</td><td>(1)</td><td>(0)</td><td>(0)</td><td>(0)</td></tr>
<tr><td>Minimal</td><td>0</td><td>0</td><td>2</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Mild</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Pigment-laden macrophage (Total)</td><td>(0)</td><td>(0)</td><td>(2)</td><td>(0)</td><td>(2)</td><td>(0)</td><td>(1)</td><td>(0)</td></tr>
<tr><td>Minimal</td><td>0</td><td>0</td><td>2</td><td>0</td><td>2</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Mild</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
</table>
</td></tr>
</table>

Toxicokinetics	• Systemic exposure of sunvozertinib (C_{max} and AUC_{0-24}) increased in a broadly dose proportional manner. • There was no notable sex difference or accumulation. TK parameters refer to Table 11.

Table 11 TK Parameters in 4-Week Rat Study

Dose Phase	Day 1						Day 42					
Sex	Male			Female			Male			Female		
Dose (mg/kg/day)	25	50	65	25	50	65	25	15	35	25	15	35
T_{max} (hr)	4.0	4.0	4.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
C_{max} ± SD (μmol/L)	0.82± 0.06	1.32± 0.16	1.74± 0.23	0.73± 0.22	1.70± 0.10	2.09± 0.24	1.04± 0.09	0.62± 0.06	1.32± 0.10	1.04± 0.07	0.87± 0.08	1.46± 0.12
AUC_{last} ±SD (hr*μmol/L)	9.41± 0.66	18.9± 1.30	24.7± 1.94	8.57± 0.65	19.0± 0.78	29.2± 1.88	11.4± 0.53	6.29± 0.21	16.6± 1.15	9.99± 0.44	6.40± 0.35	16.9± 1.00

Source: Applicant Table.

Study Title (Number): DZD9008 - 13 Week Oral (Gavage) Toxicity Study in the Dog with a 4 Week Treatment-Free Period (JXB0024)

Key Study Findings

- Male and female dogs were orally administered (gavage) with sunvozertinib at 1, 3 or 6 mg/kg/day. The NOAEL is 6 mg/kg/day.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	1, 3 and 6 mg/kg/day, once daily for 13 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxypropyl methylcellulose (HPMC) (w/v) with 0.1% Tween 80 (v/v) in water
Species/Strain:	Beagle dog
Number/Sex/Group:	Main study: 3 sex/group; recovery (control and high dose group only): 2 sex/group
Age:	9 months
Satellite groups:	No

Observations and Results: changes from control

Mortality	No sunvozertinib related mortality.
Clinical signs	Reversible abnormal feces, including loose or liquid feces, abnormal colored feces and gelatinous feces, were noted at 3 and/or 6 mg/kg/day.
Body weight	No drug related finding.
Food consumption	No drug related finding.
Ophthalmoscopy	No drug related finding.
ECG	No drug related finding.
Hematology	Reversible slight changes of red blood cell, haemoglobin and hematocrit were noted in

<table>
<tr><td></td><td>both sexes at 6 mg/kg/day at the end of dosing phase.
<table>
<tr><td colspan="2">Dose (mg/kg/day)</td><td colspan="2">1</td><td colspan="2">3</td><td colspan="2">6</td></tr>
<tr><td colspan="2">Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>Red blood cell</td><td>Week 13</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-9.1%</td><td>-9.7%</td></tr>
<tr><td>Haemoglobin</td><td>Week 13</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-10.1%</td><td>-8.1%</td></tr>
<tr><td>Hematocrit</td><td>Week 13</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-9.5%</td><td>-6.5%</td></tr>
</table>
Week 13 is the end of dosing phase.</td></tr>
<tr><td>Coagulation</td><td>No drug related finding.</td></tr>
<tr><td>Clinical Chemistry</td><td>Reversible slight decreases of potassium and albumin were noted in males ≥ 3 mg/kg/day and females ≥ 1 mg/kg/day at the end of dosing phase.
<table>
<tr><td colspan="2">Dose (mg/kg/day)</td><td colspan="2">1</td><td colspan="2">3</td><td colspan="2">6</td></tr>
<tr><td colspan="2">Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>K</td><td>Week 13</td><td>-</td><td>-5.7%</td><td>-5.7%</td><td>-11.2%</td><td>-</td><td>-7.9%</td></tr>
<tr><td>Albumin</td><td>Week 13</td><td>-</td><td>-5.2%</td><td>-9.6%</td><td>-8.0%</td><td>-24.1%</td><td>-18.4%</td></tr>
</table>
Week 13 is the end of dosing phase.</td></tr>
<tr><td>Urinalysis</td><td>No drug related finding</td></tr>
<tr><td>Gross pathology</td><td>Reversible various changes in the lungs were noted at the end of dosing phase.
<table>
<tr><td>Dose (mg/kg/day)</td><td colspan="2">0</td><td colspan="2">1</td><td colspan="2">3</td><td colspan="2">6</td></tr>
<tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr>
<tr><td>Animal Number (End of dosing phase)</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td><td>3</td></tr>
<tr><td>Lung</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Abnormal colour (Total)</td><td>(0)</td><td>(1)</td><td>(1)</td><td>(1)</td><td>(0)</td><td>(1)</td><td>(2)</td><td>(1)</td></tr>
<tr><td>General</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Right cranial lobe</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Left cranial lobe</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td></tr>
<tr><td>Left median lobe</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>Right caudal lobe</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Abnormal area (Total)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(1)</td></tr>
<tr><td>Left median lobe</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Abnormal consistency (Total)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(0)</td><td>(1)</td></tr>
<tr><td>Left median lobe</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Gross Pathology (End of recovery phase)</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table></td></tr>
<tr><td>Organ weight</td><td>No drug related finding.</td></tr>
<tr><td>Histopathology</td><td>No drug related finding.</td></tr>
<tr><td>Toxicokinetics</td><td>• Systemic exposure of sunvozertinib (C_{max} and AUC_{0-24}) increased in a dose proportional manner.
• There was no sex difference or accumulation.
TK parameters refer to Table 12.</td></tr>
</table>

Table 12 TK Parameters of Sunvozertinib in 13-Week Dog Study

Dose Phase	Toxicokinetics Parameter [a]	Dose (mg/kg/day)					
		1	3	6	1	3	6
		Male	Male	Male	Female	Female	Female
Day 1	T_{max} [Range] (hr)	4.0 - 4.0	2.0 - 2.0	2.0 - 8.0	2.0 - 12.0	2.0 - 2.0	0.5 - 12.0
	C_{max} ± SD (µmol/L)	0.03±0.01	0.11±0.02	0.20±0.16	0.02±0.01	0.08±0.01	0.17±0.08

	AUC_{0-24} ± SD (hr*µmol/L)	0.31±0.10	1.18±0.26	2.38±1.69	0.28±0.17	0.85±0.22	2.14±0.92
Day 90	T_{max} [Range] (hr)	2.0 - 4.0	4.0 - 8.0	4.0 - 8.0	0.5 - 4.0	0.5 - 4.0	0.5 - 12.0
	C_{max} ± SD (µmol/L)	0.03±0.01	0.08±0.04	0.13±0.04	0.04±0.02	0.11±0.05	0.19±0.12
	AUC_{0-24} ± SD (hr*µmol/L)	0.47±0.04	1.34±0.88	2.23±0.77	0.37±0.14	1.43±0.86	2.48±1.42

Source: Applicant Table.
[a]:C_{max} (µmol/L) = ng/mL/(584.09 g/mol), AUC_{0-24} (µmol*h/L) =ng*h/mL/(584.09 g/mol).

Study Title (Number): A 28-Day Oral Toxicity and Toxicokinetic Study of DZD9008 with a 28-Day Recovery Period in Beagle Dogs (78103-18-327)

Key Study Findings

- Beagle dogs were orally administered (gavage) with sunvozertinib at 3, 6, 12/8 (males) or 12 (females) mg/kg/day. The NOAEL is 3 mg/kg/day for males and 6 mg/kg/day for females. The dose of high dose group in males was adjusted from 12 to 8 mg/kg/day from Day 13 due to GI tract toxicities.
- Major clinical signs included reversible and dose dependent diarrhea, vomiting, body weight loss and poor appetite at ≥ 6 mg/kg/day in males and 12 mg/kg/day in females.
- Microscopic findings were seen in the colon (gland ectasia).

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	3, 6, 12/8 (males) or 12 (females) mg/kg/day, once daily for 4 weeks
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxypropyl methylcellulose (HPMC) (w/v) with 0.1% Tween 80 (v/v) in sterile water for injection
Species/Strain:	Beagle dog
Number/Sex/Group:	Main study: 3 sex/group; recovery: 2 sex/group
Age:	8-10 months
Satellite groups:	No

Observations and Results: changes from control

Mortality	No sunvozertinib related mortality.
Clinical signs	Major clinical sign included reversible and dosage dependent abnormal feces, vomiting thinness, decreased activity and reduced food intake in males ≥ 3 mg/kg/day and females ≥ 6 mg/kg/day.
Body weight	Reversible body weight decrease was mainly noted in males ≥ 6 mg/kg/day and females at 12 mg/kg/day.
Food consumption	Reversible low food intake was noted in males ≥ 6 mg/kg/day and females at 12 mg/kg/day.
Ophthalmoscopy	No drug related finding.

ECG

No drug related finding.

Hematology

During the dosing phase, hematology changes (obvious or statistical difference) include increases in white blood cell (both sexes at high dose), neutrophile (both sexes at high dose), and monocyte (both sexes at high dose, females at 6 mg/kg/day and males at 3 mg/kg/day). Above changes were full to partially reversible.

Dose (mg/kg/day)	3		6		12/8	12
Sex	M	F	M	F	M	F
White blood cell count						
Day15/16	+9.6%	+9.8%	+15.7%	+23.1%	**+53.9%****	**+37.1%**
Day 29	+22.8%	+16.8%	-1.5%	+12.7%	+3.3%	**+26.4%**
End of recovery phase	+27.6%	+3.9%	+31.3%	+7%	+32.8%	-4.4%
Neutrophil						
Day15/16	+9.1%	+10.9%	+27.4%	+42.2%	**+69.6%****	**+57.7%**
Day 29	+30.4%	+13.2%	-1.4%	+9.4%	+3.8%	**+29.3%**
End of recovery phase	+36.9%	-0.9%	+51.3%	+6.3%	+45.4%	-6.1%
Monocyte						
Day15/16	+28.2%	+34.1%	+47.1%	**+90.8%***	**+90.7%***	**+104.6%***
Day 29	**+78.6%***	+38%	+61.1%	**+84.7%**	**+52%**	**+65.6%**
End of recovery phase	+10.3%	+14.3%	+71.3%	+34.3%	+40.2%	+57.1%

*: $p < 0.05$, **: $p < 0.01$. **Bold data** are sunvozertinib related changes.
The data were calculated as following: (data in each dose – control data)/control data *100%.

Coagulation

No drug related finding.

Clinical Chemistry

During the dosing phase, clinical chemistry changes (obvious or statistical difference) include decreases in serum proteins (total protein, albumin, globulin and/or A/G ratio) in animals at ≥ 6 mg/kg/day, decreases in serum calcium (in females given 12 mg/kg/day), increases in cholesterol (CHO) in animals at ≥ 3 mg/kg/day and increases in serum chloride (Cl) in animals at ≥ 6 mg/kg/day. Above changes were reversible.

Dose (mg/kg/day)	3		6		12/8	8
Sex	M	F	M	F	M	F
Total protein						
Day15/16	-4.2%	-4.5%	**-9.7%**	-4.1%	**-7.9%**	**-17.5%****
Day 29	-1.2%	-2.2%	**-9%**	-4.7%	-3.4%	**-14.5%**
End of recovery phase	+8.6%	-2.2%	+5.4%	-6%	+8%	+6.5%
Albumin						
Day15/16	-3.1%	-6.9%	**-13.7%**	**-7.6%**	**-20.5%***	**-23.3%****
Day 29	+0.9%	-9.1%	**-13.1%**	**-12.3%**	**-11.1%**	**-26.9%****
End of recovery phase	+23.3%	-1.3%	+18.8%	-4.7%	+19.1%	+2.5%
Globulin						
Day15/16	-5.3%	-1.3%	-5.5%	+0.4%	+5%	**-9.9%**
Day 29	-3.3%	+8.2%	-4.6%	+6.7%	+4.9%	+4%
End of recovery phase	-5.7%	-3.3%	-7.6%	-7.6%	-2.8%	+11.5%
A/G ratio						
Day15/16	+1.9%	-5.7%	-7.4%	-7.7%	**-24.2%***	**-15.3%**
Day 29	+3.9%	-16.2%	-8.9%	**-18.1%**	**-15.1%**	**-30.1%****
End of recovery phase	+28.1%	+0.8%	+26.6%	+1.6%	+20.1%	-9.1%
Cholesterol						
Day 15/16	**+31%**	**+49.9%**	**+37.8%**	**+46.5%**	**+68%***	**+78.5%****
Day 29	**+27.1%**	**+61.1%***	**+37.3%**	**+33%**	**+57.1%***	**+78%****
End of recovery phase	+18.7%	+13.2%	-16.8%	-14.7%	-5.5%	+16.5%
Cl						
Day 15/16	0%	+0.8%	+0.9%	+0.4%	**+2.1%***	**+3.5%****
Day 29	+0.5%	+0.3%	**+1.7%**	**+1.8%**	**+1.3%**	**+2%***

	End of recovery phase	-3.2%	+0.3%	-0.7%	+1.2%	-0.7%	+0.4%
	Ca						
	Day 15/16	+1.4%	-2.8%	-1.1%	-1.4%	-3.5%	**-9.7%****
	Day 29	+0.8%	-2.7%	-2.7%	-4.5%	-2.9%	**-10.8%****
	End of recovery phase	+6.5%	-1.1%	+2.5%	-4.6%	+5.5%	-0.9%

*: $p < 0.05$, **: $p < 0.01$. **Bold data** are sunvozertinib related changes.
The data was calculated as following: (data in each dose – control data)/control data *100%.

Urinalysis	No drug related finding.
Gross pathology	No drug related finding.
Organ weight	No drug related finding.
Histopathology	Reversible gland ectasia in colon was noted in one female at 12 mg/kg/day at the end of dosing phase.

Dose (mg/kg/day)	0		3		6		12/8	12
Sex	M	F	M	F	M	F	M	F
Number Evaluated (End of Dosing Phase):	3	3	3	3	3	3	3	3
Colon								
Ectasia; glandular (Total)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)
Mild	0	0	0	0	0	0	0	1

Toxicokinetics	• Systemic exposure of sunvozertinib (C_{max} and AUC_{0-24}) increased in a dose proportional manner. • There was no sex difference or accumulation. TK parameters refer to Table 13.

Table 13 TK Parameters in 4-Week Dog Study

Dose Phase	**Day 1**						**Day 28**					
Sex	**Male**			**Female**			**Male**			**Female**		
Dose (mg/kg/day)	**3**	**6**	**12**	**3**	**6**	**12**	**3**	**6**	**8**	**3**	**6**	**12**
Median T_{max} (hr)	2.0	4.0	12.0	2.0	4.0	4.0	4.0	2.0	4.0	2.0	2.0	4.0
C_{max} ± SD (µmol/L)	0.09 ± 0.045	0.14 ± 0.06	0.20 ± 0.07	0.23 ± 0.11	0.23 ± 0.18	0.17± 0.05	0.09± 0.04	0.18± 0.10	0.165± 0.135	0.15 ± 0.07	0.145 ± 0.07	0.24± 0.21
AUC_{last} ± SD (hr*µmol/L)	0.92 ± 0.175	1.70 ± 0.555	2.97 ± 0.32	1.63 ± 0.37	1.91 ± 1.23	2.42 ± 0.54	1.11 ± 0.125	2.22 ± 0.99	2.09 ± 0.99	1.41 ± 0.37	1.58 ± 0.57	3.09 ± 2.35

Source: Applicant Table.

Study Title (Number): One Month Oral Toxicity Study of DZ00000586 in Male Wistar Han Rats (ICCIN-2530)

Key Study Findings

- Rats were orally dosed at 25, 50, 100 or 200 mg/kg/day for up to 28 days.
- Unscheduled death (3/3 rats) was noted at 100 and 200 mg/kg/day. Severe GI tract effects, diarrhea and body weight loss were noted. Doses of 100 and 200 mg/kg/day were not tolerated.
- Soft/watery feces, body weight loss and poor appetite were noted at ≥ 100 mg/kg/day.

- Decreases of serum alkaline phosphatase, total cholesterol and triglyceride were observed at 100 mg/kg/day. Decrease in serum albumin was noted at 50 mg/kg/day.
- Microscopic findings were present in skin (crust formation in the epidermis), GI tract (erosion of mucosa epithelium, necrosis and inflammation), eye (corneal epithelial atrophy), pancreas (acinar atrophy) and thymus (lymphocyte depletion) at 100 and /or 200 mg/kg/day.

GLP compliance: No

Study Title (Number): A 14-Day Dose Range Finding Toxicity and Toxicokinetic Study of DZD9008 Following Oral Administration in Beagle Dogs (78103-18-338)

Key Study Findings

- Dogs were orally dosed at 15, 25, 50, or 75 mg/kg/day for up to 14 days.
- All doses were not tolerated. Mortality occurred at doses ≥ 50 mg/kg/day.
- Sunvozertinib related toxicities, including adverse clinical signs (emesis and diarrhea), severe body weight loss, low food intake and altered clinical pathology parameters, were observed at all dosages.
- Microscopic findings were present in GI tract, eye, pancreas, thyroid, tongue, esophagus, lacrimal gland, vagina, kidney, thymus, spleen, lymph node, adrenal gland, bone marrow, and mandibular salivary gland.

GLP compliance: No

The FDA's Assessment:

FDA did not review the non-GLP one-month toxicology study in rats, the 14-day dose range finding study in dogs, or the single dose toxicology studies in rats and dogs as these studies were not relevant for this stage of development. Of note, clinically relevant findings in the non-GLP one-month toxicology study in rats included inflammation and erosion/necrosis of mucosal epithelium in the GI tract (small/large intestine and stomach), and atrophy of the corneal epithelium in the eye at 100 and 200 mg/kg.

4-Week Repeat-Dose Toxicology Studies

The 4-week repeat-dose toxicology studies in rats and dogs were previously reviewed under IND 142003.

FDA generally agrees with the Applicant's conclusions in the 4-week repeat-dose toxicology study in rats except for the following edit. The Applicant presents all ophthalmoscopy findings as being reversible by the end of the recovery period; however, only the animals with iris synechia and pinpoint multifocal opacity of the anterior lens capsule were present in the recovery groups and showed reversibility. All animals exhibiting persistent pupillary membrane (PPM) were not

present in the recovery groups; therefore, reversibility of PPM could not be determined in this study.

FDA generally agrees with the Applicant's conclusions in the 4-week repeat-dose toxicology study in dogs but notes that two males receiving 12/8 mg/kg exhibited slight to moderate degeneration of the seminiferous tubules in the testes in addition to the findings described in the Applicant's position.

13-Week Repeat-Dose Toxicology Studies

Study Title (No.): DZD9008 - 13 Week Oral (Gavage) Toxicity Study in the Rat with a 4 Week Treatment-Free Period (JXB0023)

FDA generally agrees with the Applicant's conclusions with the additional findings included below. Target organs of toxicity included the eye, mammary gland (males only), lung, lymph nodes, and skin, in addition to hematologic toxicities. Of note, the Applicant incorrectly indicates that two female recovery animals at 35 mg/kg exhibited slight to moderate atrophy of the mammary gland; however, these findings were observed in two male recovery animals at 35 mg/kg.

Key Findings

See Applicant's position as well as the additional details below:

- **Clinical Chemistry** – reversible ↑ phosphate (up to 13%) in females
- **Histopathology** –minimal to slight folliculitis and slight to marked inflammation of the tail that was reversible

Body Weights	• In males at 15 mg/kg, a decrease in body weight compared to control animals (-10%) was observed starting on Day 85. • Decreases in body weight in all other animals were less than 10% throughout the dosing period. Body weight decreases in female animals at 35 mg/kg were generally reversible while body weight decreases in male animals at 35 mg/kg persisted through the recovery period.
Ophthalmoscopy	• Hemorrhage of the anterior chamber of the eye was observed in one male and one female animal at 35 mg/kg on Day 86 and persisted through the recovery period.
Hematology	**% Change Compared to Control (Day 87)**

Sex	Male			Female		
Dose (mg/kg/day)	15	25	35	15	25	35
Basophils	-	-	-	-	-	100
Large Unstained Cells	-	-	-	50	21	36
Monocytes	-	-	31	-	-	65

- All changes in high dose animals were reversible by the end of the recovery period.

Clinical Chemistry

% Change Compared to Control (Day 87)

Sex	Male			Female		
Dose (mg/kg/day)	15	25	35	15	25	35
Phosphate	-	-	-	12	9	13

- Changes in high dose female animals were reversible by the end of the recovery period.

Organ Weights

% Change from Control (Absolute Organ Weights)

Sex	Male			Female		
Dose (mg/kg/day)	15	25	35	15	25	35
Kidney	-14	-11.5	-12.5	-8.5	-9	-8.5
Liver	-21.5	-9.5	-14.5	-14	-11	-11
Spleen	-34.5	-26	-34.5	-15.5	-9.5	-13

- Decreases in absolute kidney, liver, and spleen weights were observed across all dose groups in rats with the largest decreases being observed in the spleens in male animals.

Histopathology

Sex	M				F			
Dose (mg/kg/day)	0	15	25	35	0	15	25	35
Number of Animals	10	10	10	10	10	10	10	10
TERMINAL SACRIFICE								
TAIL	0	0	0	2	0	0	0	5
FOLLICULITIS								
Minimal	0	0	0	0	0	0	0	2
Slight	0	0	0	1	0	0	0	1
INFLAMMATION								
Slight	0	0	0	1	0	0	0	0
Moderate	0	0	0	1	0	0	0	1

- Folliculitis/inflammation findings on the tail were associated with dry

	skin on tails and tail ridging. • None of the above changes were present in recovery animals.
Toxicokinetics	

Day	Toxicokinectic Parameter	Dose (mg/kg)					
		Male			Female		
		15	25	35	15	25	35
1	C_{max} (ng/mL)	155	273	484	187	332	342
	AUC_{0-24} (ng·h/mL)	1840	3230	5260	1920	3400	4590
87	C_{max} (ng/mL)	166	352	440	186	403	412
	AUC_{0-24} (ng·h/mL)	2270	5270	6370	2240	4620	5730

Study Title (No.): DZD9008 - 13 Week Oral (Gavage) Toxicity Study in the Dog with a 4 Week Treatment-Free Period (JXB0024)

FDA generally agrees with the Applicant's conclusions from the 13-week repeat-dose toxicology study in dogs. Target organs of toxicity included the GI tract, liver, lymph nodes, and lungs in addition to hematologic toxicities. Additional noteworthy findings are included in the table below.

Key Findings

See Applicant's position as well as the additional details below:

- **Clinical Chemistry** - ↓ albumin/globulin ratio (driven by ↓ albumin); ↑ cholesterol, triglycerides; all findings reversible
- **Histopathology** – minimal hyperplasia and inflammation in the liver; minimal to moderate inflammation and minimal hyperplasia in the lungs; minimal to moderate erythrophagocytosis in the lymph nodes; all findings reversible or trended towards recovery

Hematology	**% Change Compared to Control (Day 91)**
Clinical Chemistry	**% Change Compared to Control (Day 91)**

Sex	Male			Female		
Dose (mg/kg/day)	1	3	6	1	3	6
Basophils	-	-	-42	-	-	-60

- At 6 mg/kg, these findings were reversible in males and trended towards recovery in females by the end of the recovery period.

Sex	Male			Female		
Dose (mg/kg/day)	1	3	6	1	3	6
Albumin	-	-10	-24	-	-8	-18
Globulin	-	7	4	-	6	12
Albumin/Globulin Ratio	-	-16	-28	-	-14	-27
Cholesterol	-	17	31	-	39	39
Triglycerides	-	-	-	-	49	57

- These findings were reversible in all animals by the end of the recovery period.

Histopathology

Sex	M				F			
Dose (mg/kg/day)	0	1	3	6	0	1	3	6
TERMINAL SACRIFICE								
LIVER	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
HYPERPLASIA, Bile ducts								
Minimal	0	0	0	0	0	0	1	1
INFLAMMATORY CELLS, Focal/multifocal								
Minimal	0	0	0	1	0	1	1	1
LUNG	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
HYPERPLASIA, Epithelium, bronchioles								
Slight	0	0	0	1	0	1	0	0
INFLAMMATION, Broncho-alveolar								
Minimal	1	1	1	1	0	1	0	0
Slight	0	0	0	1	0	1	0	1
Moderate	0	0	0	1	0	0	1	0
INFLAMMATION, Granulomatous								
Minimal	0	0	0	1	0	0	0	0
HEMORRHAGE/FLOODING, Alveolar								
Moderate	0	0	0	1	0	0	0	0
LYMPH NODE	**0**	**0**	**1**	**2**	**0**	**0**	**1**	**0**
ERYTHROPHAGOCYTOSIS								
Moderate	0	0	1	2	0	0	0	0
LYMPH NODE, MANDIBULAR	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
ERYTHROPHAGOCYTOSIS								
Minimal	0	0	0	0	0	1	0	0
Slight	0	0	1	0	0	0	1	0

<table>
<tr><td></td><td>

A single high dose male animal exhibited moderate alveolar hemorrhage/flooding in the lung that was associated with moderate broncho-alveolar inflammation, minimal granulomatous inflammation, and epithelial hyperplasia in the bronchioles in the lungs.
Erythrophagocytosis was observed in animals that did not exhibit decreases in circulating red blood cells, making the toxicological significance of these findings unclear.
Minimal liver inflammation was present in two female animals at 6 mg/kg, and minimal lung inflammation in two male animals and one female animal at 6 mg/kg at the end of the recovery period.
All other findings were not present in recovery animals at the end of the recovery period.

</td></tr>
<tr><td>Toxicokinetics</td><td>
<table>
<tr><th rowspan="3">Day</th><th rowspan="3">Toxicokinectic Parameter</th><th colspan="6">Dose (mg/kg)</th></tr>
<tr><th colspan="3">Male</th><th colspan="3">Female</th></tr>
<tr><th>1</th><th>3</th><th>6</th><th>1</th><th>3</th><th>6</th></tr>
<tr><td rowspan="2">1</td><td>C_{max} (ng/mL)</td><td>14.7</td><td>62</td><td>115</td><td>10.7</td><td>49.1</td><td>99.3</td></tr>
<tr><td>AUC_{0-24} (ng·h/mL)</td><td>182</td><td>688</td><td>1390</td><td>162</td><td>499</td><td>1250</td></tr>
<tr><td rowspan="2">90</td><td>C_{max} (ng/mL)</td><td>18.3</td><td>47</td><td>78.5</td><td>21.5</td><td>62.8</td><td>113</td></tr>
<tr><td>AUC_{0-24} (ng·h/mL)</td><td>272</td><td>784</td><td>1300</td><td>215</td><td>837</td><td>1450</td></tr>
</table>
</td></tr>
</table>

5.5.2 Genetic Toxicology

The Applicant's Position:

A complete battery of genotoxicity studies, including a bacterial reverse mutation assay (Ames), an *in vitro* chromosome aberration assay in Chinese hamster ovary cells, and an *in vivo* micronucleus assay in Wistar Han rats, were conducted in compliance with GLP regulations.

There were no findings to indicate any potential for genotoxicity with sunvozertinib administration.

Study Title (Number): DZD9008: Bacterial Reverse Mutation Assay in *Salmonella Typhimurium* and *Escherichia Coli* (Ames) (78106-18-729)

Key Study Findings

- Sunvozertinib did not induce reverse mutations in all tested strains with or without metabolic activation.

GLP compliance: Yes.

Test system: *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) and *Escherichia coli* WP2 *uvr*A in the presence or absence of rat liver S9 extract.

Study is valid: Yes.

Study Title (Number): DZD9008: *In Vitro* Chromosome Aberration Assay in Chinese Hamster Ovary Cells (78106-18-730)

Key Study Findings

- Sunvozertinib did not induce chromosome aberration in Chinese hamster ovary cells with or without metabolic activation.

GLP compliance: Yes.

Test system: Chinese hamster ovary cell in the presence or absence of rat liver S9 extract.

Study is valid: Yes.

Study Title (Number): DZD9008: *In Vivo* Micronucleus Assay and Toxicokinetics Study in Rats (78106-18-731)

Key Study Findings

- Sunvozertinib did not increase the micronucleated polychromatic erythrocytes in rats after oral administration.

GLP compliance: Yes.

Test system: Wistar Han rats were administered with sunvozertinib via oral gavage for 3 consecutive days at 100, 300 or 1000 mg/kg/day. Bone marrows were collected 4 hours (males) or 2 hours (females) after last dose.

Study is valid: Yes.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions of the submitted genotoxicity assays. Of note, in the definitive Bacterial Reverse Mutation Assay (Ames) sunvozertinib was tested up to 700 µg/plate in *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and up to 2000 µg/plate in *Escherichia coli* (WP2 *uvr*A). In the Chromosome Aberration Assay, sunvozertinib was tested up to 25 µg/mL (3-hour treatment, S9 activated), 40 µg/mL (3-hour treatment, S9 non-activated), or 12 µg/mL (20-hour treatment, S9 non-activated). Standard positive controls were used to confirm the sensitivity and validity of each genotoxicity assay.

5.5.3 Carcinogenicity

The Applicant's Position:

As indicated in the International Council for Harmonisation (ICH) S9 guidance, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer, therefore, no carcinogenicity studies were conducted

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not needed to support the use of sunvozertinib in the currently proposed indication per ICH S9.

5.5.4 Reproductive and Development Toxicology

The Applicant's Position:

Sunvozertinib was administered orally to rats and rabbits during the period of organogenesis to assess embryo-fetal development toxicity. Two GLP and two DRF embryo-fetal development toxicity studies were conducted in rats and rabbits, respectively. In the embryo-fetal development toxicity studies, sunvozertinib resulted in decreased body weight and abortion in pregnant rats and/or rabbits, dead fetuses, decreased fetal weight, heart malformations, increased supernumerary bone of fontanelle bone, and misaligned sternebra in fetus. (b) (4)

Embryo-Fetal Development

Study Title (Number): DZD9008: Oral Dose Study on Embryo-fetal Development Toxicity and Toxicokinetics in Rabbits (665-0081-DR)

Key Study Findings

- Sunvozertinib-related heart malformations, including dilated aorta, dilated aortic arch, narrow pulmonary artery, two-chambered heart, and ventricular septum defect, were noted at 1.5 and 5 mg/kg/day. Dilated aorta and aortic arch were also noted at 0.5 mg/kg/day. As incidence was still within the range of historical control data, the relationship to sunvozertinib is not clear. In addition, increased supernumerary bone of fontanelle bone was also noted at ≥1.5 mg/kg/day.
- NOAEL of sunvozertinib for maternal toxicity was 5 mg/kg/day, whilst the NOAEL for embryo-fetal development toxicity was not established.

GLP compliance: Yes.

Methods	
Dose and frequency of dosing:	0.5, 1.5, 5 mg/kg/day, once daily on GD 6-19
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxypropyl methylcellulose (HPMC) (w/v) with 0.1% Tween 80 (v/v) in sterile water for injection
Species/Strain:	New Zealand white rabbit
Number/Sex/Group:	Main study: 22, 24, 23, 23 pregnant females at 0, 0.5, 1.5 and 5 mg/kg/day, respectively. TK animal: 5, 4, 4 and 3 pregnant females at 0, 0.5, 1.5 and 5 mg/kg/day, respectively.
Age:	4-7 months
Satellite groups:	Toxicokinetics assessment

Observations and Results: changes from control

<table>
<tr><td>Mortality</td><td>No sunvozertinib related mortality.</td></tr>
<tr><td>Clinical signs</td><td>No remarkable finding.</td></tr>
<tr><td>Body weight</td><td>Adjusted body weight gain decreased (-13.39%, -31.77%, -36.95%, respectively, relative to control) at 0.5, 1.5, or 5 mg/kg/day.</td></tr>
<tr><td>Food consumption</td><td>Food consumption decreased (up to -13.3%, -18.5%, -19.1%, respectively, relative to control) at 0.5, 1.5, or 5 mg/kg/day.</td></tr>
<tr><td>Gross pathology</td><td>No drug related finding.</td></tr>
<tr><td>Histopathology</td><td>Histopathology changes in fetuses, including heart malformations and increased supernumerary bone of fontanelle bone were noted at ≥ 1.5 mg/kg/day.
Dilated aorta and aortic arch were also noted in fetuses at 0.5 mg/kg/day, as the incidence was still within the range of historical control data, the relationship to sunvozertinib is not clear.
<table>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>0.5</th><th>1.5</th><th>5</th></tr>
<tr><td>Number of Pregnant Animals</td><td>Female:22</td><td>Female:24</td><td>Female:23</td><td>Female:23</td></tr>
<tr><td>Visceral Examination of Fetuses[a]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Heart, Aorta, dilated</td><td>-</td><td>0.6%/5.00%</td><td>1.0%/9.09%</td><td>1.0%/8.70%</td></tr>
<tr><td>Heart, Aortic arch, dilated</td><td>-</td><td>0.6%/5.00%</td><td>1.0%/9.09%</td><td>1.0%/8.70%</td></tr>
<tr><td>Heart, Ventricular septum, defect</td><td>-</td><td>-</td><td>0.5%/4.55%</td><td>-</td></tr>
<tr><td>Heart, Pulmonary artery, narrow</td><td>-</td><td>-</td><td>0.5%/4.55%</td><td>1.0%/8.70%</td></tr>
<tr><td>Two-chambered heart, right A-V valve absent</td><td>-</td><td>-</td><td>-</td><td>0.5%/4.35%</td></tr>
<tr><td>Skeletal Anomalies of Fetuses[a]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Supernumerary bone of fontanelle bone</td><td>1.0%/4.55%</td><td>-</td><td>3.7%/13.64%</td><td>2.9%/13.04%</td></tr>
</table>
[a]: data presented as fetus incidence/litter incidence. Bold data are sunvozertinib related changes.</td></tr>
<tr><td>Toxicokinetics</td><td>• The TK of sunvozertinib and its metabolite DZ0753 were analyzed on GD 6 and GD 19.
• Systemic exposure of sunvozertinib and DZ0753 (C_{max} and AUC_{0-24}) increased in a dose proportional manner.
• There was no marked accumulation.
TK parameters refer to Table 14.</td></tr>
</table>

Table 14 TK Parameters in Embryo-Fetal Development Toxicity Study in Rabbits

TK Parameters of Sunvozertinib in Rabbit Plasma

Gestation Day	Toxicokinetics Parameter [a]	Dose (mg/kg/day)		
		0.5	1.5	5
		Female	Female	Female
GD 6	Median T_{max} (hr)	2.0	2.0	1.0
	C_{max} ± SD (µmol/L)	0.03 ± 0.01	0.09 ± 0.02	0.46 ± 0.12
	AUC_{0-24} ± SD (hr*µmol/L)	0.20 ± 0.06	0.51 ± 0.11	2.04 ± 0.50
GD 19	Median T_{max} (hr)	2.0	2.0	1.0

	C_{max} ± SD (µmol/L)	0.04 ± 0.01	0.15 ± 0.04	0.69 ± 0.30
	AUC_{0-24} ± SD (hr*µmol/L)	0.27 ± 0.03	0.91 ± 0.37	3.54 ± 1.58

TK Parameters of DZ0753 in Rabbit Plasma

Gestation Day	Toxicokinetics Parameter [a]	Dose (mg/kg/day)		
		0.5	1.5	5
		Female	Female	Female
GD 6	Median T_{max} (hr)	2.0	2.0	1.0
	C_{max} ± SD (µmol/L)	0.007 ± 0.002	0.02 ± 0.01	0.09 ± 0.03
	AUC_{0-24} ± SD (hr*µmol/L)	0.05 ± 0.02	0.14 ± 0.04	0.45 ± 0.13
GD 19	Median T_{max} (hr)	2.0	2.0	1.0
	C_{max} ± SD (µmol/L)	0.008 ± 0.002	0.025 ± 0.008	0.12 ± 0.05
	AUC_{0-24} ± SD (hr*µmol/L)	0.07 ± 0.01	0.22 ± 0.09	0.83 ± 0.40

Source: Applicant Table.
[a:] C_{max} (µmol/L) = ng/mL/(584.09 g/mol), AUC_{0-24} (µmol*h/L) =ng*h/mL/(584.09 g/mol).

Study Title (Number): An Embryo-fetal Development and Toxicokinetic Study of DZD9008 Administered by Oral Gavage in Wistar Han Rats (78111-220447)

Key Study Findings

- Sunvozertinib resulted in lower body weight, body weight gain and food consumption than controls at ≥ 10 mg/kg/day.
- Sunvozertinib-related effects on the embryo-fetal included a higher incidence of misaligned sternebra at 40 mg/kg/day.
- NOAEL of sunvozertinib for maternal and embryo-fetal development toxicity was 40 mg/kg/day.

GLP compliance: Yes.

Methods	
Dose and frequency of dosing:	10, 20, 40 mg/kg/day, once daily on GD 6-17
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxypropyl methylcellulose (HPMC) (w/v) with 0.1% Tween 80 (v/v) in sterile water for injection
Species/Strain:	Wistar Han rat
Number/Sex/Group:	Main study: 25, 23, 25, 23 pregnant females at 0, 10, 20 and 40 mg/kg/day, respectively. TK animal: 5 females at 0 mg/kg/day; 10 females/group at 0.5, 1.5 and 5 mg/kg/day.
Age:	10-13 weeks
Satellite groups:	Toxicokinetics assessment

Observations and Results: changes from control

Mortality	No sunvozertinib related mortality.

<table>
<tr><td>Clinical signs</td><td>No remarkable finding.</td></tr>
<tr><td>Body weight</td><td>Lower body weight and body weight gain than controls were noted at ≥ 10 mg/kg/day.</td></tr>
<tr><td>Food consumption</td><td>Lower food consumption than controls were noted at ≥ 10 mg/kg/day.</td></tr>
<tr><td>Gross pathology</td><td>No drug related finding.</td></tr>
<tr><td>Histopathology</td><td>Sunvozertinib-related misaligned sternebra was noted in fetuses at 40 mg/kg/day.
<table>
<tr><td>Dose (mg/kg/day)</td><td>0</td><td>10</td><td>20</td><td>40</td></tr>
<tr><td>Number of Pregnant Animals</td><td>Female:25</td><td>Female:23</td><td>Female:25</td><td>Female:23</td></tr>
<tr><td>Skeletal Anomalies of Fetuses</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Misaligned sternebra[a]</td><td>0.6%/4.0%</td><td>0.8%/4.3%[b]</td><td>0%/0%</td><td>4.1%/17.4%[b]</td></tr>
</table>
[a]: data presented as fetus incidence/litter incidence. b: The finding noted at 10 mg/kg/day is not considered as sunvozertinib related due to the comparable incidence with controls, however, the finding at 40 mg/kg/day was likely sunvozertinib related. Bold data are sunvozertinib related changes.</td></tr>
<tr><td>Toxicokinetics</td><td>• The TK of sunvozertinib and its metabolite DZ0753 were analyzed on GD 6 and GD 17.
• Systemic exposure of sunvozertinib and DZ0753 (C_{max} and AUC_{0-24}) generally increased in a dose proportional manner.
• There was no marked accumulation.
TK parameters refer to Table 15.</td></tr>
</table>

Table 15 TK Parameters in Embryo-Fetal Development Toxicity Study in Rats

TK Parameters of Sunvozertinib in Rat Plasma

Gestation Day	Toxicokinetics Parameter [a]	Dose (mg/kg/day)		
		10	20	40
		Female	Female	Female
GD 6	T_{max} (hr)	2.0	2.0	2.0
	C_{max} ± SD (µmol/L)	0.34 ± 0.06	0.73 ± 0.06	1.55 ± 0.16
	AUC_{0-24} ± SD (hr*µmol/L)	3.25 ± 0.22	6.92 ± 0.35	14.1 ± 0.56
GD 17	T_{max} (hr)	4.0	4.0	2.0
	C_{max} ± SD (µmol/L)	0.30 ± 0.02	0.54 ± 0.06	0.59 ± 0.02
	AUC_{0-24} ± SD (hr*µmol/L)	3.13 ± 0.10	7.16 ± 0.82	8.57 ± 0.50

TK Parameters of DZ0753 in Rat Plasma

Gestation Day	Toxicokinetics Parameter [a]	Dose (mg/kg/day)		
		10	20	40
		Female	Female	Female
GD 6	T_{max} (hr)	2.0	2.0	2.0
	C_{max} ± SD (µmol/L)	0.01 ± 0.003	0.02 ± 0.001	0.06 ± 0.006
	AUC_{0-24} ± SD (hr*µmol/L)	0.08 ± 0.007	0.19 ± 0.01	0.50 ± 0.04
GD 17	T_{max} (hr)	2.0	2.0	2.0
	C_{max} ± SD (µmol/L)	0.009 ± 0.001	0.02 ± 0.006	0.02 ± 0.002
	AUC_{0-24} ± SD (hr*µmol/L)	0.10 ± 0.004	0.24 ± 0.03	0.28 ± 0.03

Source: Applicant Table.
a: C_{max} (µmol/L) = ng/mL/(584.09 g/mol), AUC_{0-24} (µmol*h/L) =ng*h/mL/(584.09 g/mol).

Study Title (Number): DZD9008: Oral Dose Range Finding Study on Embryo-fetal Development Toxicity in Rabbits (665-0080-DR)

Key Study Findings

- Pregnant rabbits were orally dosed with sunvozertinib at 5, 15, or 45/30 mg/kg/day on GDs 6-19.
- Sunvozertinib resulted in maternal mortalities and adverse maternal toxicities (clinical signs, decreased body weight and food consumption) and embryo-fetal development toxicities (decreases in number of live fetuses and increases in number of non-viable fetuses as well as significantly decreased fetal weight and fetal crown-rump length) at 45/30 mg/kg/day. In addition, fetal toxicities, dose-related decreased fetal weight and fetal crown-rump length were noted at 5 and 15 mg/kg/day.

GLP compliance: No.

Study Title (Number): A Dose Range Finding Embryo-fetal Development Study of DZD9008 Administered by Oral Gavage in Wistar Han Rats (78111-220446)

Key Study Findings

- Pregnant rats were orally dosed with sunvozertinib at 15, 30 or 45 mg/kg/day on GDs 6-17.
- No sunvozertinib-related mortality was noted.
- Sunvozertinib resulted in dam changes, including lower body weight and/or body weight gain, and lower food consumption than controls, at ≥15 mg/kg/day. In addition, the clinical observations (staining and hunched posture), small thymus and large adrenal gland noted at ≥ 30 mg/kg/day were potentially sunvozertinib-related.
- Sunvozertinib-related effects on the embryo-fetal included dose-related lower fetal body weight at ≥ 15 mg/kg/day.

GLP compliance: No.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of the embryo-fetal development (EFD) studies in rabbits and rats with the additional pertinent details summarized below; however, FDA notes that the clinically recommended dose is 200 mg.

Study Title/Number: Oral Dose Study on Embryo-fetal Development Toxicity and Toxicokinetics in Rabbits / Study No. 665-0081-DR

Key Study Findings: See Applicant's position.

Methods: See Applicant's position. The dose justification to use 5 mg/kg as the high dose in the current study was based on the rabbit dose range-finding EFD study #665-0080-DR which

showed that at 15 mg/kg/day there was decreased maternal food consumption, fetal weight, and fetal crown-rump length.

Observations and Results

<table>
<tr><th>Parameters</th><th>Major Findings</th></tr>
<tr><td>Mortality</td><td>No drug-related mortalities.

Four animals were found dead or euthanized at 0.5 mg/kg from gestational day (GD) 17 to GD25. One pregnant animal (2501) was euthanized on GD 17 after being found paralyzed in the hindlimbs, which was associated blood clots around the spinal cord and attributed to the animal restrain procedure. Two pregnant animals (2514 and 2520) were found dead on GD17 due to gavage error confirmed by histopathology and/or clinical observations. One pregnant animal (2512) aborted on GD25 and was euthanized. Due to lack of dose correlation, the abortion was likely not related to sunvozertinib.</td></tr>
<tr><td>Necropsy Findings
Cesarean Section Data</td><td>Unremarkable.</td></tr>
<tr><td colspan="2">Cesarean Section Findings (Embryo-fetal Development Study; Rabbits)
<table>
<tr><th>Dose (mg/kg)</th><th>0</th><th>0.5</th><th>1.5</th><th>5</th></tr>
<tr><td># Mated females</td><td>27</td><td>27</td><td>27</td><td>27</td></tr>
<tr><td># Pregnant (%)</td><td>22 (81.5%)</td><td>24 (88.9%)</td><td>23 (85.2%)</td><td>23 (85.2%)</td></tr>
<tr><td>Mean # corpora lutea</td><td>12</td><td>13</td><td>12</td><td>12</td></tr>
<tr><td>Mean # implantats</td><td>9</td><td>9</td><td>10</td><td>9</td></tr>
<tr><td>Mean % pre-implantation loss</td><td>26.4%</td><td>27.1%</td><td>19.0%</td><td>22.7%</td></tr>
<tr><td>Mean % post-implantation loss</td><td>4.1%</td><td>8.2%</td><td>10.5%</td><td>6.1%</td></tr>
<tr><td>Mean # early resorptions</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Mean # embryonic resorptions</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>Mean # dead fetuses</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Mean # live fetuses</td><td>9</td><td>9</td><td>9</td><td>9</td></tr>
<tr><td>Mean fetal sex ratio (% males)</td><td>52.4%</td><td>51.2%</td><td>51.6%</td><td>55.2%</td></tr>
<tr><td>Mean fetal body weight (g)</td><td>42.3</td><td>43.6</td><td>42.2</td><td>41.6</td></tr>
</table>
Mean % pre- and post-implantation loss were calculated by Applicant [% Pre-implantation Loss= (No. of Corpora Lutea – No. of Implantations) / No. of Corpora Lutea × 100; % Post-implantation Loss = (No. of implantations – total No. of Live Fetuses) / No. of implantations × 100]
(Adapted from Applicant's Submission)</td></tr>
<tr><td>Necropsy Findings
Offspring</td><td>External variations observed included cleft palate and bilateral hyperflexion in one fetus at 5 mg/kg.

Of note, the fetus with the two-chambered heart and absent A-V valve findings at 5 mg/kg also exhibited a dilated aorta and aortic arch. Visceral malformations in the lung included a fused left lobe in one fetus at 5 mg/kg and instances of absent median lobes at ≥ 0.5 mg/kg.

Visceral variations observed included small spleens in four fetuses at 0.5 mg/kg and one fetus at 5 mg/kg as well as folds in the right retina at ≥ 0.5 mg/kg.</td></tr>
</table>

In addition, to increased instances of supernumerary bone of the fontanellar bone at ≥ 1.5 mg/kg noted by the Applicant, additional skeletal variations observed included bent hyoid in the skull at 1.5 mg/kg, and increased instances of shortened 13th right ribs at ≥ 1.5 mg/kg.

Fetal Malformations and Variations (Embryo-fetal development Study; Rabbits)

Dose (mg/kg)	0	0.5	1.5	5
Number of Fetuses / Litters Examined	**187/22**	**171/20**	**209/22**	**204/23**
External variation: # of fetuses affected (% of litters)				
Cleft palate	0 (0%)	0 (0%)	0 (0%)	1 (4.3%)
Bilateral forelimb hyperflexion	0 (0%)	0 (0%)	0 (0%)	1 (4.3%)
Number of Fetuses / Litters Examined	**187/22**	**171/20**	**209/22**	**203/23**
Visceral malformation: # of fetuses affected (% of litters)				
Heart, two-chambered	0 (0%)	0 (0%)	0 (0%)	1 (4.4%)
Right A-V valve, absent	0 (0%)	0 (0%)	0 (0%)	1 (4.4%)
Ventricular septum, defect	0 (0%)	0 (0%)	1 (4.6%)	0 (0%)
Aorta, dilated	0 (0%)	1 (5.0%)	2 (9.1%)	2 (8.7%)
Aortic arch, dilated	0 (0%)	1 (5.0%)	2 (9.1%)	2 (8.7%)
Pulmonary artery, narrow	0 (0%)	0 (0%)	1 (4.6%)	2 (8.7%)
Lung, left lobe, fused	0 (0%)	0 (0%)	0 (0%)	1 (4.4%)
Lung, median lobe, absent	0 (0%)	3 (15%)	3 (13.6%)	1 (4.4%)
Visceral variation: # of fetuses affected (% of litters)				
Spleen, small	0 (0%)	4 (10.0%)	0 (0%)	1 (4.4%)
Eye, retina, right, fold	0 (0%)	1 (5.0%)	1 (4.6%)	1 (4.4%)
Number of Fetuses / Litters Examined	**187/22**	**171/20**	**209/22**	**203/23**
Skeletal variation: # of fetuses affected (% of litters)				
Skull, hyoid, bent	0 (0%)	0 (0%)	2 (9.1%)	0 (0%)
Skull, fontanelles, supernumerary bone	1 (4.6%)	0 (0.0%)	4 (13.6%)	3 (13.0%)
13th rib, right, short	1 (4.6%)	1 (5.0%)	4 (18.2%)	3 (13.0%)

% per litter = (Total # of litters with malformation or variation / Total # litters) x 100
(Adapted from Applicant's Submission)

Toxicokinetics

Sunvozertinib and DZ0753 exposure (AUC and C_{max}) generally increased dose-proportionally.

At 0.5, 1.5, or 5 mg/kg/day on GD 28, fetal mean plasma concentrations for sunvozertinib were 1.01, 4.18, and 18.4 ng/mL, respectively, and DZ0753 were BLLOQ, BLLOQ, and 0.56 ng/mL, respectively.

Toxicokinetic Parameters for Sunvozertinib

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	T_{max} (h)
GD 6	0.5	18	117	2
	1.5	50	300	2
	5	268	1190	1
GD 19	0.5	23	156	2
	1.5	85	530	2
	5	405	2070	1

Toxicokinetic Parameters for Metabolite DZ0753

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	T_{max} (h)
GD 6	0.5	4	28	2
	1.5	11	80	2
	5	54	259	1
GD 19	0.5	5	40	2
	1.5	14	124	2
	5	69	472	1

h=hours; AUC_{0-24} = AUC from time zero to 24 hours post dose
(Adapted from Applicant's Submission)

Study Title/Number: An Embryo-fetal Development and Toxicokinetic Study of DZD9008 Administered by Oral Gavage in Wistar Han Rats / Study No. 78111-220447

Key Study Findings: See Applicant's position.

Methods: See Applicant's position. The dose justification to use 40 mg/kg as the high dose in the current study was based on the rat dose range-finding EFD study #78111-220446 which showed that at 45 mg/kg/day there was an increased incidence of decreased thymus size and a significant reduction in mean fetal body weight compared to control.

Observations and Results

Parameters	Major Findings
Body Weights and Food Consumption	There was a statistically significant decrease in mean body weight up to -8.7% on GD 15-21 in rats dosed with 40 mg/kg sunvozertinib compared to controls. On GD 6-9, lower mean body weight gains (up to -50%) were observed in rats dosed with ≥10 mg/kg sunvozertinib compared to controls. On GD 12-21, lower mean body weight gains (up to -31%) were observed in rats dosed with 40 mg/kg sunvozertinib compared to controls. Lower mean food consumption (up to -16.4%) was observed in rats dosed with ≥20 mg/kg sunvozertinib compared to controls.
Necropsy Findings Cesarean Section Data	Pre-implantation loss showed statistically significant increase in 40 mg/kg/day dose group, but it was not considered sunvozertinib-related since the animals were dosed after embryonic implantation.

Cesarean Section Findings (Embryo-fetal Development Study; Rats)

Dose (mg/kg)	0	10	20	40
# Mated females	29	29	34	25
# Pregnant (%)	25 (86.2%)	23 (79.3%)	25 (73.5%)	23 (92.0%)
Mean # corpora lutea	14.2	14.0	14.0	14.2

Mean # implantation sites	13.5	12.4	13.0	11.7
Mean % pre-implantation loss	5.1%	11.4%	7.1%	18.0%*
Mean % post-implantation loss	5.2%	8.7%	7.2%	6.8%
Mean # early resorptions	0.0	0.0	0.0	0.0
Mean # embryonic resorptions	0.6	1.0	1.0	0.7
Mean # dead fetuses	0	0	0	0
Mean # live fetuses	12.8	11.4	12.0	11.1
Mean fetal sex ratio (% males)	45.6%	51.3%	46.3%	51.3%
Mean fetal body weight (g)	4.8	5.0	4.9	4.9

*, p<0.05 vs controls; Mean % pre- and post-implantation loss were calculated by Applicant [% Pre-implantation Loss= (No. of Corpora Lutea – No. of Implantations) / No. of Corpora Lutea × 100; % Post-implantation Loss = (No. of implantations – total No. of Live Fetuses) / No. of implantations × 100]

(Adapted from Applicant's Submission)

Necropsy Findings Offspring	In addition to the misaligned sternebra noted by the Applicant, increased number of phalange (forelimb) ossification sites were noted at ≥20 mg/kg/day compared to controls (results not shown in Table below). The high incidence of short/full supernumerary rib was not considered sunvozertinib-related due to the incidence being comparable with controls and the higher incidence of supernumerary rib occurring in Wistar Han species (Takeuchi et al., 2011; Noritake et al., 2013). There were no sunvozertinib-related malformations, external variations, or visceral variations.

Fetal Malformations and Variations (Embryo-fetal development Study; Rats)

Dose (mg/kg)	0	10	20	40
Number of Fetuses / Litters Examined	**155/25**	**125/23**	**139/24**	**122/23**
Skeletal variation: # of fetuses affected (% of litters)				
Sternebra, various, misaligned	1(4%)	1(4.3%)	0(0.0%)	5(17.4%)
Supernumerary rib, cervical/thoracolumbar, full	13(24%)	13(26.1%)	15(29.2%)	6(13%)
Supernumerary rib, cervical/thoracolumbar, short	80(92%)	70(100%)	76(91.7%)	56(91.3%)

% per litter = (Total # of litters with malformation or variation / Total # litters) x 100

(Adapted from Applicant's Submission)

Toxicokinetics	Sunvozertinib and DZ0753 exposure (AUC and C_{max}) increased dose-proportionally on GD 6, but lower than dose-proportionally between 20 and 40 mg/kg on GD 17.

	At 10, 20, or 40 mg/kg/day on GD 20, fetal mean plasma concentrations at 4 hours post dose for sunvozertinib were 27.4, 32.9, and 93.9 ng/mL, respectively, and DZ0753 were BLLOQ, 0.209, and 1.1 ng/mL, respectively.

Toxicokinetic Parameters for Sunvozertinib

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	T_{max} (h)
GD 6	10	201	1899	2
	20	426	4041	2
	40	907	8208	2
GD 17	10	173	1831	4
	20	314	4185	4
	40	347	5003	2

Toxicokinetic Parameters for Metabolite DZ0753

Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	T_{max} (h)
GD 6	10	5.58	44.2	2
	20	13	109	2
	40	35	282	2
GD 17	10	5.05	54.4	2
	20	12.9	138	2
	40	11.8	159	2

h=hours; AUC_{0-24} = AUC from time zero to 24 hours post dose
(Adapted from Applicant's Submission)

Study Title/Number: Oral Dose Range Finding Study on Embryofetal Development Toxicity in Rabbits / Study No. 665-0080-DR

Time-mated female rabbits (9/group) were administered sunvozertinib 0, 5, 15, and 45/30 mg/kg once daily via oral gavage during GD 6-19. On GD 12, animals receiving 45 mg/kg were reduced to 30 mg/kg due to mortality, decreased body weight, and decreased food consumption. Surviving animals were euthanized on GD 29. Fetal examinations for this study were limited to weight, sex, crown-rump length, and gross external alterations. Toxicokinetics analysis showed systemic exposure increased generally proportional to dose, with no accumulation observed. At 45/30 mg/kg, six pregnant animals were found dead or had aborted and exhibited soiled coats, decreased defecation, decreased body weights, embryo-like material in the bedding, and/or prostration and cold to touch. At necropsy, gross findings included focal dark red discoloration of the kidney and white solid content in the right atrium of the heart in two animals. Additional maternal toxicities in surviving animals not described by the Applicant included decreased defecation at ≥ 15 mg/kg and decreased gravid uterine weight at 45/30 mg/kg. Additionally, post-implantation losses were observed at 45/30 mg/kg.

Study Title/Number: A Dose Range Finding Embryo-fetal Development Study of DZD9008 Administered by Oral Gavage in Wistar Han Rats / Study No. 78111-220446

Time-mated female Wistar Han rats (8/group) were administered 0, 15, 30, or 45 mg/kg sunvozertinib once daily via oral gavage during GD 6-17 and were euthanized on GD 21. Fetal examinations in this non-GLP study were limited to weight, sex, crown-rump length, and gross external alterations. Toxicokinetics were not evaluated. There were no early mortalities. Treatment with sunvozertinib resulted in an increased incidence of anus/nose staining at doses ≥30 mg/kg and hunched posture at 45 mg/kg. Sunvozertinib induced maternal toxicity was characterized lower body weight/body weight gain than controls at ≥30 mg/kg from GDs 6-21 and decreased food consumption than controls at ≥15 mg/kg. At necropsy, decreased thymus size

was noted in one animal at 30 mg/kg and three animals at 45 mg/kg. Increased adrenal glands were noted in one animal at 30 mg/kg and one animal at 45 mg/kg. At 45 mg/kg, sunvozertinib induced a 10% decrease in mean fetal body weight compared to control. There were no sunvozertinib-related changes to ovarian and uterine parameters, fetal crown rump length, or fetal external examination.

5.5.5 Other Toxicology Studies

The Applicant's Position:

A GLP *in vitro* neutral red uptake phototoxicity assay was conducted in BALB/c 3T3 mouse fibroblasts with sunvozertinib. Sunvozertinib was not found to be phototoxic in this study.

Study Title (Number): *In Vitro* 3T3 Neutral Red Uptake Phototoxicity Test (BJ13QC)

Key Study Findings

- Sunvozertinib has no phototoxic potential.

GLP compliance: Yes.

Test system: BALB/c 3T3 fibroblast cells in the presence or absence of UVA.

Study is valid: Yes.

The FDA's Assessment:

FDA agrees with the Applicant's conclusions. Sunvozertinib did not demonstrate phototoxic potential (Photoirritancy Factor [PIF]=1.182 in the main assay) compared to positive control, chlorpromazine (PIF = 9.687) under the conditions of this in vitro assay. The criterion for "phototoxic" is PIF ≥ 5. The performance of the positive control confirmed the sensitivity and validity of the study.

X	X

Brian Christmas, PhD
Asurayya Worrede, PhD
Primary Reviewers

Claudia Miller, PhD
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6. Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

The Applicant is seeking approval of sunvozertinib for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations (exon20ins), whose disease has progressed on or after platinum-based chemotherapy. (b) (4)

The Clinical Pharmacology review addressed the following three key review issues:

ISSUE #1 – Recommended Dosage: The major review issue for the Clinical Pharmacology team is the (b) (4) FDA recommended dosage is 200 mg orally QD with food, based on the following review considerations:

- Dosage Randomization: The Applicant conducted a pivotal trial, WU-KONG1 Part B (WU-KONG1B), to compare two dosages 200 mg QD (N=91) and 300 mg QD (N=93) in a randomized design, which supported a comparison of activity, safety, tolerability and exposure-response (E-R) analyses between the two dosages for the proposed indication. Of note, the FDA Clinical and Statistical review teams also considered additional patients (n=18) who received sunvozertinib 300 mg QD in WU-KONG1B but were not randomized.

- Efficacy: The overall response rates (ORR) for the 200 mg QD and 300 mg QD dosage randomization cohorts were comparable (46% vs 47%). There were no clinically significant differences in E-R relationships for ORR observed over the dose range of 200 to 300 mg evaluated in WU-KONG1B and WU-KONG6.

- Safety and tolerability: Higher rates of dose modifications (e.g., dose reductions) and incidence of Grade ≥3 adverse events (AEs) (e.g., diarrhea and increased blood creatine phosphokinase/CPK) were observed at 300 mg QD compared to 200 mg QD from the dosage randomized cohorts in WU-KONG1B. Positive trends of E-R relationships were observed for any grade and grade ≥3 anemia and blood CPK increased over the dose range of 200 mg to 300 mg.

(b) (4)

ISSUE #2 – Intrinsic Factors: No clinically significant differences in the pharmacokinetics of sunvozertinib were observed based on age, sex, race, body weight, smoking status, mild to

moderate renal impairment, and mild to moderate hepatic impairment. The effect of severe renal and hepatic impairment on the pharmacokinetics of sunvozertinib have not been studied.

(b) (4)

No dose adjustment is needed for age, sex, race, body weight, smoking status, renal impairment, and hepatic impairment in the intended patient population.

ISSUE #3 – Extrinsic Factors:

- Sunvozertinib is a substrate of CYP3A and P-gp. Clinical DDI studies were conducted with itraconazole (P-gp and strong CYP3A inhibitor) and carbamazepine (strong CYP3A inducer). PBPK modeling was used to predict the effect of moderate/weak CYP3A inhibitors and inducers.
    - The labeling recommends avoiding concomitant use of strong CYP3A inhibitors as itraconazole increased sunvozertinib exposure by 1.5-fold and such effect is expected to be driven by CYP3A inhibition. If concomitant use cannot be avoided, dose reduction from 200 mg to 150 mg is recommended based on magnitude of sunvozertinib exposure increase and available dosage strengths (150 mg and 200 mg tablets). Concomitant use of moderate CYP3A inhibitors without dose adjustment is allowed based on a balance of potential exposure increase with and established safety and efficacy profiles for the 200 mg QD and 300 mg QD dose levels.
    - The labeling recommends avoiding concomitant use of strong and moderate CYP3A inducers based on the observed or predicted 40-50% decrease in sunvozertinib exposures. If concomitant use cannot be avoided, a dose increase from 200 mg to 400 mg is recommended based on the magnitude of sunvozertinib exposure changes and available dosage strengths. No clinically significant effect on sunvozertinib pharmacokinetics is predicted with weak CYP3A inducers.
- In vitro, sunvozertinib inhibits CYP3A4 and CYP2D6, and induces CYP3A4 and CYP2C8.
    - CYP3A4: The labeling recommends avoiding concomitant use with hormonal contraceptives (a special group of CYP3A substrates) but not the other CYP3A substrates as sunvozertinib decreased midazolam (sensitive CYP3A4 substrate) exposure by 23% and causes embryo-fetal toxicity.
    - CYP2D6 and CYP2C8: No clinically significant effect on the pharmacokinetics of CYP2D6 substrate is predicted. CYP2C8 is generally less inducible than CYP3A4. No dedicated DDI study was conducted as the induction potential of sunvozertinib on CYP2C8 is expected to be small and not clinically meaningful.
- In vitro, sunvozertinib inhibits P-gp, BCRP and OATP1B1. The labeling recommends monitoring for increased adverse reactions of P-gp or BCRP substrates, where minimal concentration changes may lead to serious adverse reactions based on two observations: 1)

Sunvozertinib increased digoxin (P-gp substrate) and rosuvastatin (BCRP and OATP1B1 substrate) exposure by 1.4-fold. 2) No change was observed in the endogenous biomarker for OATP1B (plasma CP-I) with or without sunvozertinib coadministration.

- Sunvozertinib displays pH-dependent solubility. However, population pharmacokinetics analysis showed that concomitant use of a proton pump inhibitor does not result in a clinically significant effect on the pharmacokinetics of sunvozertinib. Concomitant use with acid reducing agents is allowed.

6.1.1 Recommendations

The Office of Clinical Pharmacology recommends the approval of NDA 219839 from a clinical pharmacology perspective. The key review issue with the specific recommendations/comments are summarized in **Table 16**.

Table 16. Key Clinical Pharmacology Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness is the ORR observed in Part B of WU-KONG1 (See Section 8.1.2.8).
General dosing instructions	(b) (4) the FDA recommended dosage is 200 mg orally QD with food, based on the following review considerations: • Dosage Randomization: The Applicant conducted a pivotal trial, WU-KONG1B, to compare two dosages 200 mg QD (N=91) and 300 mg QD (N=93) in a randomized design, which supported a comparison of activity, safety, tolerability and E-R analyses between the two dosages for the proposed indication. • Efficacy: The overall response rates (ORR) for the 200 mg QD and 300 mg QD dosage randomization cohorts were comparable (46% vs 47%). There were no clinically significant differences in E-R relationships for ORR observed over the dose range of 200 to 300 mg evaluated in WU-KONG1B and WU-KONG6. • Safety and tolerability: Higher rates of dose modifications (e.g., dose reductions) and incidence of Grade ≥3 adverse events (AEs) (e.g., diarrhea and increased blood creatine phosphokinase/CPK) were observed at 300 mg QD

	compared to 200 mg QD from the dosage randomized cohorts in WU-KONG1B. Positive trends of E-R relationships were observed for Any Grade and Grade ≥3 anemia and increased blood CPK over the dose range of 200 mg to 300 mg. (b) (4) • Food effect: Suvozertinib is recommended to be taken with food. Although no clinically significant differences in the PK of sunvozertinib were observed when it was taken under fasted condition or with a high-fat or low-fat meal, a subgroup analysis for patients under a modified fasted condition (n=33) versus a low-fat fed (n=38) condition in WU-KONG1A showed that GI disorders is lowered with low-fat food (nausea/vomiting; 32% low-fat vs. 67% modified fasted).
Dosing in patient subgroups (intrinsic and extrinsic factors)	Hepatic impairment: No dosage adjustment is recommended in patients with mild (bilirubin ≤ ULN and AST > ULN or bilirubin >1 to 1.5x ULN and any AST) and moderate (bilirubin ≥ 1.5 to 3 x ULN and any AST) hepatic impairment. The effect of severe hepatic impairment (bilirubin > 3x ULN and any AST) on sunvozertinib exposure is unknown. Renal impairment: No dosage adjustment is recommended in patients with mild-to-moderate renal impairment (CLcr 30 to 89 mL/min). The effect of severe renal impairment (CLcr 15 to 29 mL/min) on sunvozertinib exposure is unknown. Age: No clinically significant differences in the PK of sunvozertinib were observed based on age (19 to 96 years). Body weight: No clinically significant differences in the PK of sunvozertinib were observed based on body weight (30 to 118 kg). Sex and race: No dosage adjustment is recommended based on

	sex or race (Asian 62%, White 28%, Black or African American 8%). Postmarketing requirements (PMRs) for assessing the effect of severe renal and hepatic impairment on sunvozertinib exposure will not be issued (b) (4)
Drug-drug interactions	<u>Sunvozertinib as a substrate:</u> • Avoid concomitant use with strong CYP3A inhibitors. If concomitant use cannot be avoided, reduce the dose from 200 mg to 150 mg. • Avoid concomitant use with strong and moderate CYP3A inducers. If concomitant use cannot be avoided, increase the dose from 200 mg to 400 mg. <u>Sunvozertinib as a precipitant:</u> • Avoid concomitant use with hormonal contraceptives and use effective non-hormonal contraception during treatment and for 2 weeks after the last dose. • Monitor for increased adverse reactions of P-gp or BCRP substrates, where minimal concentration changes may lead to serious adverse reactions.
Acid reducing agent	Concomitant use of acid reducing agents (e.g., proton pump inhibitors) does not result in a clinically significant effect on sunvozertinib PK.
QTc assessment	At 300 mg QD, a clinically significant QTc interval prolongation was not observed.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable since the to-be-marketed tablets were administered in WU-KONG1B.
Labelling	The proposed clinical pharmacology pertinent labeling is acceptable based on the Applicant and FDA reaching agreement with FDA recommended revisions.

Source: Reviewer-generated table.

6.1.2 Post-Marketing Requirements and Commitments

Clinical Pharmacology does not have any PMRs or postmarketing commitments (PMCs) for this submission.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology program includes nonclinical *in vitro* studies and eight clinical studies (three clinical studies in patients and five clinical pharmacology studies in patients or noncancer participants).

Nonclinical *in vitro* studies were performed to evaluate the factors that may impact the drug disposition in human, and to assess DDI potential of sunvozertinib as substrate, inhibitor or inducer of metabolizing enzymes or transporters. The data also included the PK properties following single and multiple doses of sunvozertinib in NSCLC patients and following single dose in healthy participants, as well as population PK analysis. Three phase 1/2 clinical studies in NSCLC patients assessed the PK in addition to safety and efficacy of sunvozertinib. Five clinical pharmacology studies were conducted in healthy participants or NSCLC patients to assess the clinical pharmacology properties of sunvozertinib.

Three clinical studies for assessment of PK, efficacy and safety in NSCLC patients:

- WU-KONG1, a phase 1/2 multinational study in NSCLC patients with EGFR or HER2 mutations. This study included two parts: part A (phase 1) and part B (phase 2 pivotal study).
- WU-KONG2, a phase 1 study in NSCLC patients with EGFR or HER2 mutations, conducted in China.
- WU-KONG6, a phase 2 pivotal study in NSCLC patients with EGFR exon20ins, conducted in China.

Five clinical pharmacology studies:

- WU-KONG11, a [^{14}C]-Radiolabelled human mass balance study in healthy male participants.
- WU-KONG27, a dedicated PK study in participants with moderate hepatic impairment and normal hepatic function.
- WU-KONG12, a single ascending dose (SAD), relative bioavailability between tablet and suspension formulation, and food effect study in healthy participants.
- WU-KONG7, a DDI study of sunvozertinib as a substrate with strong CYP3A inhibitor and inducer in healthy participants.
- WU-KONG19, a DDI study of sunvozertinib as the perpetrator of CYP3A, P-gp, BCRP and OATP1B1 in NSCLC patients.

Integrated analysis across studies included physiological based pharmacokinetic (PBPK), population PK (PopPK) analysis, and Exposure-Response (E-R) analysis for efficacy and safety, as well as Concentration-QTc (C-QTc) analyses.

- The PBPK model of sunvozertinib was built with the nonclinical and clinical data, and then applied for the assessment of the DDI risk of sunvozertinib as a CYP3A substrate, as well as an inhibitor of CYP2D6.
- PopPK PK analysis was performed to evaluate the effect of intrinsic and extrinsic factors on PK of sunvozertinib. E-R analysis was performed in early and late phase studies for efficacy (response rate) and selected safety endpoints to support dose selection.
- The effect of sunvozertinib on the QT/QTc interval was evaluated by C-QTc modeling analyses using the matched ECG and PK data collected in the pivotal phase 2 clinical studies (WU-KONG1B and WU-KONG6).

The Applicant's Position:

The clinical pharmacology program provides comprehensive assessments of PK characteristics, impacts of intrinsic/extrinsic factors on sunvozertinib exposure, exposure-response relationship with efficacy and safety endpoints, effect on QT/QTc interval to support sunvozertinib dose selection for marketing.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position that the clinical pharmacology program is comprehensive to support the currently recommended indication. In addition to the clinical studies mentioned above, a confirmatory trial (WU-KONG 28) is currently ongoing to compare sunvozertinib (300 mg QD) versus carboplatin-pemetrexed chemotherapy for the first-line treatment of patients with NSCLC with EGFR exon20ins mutations. (b) (4) now is completely enrolled as of June 2025.

However, based on FDA's clinical pharmacology and pharmacometrics reviews, FDA disagrees with the Applicant's proposed dosage. Instead, the FDA recommended dosage is 200 mg orally QD as the optimized dosage, with food. For details on the recommended dosage, refer to Section 6.3.2.2 and Section 19.4.2 of the Assessment Aid.

Besides, FDA clarifies that:

1) The five clinical pharmacology studies were conducted in healthy participants (N=3), patients with NSCLC (N=1) and noncancer patients (N=1).
2) The impact of concomitant use of acid reducing agents (e.g., proton pump inhibitor) on sunvozertinib PK was evaluated by the PopPK analysis as part of the extrinsic factor evaluation (see details in Section 6.2.2.2 and Section 19.4.1)

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

[*Source*: Module 2.7.2/Section 3.8]

(b) (4)

1) **Dose range determination based on nonclinical data**: Prior to clinical development, the target exposure (dose) for antitumor activity was defined by an integrated analysis of nonclinical pharmacology data, including relationship between PK, pharmacodynamics (inhibition of EGFR phosphorylation) and tumor growth inhibition, as well as predicted human PK.

   Nonclinical studies showed that in xenograft model carrying EGFR exon20ins, the exposure at (b) (4)mg/kg BID or above is required to achieve tumor regression (Section 5.3, Table 8) (b) (4) as shown in Figure 3.

Figure 3 Steady State Exposure of Sunvozertinib at 50 to 400 mg QD vs Target Exposure Derived from the Xenograft Models Carrying EGFR Exon20ins

Note: (b) (4)

2) **Efficacious dose range determination and confirmation**: In phase 1 dose escalation studies, the dose range of 50 mg to 400 mg was explored to identify maximum tolerated dose (MTD), and the dose range of 200 mg to 400 mg was further evaluated in dose expansion stage to narrow down the dose range (200 mg and 300 mg) for the phase 2 pivotal trial.

   Anti-tumor efficacy was observed at the dose levels of 100 mg and above. Sunvozertinib at 400 mg showed less optimal efficacy, compared to 200 mg and 300 mg (Module 2.7.3/Section 3.4). In addition, 400 mg was less tolerable than 300 mg QD or below, given the higher incidences of SAE, ≥ grade 3 TEAEs and TEAEs leading to dose reduction. Hence, 200 mg and 300 mg were further selected for the phase 2 pivotal study.

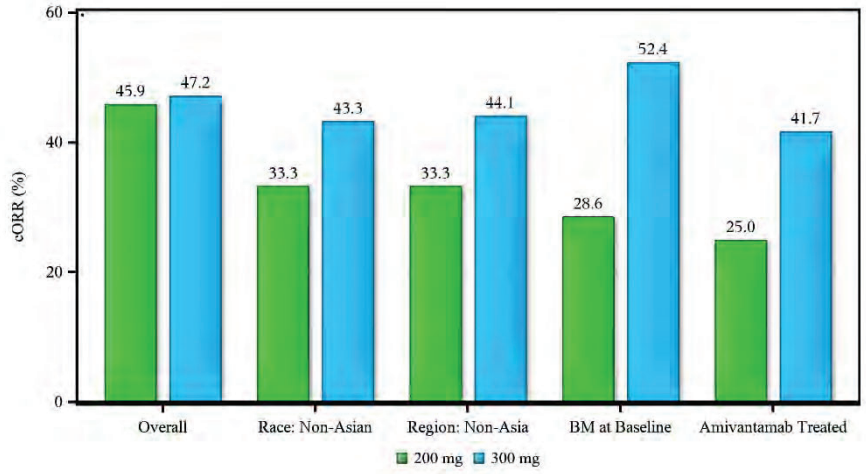
3) **Further dose optimization in phase 2 pivotal study**: The doses of 200 mg and 300 mg were evaluated using dose-randomization design. (b) (4)

(b) (4)

Clinical efficacy:

Data from the primary efficacy analysis set of WU-KONG1B demonstrated that sunvozertinib at 300 mg QD was effective (cORR: 45.8%) to achieve durable confirmed objective responses (DoR not mature, with the estimated 9-month and 12-month durable response rates of 59.3% and 50.1%, respectively), which also met the pre-specified target of this study with statistical significance. The comprehensive efficacy assessments (b) (4) as shown in Figure 4. In the exposure-efficacy analysis, no statistically significant relationship was identified between the systemic exposure and ORR across the dose range of 200 mg to 300 mg, probably due to large variability and small exposure difference between these two dose levels (Section 19.4.2.2 Figure 14).

Figure 4 cORR at 200 mg and 300 mg (Full Analysis Set, WU-KONG1B)

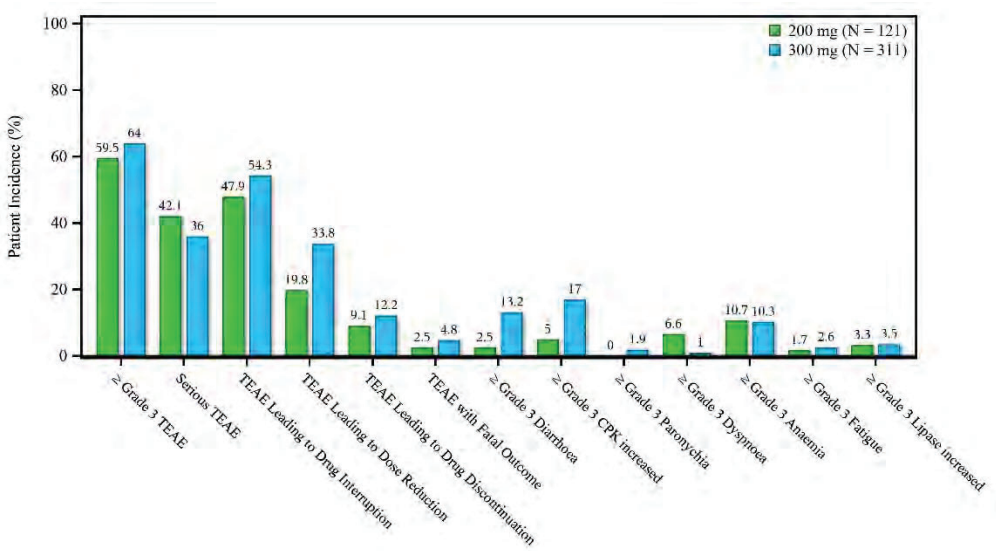


BM: Brain Metastasis; cORR: confirmed Objective Response.

Clinical Safety:

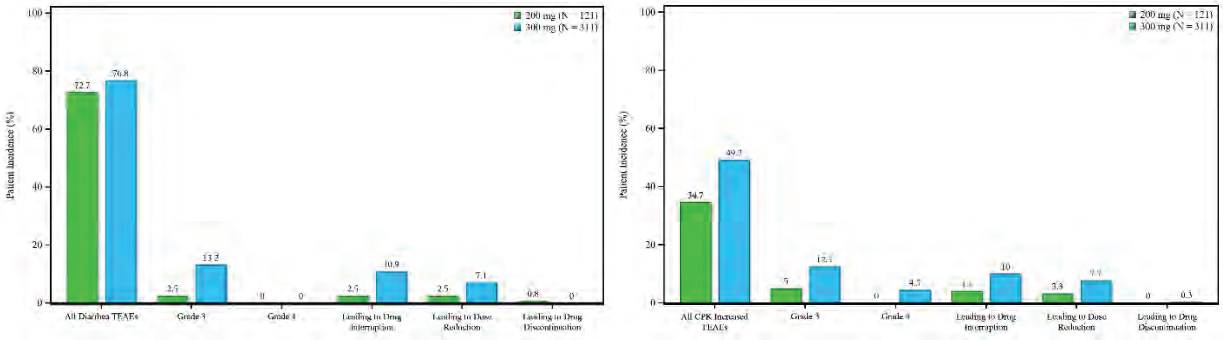
(b) (4) The median relative dose intensity was 92%. TEAEs were similar overall, with a slightly higher rate of ≥ grade 3 TEAEs at 300 mg than that of 200 mg (Figure 5), including diarrhea (2.5 vs 13.2%) and CPK increased (5% vs 17%).

Figure 5 Safety Endpoints at 200 mg and 300 mg (Overall Safety Analysis Set)



Both diarrhea and CPK increased could be monitored and well managed in the clinic with dose interruption and/or dose reduction as shown in Figure 6, and generally did not lead to treatment discontinuation. Therefore, these events were considered not to significantly impact patients continuing with sunvozertinib treatment. In exposure-safety analysis, higher exposure was associated with higher incidence of TEAEs (with grade ≥ 3) across the dose range of 50 mg to 400 mg, particularly for blood CPK increased (laboratory abnormalities), diarrhea and anemia (laboratory hemoglobin decreased) (Section 19.4.2.4 Figure 15 and Figure 16). However, the model-predicted increase in incidence of these identified TEAEs from 200 mg QD to 300 mg QD is marginal (Section 19.4.2.4 Table 48).

Figure 6 Incidence of Diarrhea (Left) and Blood CPK Increased (Right) at 200 mg and 300 mg (Overall Safety Analysis Set)



The Applicant's Position:

(b) (4)

(b) (4)

(b) (4)

Based on integrated safety analysis, both 200 mg QD and 300 mg QD demonstrated acceptable safety profiles with the median relative dose intensities of > 90% at both dosages. There was slightly higher percentage of patients experiencing ≥ grade 3 TEAEs at 300 mg than that of 200 mg, and the major contributors were diarrhea and CPK increased. These events are expected for EGFR inhibitors. Nevertheless, these events could be well managed in clinic, and generally did not lead to treatment discontinuation. Interestingly, for disease related ≥ grade 3 TEAEs, i,e., dyspnea, the incidence was lower at 300 mg than that of 200 mg, (b) (4) For those AEs of special interest, there was no obvious difference in regard to recovery rate between the two dose levels, with the majority of events recovered/recovering. (b) (4)

(b) (4)

The FDA's Assessment:

(b) (4) the FDA recommended dosage is 200 mg orally QD with food, based on the following review considerations:

- Dosage Randomization: The Applicant conducted a pivotal trial, WU-KONG1B, to compare two dosages 200 mg QD (N=91) and 300 mg QD (N=93) in a randomized design, which supported a comparison of activity, safety, tolerability and E-R analyses between the two dosages for the proposed indication.

- Efficacy: The overall response rates (ORR) for the 200 mg QD and 300 mg QD dosage randomization cohorts were comparable (46% vs 47%). There were no clinically significant differences in E-R relationships for ORR observed over the dose range of 200 to 300 mg evaluated in WU-KONG1B and WU-KONG6.

- Safety and tolerability: Higher rates of dose modifications (e.g., dose reductions) and incidence of Grade ≥3 adverse events (AEs) (e.g., diarrhea and increased blood creatine phosphokinase/CPK) were observed at 300 mg QD compared to 200 mg QD from the dosage randomized cohorts in WU-KONG1B. Positive trends of E-R relationships were observed for Any Grade and Grade ≥3 anemia and increased blood CPK over the dose range of 200 mg to 300 mg.

(b) (4)

- Food Effect: Based on the clinical pharmacology review, FDA agrees with the Applicant on administration of sunvozertinib with food. There was no clinically significant effect of food on sunvozertinib exposures when taken with a standard high-fat meal or a low-fat meal versus the fasted condition. However, in WU-KONG1A, a subgroup analysis for patients with administration under a modified fasted conditions (n=33) versus a low-fat meal (n=38) condition showed that gastrointestinal (GI) disorders are lowered with a low-fat meal (nausea/vomiting; 32% low-fat vs 67% modified fasted) compared to modified fast. For details, refer to Section 6.3.2.4.

6.2.2.2 Therapeutic Individualization

Data:

[*Source:* Module 2.7.2/Sections 3.4 and 3.5]

Specific populations

The effects of demographic and patient covariates on PK of sunvozertinib were evaluated using PopPK analysis. Acknowledging the limited data in patients with moderate hepatic impairment from patient trials, a dedicated clinical pharmacology study (WU-KONG27) was conducted to evaluate the effect of moderate hepatic impairment (Child Pugh and NCI-ODWG classification) in noncancer participants. No data are available for sunvozertinib in patients with severe hepatic and renal impairment.

Here under are the results of the impact of intrinsic factors:

- Based on PopPK analysis, no clinically meaningful difference in sunvozertinib PK were observed based on age (19 to 96 years), sex, race (White, Black and Asian), body weight (30 to 118 kg) and smoking status.
- *Renal Impairment:* Sunvozertinib was minimally excreted in the urine (~5%). Based on results of PopPK analysis, no clinically meaningful difference in sunvozertinib PK was observed in patients with mild (Cockcroft-Gault formula calculated creatinine clearance (CLcr) 60 to 89 mL/min, N = 174) or moderate (CLcr 30 to 59 mL/min, N = 90) renal

impairment, compared with patients with normal renal function (CLcr ≥ 90 mL/min, N = 198).

- *Mild Hepatic Impairment:* The human mass balance study indicated that metabolic clearance was the primary route of sunvozertinib elimination. Based on PopPK analysis, no clinically meaningful difference in sunvozertinib PK was observed in patients with mild (NCI-ODWG Group B, N = 57) hepatic impairment, compared with patients with normal hepatic function (N = 406).
- *Moderate Hepatic Impairment:* A dedicated hepatic impairment study revealed that moderate hepatic impairment (Child-Pugh B, N = 8) did not have a clinically meaningful impact on the sunvozertinib PK. When staging with NCI-ODWG criteria, moderate hepatic impairment (NCI-ODWG Group C, N = 4) increased C_{max} and $AUC_{0\text{-}inf}$ of sunvozertinib by 36% and 12%, respectively, as compared with matched healthy controls. However, the differences are not regarded clinically meaningful.

Concomitant medication instruction (sunvozertinib as victim)

In vitro, sunvozertinib is metabolized by CYP3A4/5 and also a substrate of P-gp. Therefore, coadministration of CYP3A4 inhibitors/inducers may alter sunvozertinib PK.

In a clinical pharmacology study (WU-KONG7), the effect of strong inhibitor of CYP3A4 (itraconazole) and strong inducer of CYP3A4 (carbamazepine) on sunvozertinib PK was evaluated. The effect of moderate inhibitors of CYP3A4 (erythromycin, verapamil and fluconazole) and weak or moderate inducers of CYP3A4 (dexamethasone and efavirenz) on sunvozertinib PK was evaluated using PBPK modeling.

Here under are the effects of the extrinsic factors on sunvozertinib PK:

- *Effect of CYP3A4 inhibitors*: Coadministration of multiple doses of a strong CYP3A4 inhibitor, itraconazole, increased the geomean C_{max} and $AUC_{0\text{-}inf}$ of a single oral dose of sunvozertinib by 32% and 51%, respectively. (b) (4) [redacted]
- *Effect of CYP3A4 inducers*: Coadministration of multiple doses of a strong CYP3A4 inducer, carbamazepine, decreased the geomean C_{max} and $AUC_{0\text{-}inf}$ of a single oral dose of sunvozertinib by 38% and 48%, respectively. PBPK DDI simulations of concomitant use of sunvozertinib with moderate inducer (efavirenz) predicted the decreases in C_{max} by 24% and $AUC_{0\text{-}inf}$ by 46%.

Concomitant medication instruction (sunvozertinib as perpetrator)

As a perpetrator of DDI at clinically relevant doses, sunvozertinib has the induction potential for CYP3A4 and inhibition potential for hepatic OATP1B1, intestinal P-gp and BCRP. The induction potential was demonstrated *in vitro* for CYP3A4 mRNA via nuclear receptor PXR, which also regulates the expression of transporters such as P-gp. Therefore, sunvozertinib has the induction potential for transporters, consequently decreasing the exposure of these transporter substrates.

The effect of sunvozertinib on the PK of sensitive probe substrates of CYP3A4, P-gp, BCRP and OATP1B1 was evaluated in a clinical pharmacology study (WU-KONG19).

- *Effect on CYP3A4 substrates:* Coadministration of multiple doses of 300 mg sunvozertinib with a single oral dose of midazolam decreased midazolam $AUC_{0\text{-}inf}$ and C_{max} by 23% and 15%, respectively.
- *Effect on P-gp substrates:* Coadministration of a single dose of 300 mg sunvozertinib with a single dose of digoxin increased digoxin $AUC_{0\text{-}48}$ and C_{max} by 36% and 21%, respectively. Since multiple doses of sunvozertinib did not further alter the exposure of digoxin as compared with a single dose, sunvozertinib is an inhibitor of P-gp but not a clinical inducer.
- *Effect on BCRP and OATP1B1 substrates*: Coadministration of a single dose of 300 mg sunvozertinib with a single dose of rosuvastatin increased rosuvastatin $AUC_{0\text{-}48}$ and C_{max} by 41% and 62%, respectively. Moreover, multiple doses of sunvozertinib did not further alter the exposure of rosuvastatin as compared with a single dose. No change was observed in the endogenous biomarker for OATP1B (plasma CP-I) with or without sunvozertinib coadministration. It suggested that sunvozertinib is an inhibitor of BCRP rather than OATP1B, based on the totality of evidence from clinical DDI data with a probe substrate for BCRP/OATP1B and an endogenous biomarker for OATP1B. Additionally, there was no indication of an induction of BCRP transporter by sunvozertinib.

The Applicant's Position:

No therapeutic individualization is necessary in the intended patients based on demographic factors (age, race, body weight and sex) or specific population (mild and moderate renal impairment, mild and moderate hepatic impairment).

There are clinically relevant drug-drug interactions for sunvozertinib. The proposed management strategies are presented below:

- *Effect of CYP3A inhibitors:* Avoid concomitant use of sunvozertinib with (b) (4) strong CYP3A inhibitors. If concomitant use is unavoidable, reduce sunvozertinib dosage (b) (4) No dose adjustment is necessary for sunvozertinib when coadministered with weak CYP3A4 inhibitors.
- *Effect of CYP3A4 inducers:* Avoid concomitant use of sunvozertinib and moderate or strong CYP3A4 inducers. No dose adjustment is necessary for sunvozertinib when coadministered with weak CYP3A4 inducers.
- *Effect on CYP3A4 substrates*: Avoid concomitant use of sunvozertinib with hormonal contraceptives (e.g., ethinyl estradiol), where minimal concentration changes may lead to serious therapeutic failure. Use non-hormonal contraceptive method during concomitant use and for (b) (4) after discontinuation of sunvozertinib.

- *Effect on P-gp or BCRP substrates*: Monitor for adverse reactions of the BCRP or P-gp substrates, where minimal concentration changes may lead to increased risk of adverse reactions, when coadministered with sunvozertinib.

The FDA's Assessment:

FDA agrees with the Applicant that no dose adjustment is needed in the intended patient population based on age (19 to 96 years), sex, race (Asian 62%, White 28%, Black or African American 8%), body weight (30 to 118 kg), smoking status, mild to moderate renal impairment (CLcr 30 to 89 mL/min, estimated by Cockcroft-Gault), and mild (bilirubin ≤ ULN and AST > ULN or bilirubin >1 to 1.5x ULN and any AST) to moderate (bilirubin ≥ 1.5 to 3 x ULN and any AST) hepatic impairment.

Regarding DDI, the FDA generally agrees with Applicant's analysis but updated the following two PBPK analyses based on the recommended dosage of 200 mg QD:

1) **Moderate CYP3A inhibitor:** The FDA updated PBPK simulation, using a 200 mg QD sunvozertinib FDA recommended dosage, and predicted increases in sunvozertinib C_{max} by 26% and AUC by 29%, with concomitant use of fluconazole (moderate CYP3A inhibitor).

2) **Moderate CYP3A inducer:** Similarly, the FDA updated PBPK simulation for concomitant use of sunvozertinib (200 mg QD) with efavirenz (moderate CYP3A inducer) predicted decreases of sunvozertinib C_{max} by 40% and AUC by 44%.

FDA partially agrees with proposed DDI management strategies and recommended the following:

- **CYP3A inhibitors:** FDA agrees with avoiding concomitant use of strong CYP3A inhibitors. Based on the recommended dosage of 200 mg QD and magnitude of sunvozertinib exposure increase, FDA updated the dose adjustment recommendation that, if concomitant use of strong CYP3A inhibitor is unavoidable, the sunvozertinib dosage should be reduced from 200 mg to 150 mg QD.

(b) (4) 1) The predicted increase of sunvozertinib AUC is 1.3-fold following concomitant use of fluconazole (moderate CYP3A inhibitor) at 200 mg, which result in a sunvozertinib AUC equivalent to a 260 mg dose; 2) Depending on the dose level used, some moderate CYP3A inhibitors (e.g., fluconazole at 50-100 mg) may have a smaller impact on sunvozertinib AUC. 3) While the safety profile is characterized up to 300 mg clinically, the efficacy below 200 mg is unclear. Therefore, concomitant use with moderate CYP3A inhibitors would result in an acceptable safety profile, which is lower than the exposure at 300 mg. However, a dose reduction, when concomitant use is necessary, would potentially lead to a subtherapeutic exposure, as a result of variability in the magnitude of the effect of moderate CYP3A inhibitors. Therefore, concomitant use of sunvozertinib with moderate

CYP3A inhibitors without dose adjustment is acceptable.

- **CYP3A4 inducers:** FDA agrees with avoiding strong and moderate CYP3A inducers, and with no dose adjustment needed for concomitant use of weak CYP3A inducers. Given the indicated patient population has high potential of brain metastasis, concomitant use of antiepileptic drugs is expected with many antiepileptic drugs being CYP3A inducers (e.g., carbamazepine). Therefore, based on the medical need, recommendations of dose adjustment for concomitant use of CYP3A inducers should be provided. Based on similar sunvozertinib exposure changes (40-50% decrease) observed in DDI study with strong CYP3A inducer and PBPK prediction with moderate CYP3A inducer, FDA recommends that, if concomitant use cannot be avoided, increase the sunvozertinib dose from 200 mg to 400 mg when coadministered with strong and moderate CYP3A inducers.

- **CYP3A4 substrates:** FDA agrees with the Applicant recommendation to avoid concomitant use of sunvozertinib with hormonal contraceptives and to use effective non-hormonal contraception. However, the duration of using effective non-hormonal contraception should be revised to use during treatment with sunvozertinib and for 2 weeks after the last dose instead of the Applicant proposed (b) (4) after the last dose. See Section 6.2.2.2 for details.

The Applicant also assessed the following factors for therapeutic individualization and listed them under Section 6.3.2.4:

- *Effect of food:* Of note, GI disorders were one of the most common TEAEs associated with sunvozertinib treatment. Subgroup analysis was performed to compare TEAEs in patients who received sunvozertinib under fasted and low-fat conditions. The results showed lower incidences of GI disorders, especially upper GI disorders (nausea/vomiting), in patients who took sunvozertinib with food, compared to those under fasted conditions (31.6% vs 66.7%). There was no clinically relevant effect of food on sunvozertinib PK with the to-be-marketed tablet. The patients in the pivotal safety/efficacy studies were instructed to take sunvozertinib with food to alleviate the GI toxicities. Therefore, sunvozertinib should be taken with food.

- *Effect of Acid reducing agents (ARAs):* Sunvozertinib is a weak base and displays pH dependent solubility. (b) (4) Sunvozertinib exhibited rapid dissolution in biorelevant media (FeSSIF, and pH 2.5 and 4.5 buffer representing the fed stomach). Minimal food effect also suggested that sunvozertinib was not sensitive to gastric pH change. PopPK analysis also indicated that PPI use dose not impact the absorption of sunvozertinib. Taken together, the risk of the interaction between sunvozertinib and ARA is low on fed condition. As sunvozertinib should be taken with food, the concomitant use of ARA is allowed.

- *Effect of sunvozertinib on CYP2D6 substrate: In vitro* studies showed that sunvozertinib is a weak reversible inhibitor of CYP2D6. No to weak inhibitory effect on desipramine (sensitive CYP2D6 substrate) was predicted with multiple doses of 300 mg sunvozertinib in cancer patients using PBPK modelling. Therefore, no dose adjustment for CYP2D6 substrate is necessary when sunvozertinib is coadministered.

FDA agrees with recommending sunvozertinib administration with food, no restriction for concomitant use with ARAs and no dose adjustment for concomitant use with CYP2D6 substrates. In vitro, sunvozertinib induces CYP2C8. No dedicated DDI study was conducted to evaluate the interaction potential of sunvozertinib with CYP2C8 substrate as CYP2C8 is generally less inducible than CYP3A4 and sunvozertinib decreased midazolam (sensitive CYP3A substrate) AUC by 23%. The induction potential of sunvozertinib on CYP2C8 is expected to be small and not clinically meaningful.

Additionally, FDA also assessed therapeutic individualization for patients with severe hepatic and renal impairment. The effects of severe hepatic impairment (total bilirubin > 3 x ULN and any AST) and severe renal impairment (CLcr 15 to 29 mL/min) on the pharmacokinetics of sunvozertinib have not been studied. However, PMRs will not be issued based on following reasons:

1) Sunvozertinib is primarily metabolized by CYP3A, the impact of severe hepatic impairment on sunvozertinib AUC is expected to be no larger than that of strong CYP3A inhibitors (e.g., itraconazole increased sunvozertinib AUC by 51%).

2) The safety margin of sunvozertinib has been established up to 300 mg. Based on a recommended dose of 200 mg, severe hepatic impairment is expected to increase sunvozertinib exposure no larger than the exposure achieved at 300 mg. Therefore, no dosage adjustment is needed for patients with severe hepatic impairment at the recommended 200 mg QD dosage.

3) Sunvozertinib is minimally excreted renally (~5%). An indirect effect on sunvozertinib exposure due to impaired renal function may come from its effect of altering drug metabolism or transport pathways. However, similar to severe hepatic impairment, the magnitude of sunvozertinib AUC increase is expected to be no larger than that of strong CYP3A inhibitors. Therefore, no dosage adjustment is needed for patients with severe renal impairment at the recommended 200 mg QD dosage.

6.2.2.3 Outstanding Issues

Data and the Applicant's Position:

Not applicable.

The FDA's Assessment:

No outstanding issues are identified from a clinical pharmacology perspective.

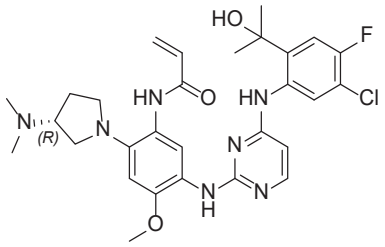
6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data and Applicant's Position:

The general overview of sunvozertinib ADME, clinical PK, and DDI potential of sunvozertinib is provided in Table 16.

Table 17 Highlights of Sunvozertinib Clinical Pharmacology

Physiochemical properties	
Chemical structure and molecular weight	Chemical Structure of sunvozertinib  Molecular formula: $C_{29}H_{35}ClFN_7O_3$ Molecular weight: 584.09 Log P = 3.91 (Determined in n-Octanol/pH11 buffer)
Aqueous solubility	Sunvozertinib has two base centers with pKa of 6.18 and 8.28. **Buffer** / **Equilibrium solubility after 24 hours (mg/mL)** pH 1.2 HCl solution: > 347 pH 4.5 citrate buffer: 25.3 pH 5.0 citrate buffer: 7.94 pH 5.2 citrate buffer: 4.24 pH 5.5 citrate buffer: 3.56 pH 6.8 phosphate buffer: 0.05 FaSSIF V1, pH 6.5: 0.34 FaSSIF V2, pH 6.5: 0.24 FeSSIF V1, pH 5.0: 17.3 FeSSIF V2, pH 5.8: 3.95 [Source: Module 2.7.1/Section 3.1.1]
Pharmacology	
Mechanism of Action	Sunvozertinib is an oral, selective EGFR tyrosine kinase inhibitor that irreversibly inhibits EGFR with exon20ins, L858R and exon19del, T790M resistance mutations, uncommon mutations, and HER2 with exon20ins. In cell models, sunvozertinib inhibits phosphorylation of mutant forms of EGFR at 2.3- to 58-fold lower concentrations than that of wild-type EGFR. Sunvozertinib induced profound tumor regression in nonclinical disease models carrying EGFR exon20ins in a dose-dependent manner while had minimal activity in animal models with wild-type EGFR.
Active Moieties	Sunvozertinib

QT Prolongation	Based on the concentration-QTc analysis, a mean effect on ΔQTcF > 10 ms can be excluded across the full observed plasma concentration ranges of sunvozertinib (b) (4)
General Information	
Bioanalysis	All PK samples were analyzed with validated bioanalytical methods in all clinical studies of sunvozertinib.
Healthy vs. Patients	Patient status (healthy participant vs patient) was identified as a significant covariate of sunvozertinib PK parameters. The population PK predicted AUC in healthy participants is ~38% lower than that in NSCLC patients.
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Population pharmacokinetic analysis estimated the geometric mean (%CV) of steady-state AUC and steady-state C_{max} of sunvozertinib were 12,089 (42%) h*ng/mL and 619 (45%) ng/mL at 300 mg QD, respectively.
Maximally Tolerated Dose or Exposure	400 mg QD was determined as the MTD.
Dose Proportionality	Sunvozertinib AUC and C_{max} generally increased dose proportionally over the dose range of 50 mg to 400 mg following repeat QD dosing in NSCLC patients. **Parameter** / **Slope** / **90% CI of the Slope** $C_{ss,\ max}$ (ng/mL) / 1.21 / (1.054, 1.372) AUC_{ss} (h*ng/mL) / 1.18 / (1.014, 1.338) [Source: Module 2.7.2/Section 3.2.5]
Accumulation	The mean accumulation ratios were about 2.8 folds in AUC and 2.2 folds in C_{max} after multiple dosing of sunvozertinib.
Variability	From integrated PK of phase 1 studies, geometric CV% of single dose C_{max} and $AUC_{0\text{-}inf}$ were 60.7% and 58.5%, respectively; geometric CV% of multiple dose $C_{ss.max}$ and AUC_{ss} were 50.1% and 46.5%, respectively.
Absorption	
Bioavailability	The absolute bioavailability of sunvozertinib is unknown.
t_{max}	Sunvozertinib median t_{max} was approximately 4 to 7 hours across 50 mg to 400 mg in NSCLC patients.
Food effect (Fed/fasted)	In WU-KONG12D, no clinically meaningful differences in AUC and C_{max} of sunvozertinib were observed following administration of a single 300 mg dose with a high-fat meal (approximately 1,000 calories, approximately 50% fat), compared to administration under fasting conditions in healthy participants. **Sunvozertinib** / **High-Fat GLS mean** / **Fasted GLS mean** / **GLS mean ratios (Fed/Fasted) (90%CI)** C_{max} (ng/mL) / 208 / 188 / 1.107 (0.953, 1.285) $AUC_{0\text{-}inf}$ (h*ng/mL) / 7473 / 6885 / 1.085 (1.003, 1.175) [Source: Module 2.7.1/Section 2.2.3]
Distribution	
Volume of Distribution	Following a single oral dose of 300 mg sunvozertinib, the mean (SD) apparent volume of distribution (Vz/F) was 1842 (1263) L in NSCLC patients.
Plasma protein binding	The *in vitro* binding of sunvozertinib to human plasma proteins ranged from approximately 89.0% to 93.5%.
Blood to plasma ratio	The human blood to plasma partitioning for sunvozertinib was 0.695.
Elimination	
Terminal Half-Life	The mean (SD) half-life ($t_{1/2}$) of sunvozertinib was 48.0 (9.3) hours.
Clearance	The mean (SD) apparent clearance (CL/F) was 25.7 (13.2) L/h.
Metabolism	

Fraction Metabolized (% dose)	*In vitro* hepatocyte inhibition data suggests that the relative contribution of CYP3A (fm, CYP3A) is 0.388.
Primary Metabolic Pathway(s)	• *In vitro*, CYP3A were the principal CYP enzymes responsible for human metabolism of sunvozertinib. Glutathione conjugation is an alternative pathway in sunvozertinib metabolism. • The demethylated metabolite DZ0753 was formed via CYP3A4. • *In vivo*, the relative abundance of DZ0753 in the systemic circulation is about 10% of sunvozertinib.
Excretion	
Primary Excretion Pathways (% dose) ±SD	Following a single oral dose of 100 mg radiolabeled sunvozertinib in healthy participants, 88.9% (84.5 to 91.7%) of the total radioactive dose was recovered in excretes, including 78.6% of the dose recovered in feces (7.3% unchanged) and 10.3% in urine (5.6% unchanged).
Drug-drug interaction	
Drug as substrate	• *In vitro,* sunvozertinib is a substrate of CYP3A and P-gp.
Inhibitor/inducer of metabolic enzymes	• *In vitro,* sunvozertinib inhibits CYP2D6 and CYP3A4 at clinically relevant concentration ranges. • *In vitro,* sunvozertinib induces CYP3A4 and CYP2C8 mRNA.
Inhibitor/inducer of transporter systems	• *In vitro,* sunvozertinib inhibits P-gp, BCRP and OATP1B1 at clinically relevant concentration ranges.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of ADME (absorption, distribution, metabolism and excretion) properties, dose proportionality and in vitro metabolism and DDI characterization of sunvozertinib.

For information on the bioanalytical method validation, refer to Section 19.4.4 of the Assessment Aid.

6.3.2 Clinical Pharmacology Questions

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

Data and the Applicant's Position:

Data from the primary efficacy analysis set of WU-KONG1B demonstrated that sunvozertinib at 300 mg QD was effective to achieve durable confirmed objective responses, which also met the pre-specified target of this study with statistical significance.

The IRC assessed cORR was 45.8% (97.5% CI: 34.8%, 56.1%). The IRC assessed DoR was not mature, and the estimated 9-month and 12-month durable response rates were 59.3% and 50.1%, respectively. (b) (4) achieved consistent treatment effect (cORR) across patient subgroups, irrespective of age, sex, race, region, smoking history, baseline brain metastasis, lines and types of prior therapies, and EGFR exon20ins subtypes. In patients with and without baseline brain metastasis, comparable cORRs were observed (51.9% vs 43.8%). Brain metastasis is an independent risk factor for overall survival of NSCLC patients, and more than 40% of patients had developed brain metastasis during their disease course (Han G, et al., 2016; Zhao

W, et al., 2022; Rangachari D, et al., 2015). In addition, anti-tumor efficacy by sunvozertinib was also observed in patients with (35.7%) or without prior amivantamab treatment (47.3%). These data suggest that sunvozertinib has an advantage of antitumor efficacy in patient without prior amivantamab treatment, compared to amivantamab in similar patient population (47.3% vs 40% Park K, et al., 2021), and also potentially overcomes the resistance to amivantmab treatment. The exposure-efficacy analysis suggested no significant E-R relationship for systemic exposure and ORR. The observation of a flat exposure-efficacy relationship predicted similar efficacy benefits across the exposure range achieved with 300 mg QD.

The most common adverse events at 300 mg QD, such as diarrhea or blood CPK increased, were well managed in the clinic, and generally did not lead to treatment discontinuation (Figure 6). In the drug label, the safety management approaches have been included to guide the future clinical use.

Therefore, sunvozertinib has a positive benefit-risk profile (b) (4)

The FDA's Assessment:

FDA agrees that WU-KONG1B provides the primary source of efficacy, which is discussed in Section 8.1.2.8 of the Assessment Aid. However, based on FDA's assessment, the exposure-response analyses for safety and efficacy do not support the Applicant's proposed dosage as an optimized dosage. Instead, FDA recommends a dosage of 200 mg orally QD with food. For details on the recommended dosage, refer to Sections 6.3.2.2, 8.1.2.8 and 19.4.2 of the Assessment Aid.

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

Data:

Please see Section 6.2.2.1 for General Dosing.

The Applicant's Position:

(b) (4) The integrated analysis, including dose-response and exposure-response analysis for both efficacy and safety, supports a favorable benefit-risk profile of this dosing regimen.

At this dosage, no clinically meaningful difference in PK was noted based on the demographic/patient covariates (age, sex, race, body weight, smoking status) and in specific populations (mild/moderate renal impairment and mild/moderate hepatic impairment). Additionally, the concentration-QT analysis demonstrated that a mean increase (>20 ms) in the QTc interval is unlikely at the proposed dosage.

The FDA's Assessment:

(b) (4) FDA recommended a dosage is 200 mg orally QD with food, based on the following review considerations:

- Dosage Randomization: The Applicant conducted a pivotal trial, WU-KONG1B, to compare two dosages 200 mg QD (N=91) and 300 mg QD (N=93) in a randomized design, which supported a comparison of activity, safety, tolerability and E-R analyses between the two dosages for the proposed indication.

- Efficacy: The overall response rates (ORR) for the 200 mg QD and 300 mg QD dosage randomization cohorts were comparable (46% vs 47%). There were no clinically significant differences in E-R relationships for ORR observed over the dose range of 200 to 300 mg evaluated in WU-KONG1B and WU-KONG6.

- Safety and tolerability: Higher rates of dose modifications (e.g., dose reductions) and incidence of Grade ≥3 adverse events (AEs) (e.g., diarrhea and increased blood creatine phosphokinase/CPK) were observed at 300 mg QD compared to 200 mg QD from the dosage randomized cohorts in WU-KONG1B. Positive trends of E-R relationships were observed for Any Grade and Grade ≥3 anemia and increased blood CPK over the dose range of 200 mg to 300 mg.

(b) (4)

- Food Effect: Based on the clinical pharmacology review, FDA agrees with the Applicant on administration of sunvozertinib with food. There was no clinically significant effect of food on sunvozertinib exposures when taken with a standard high-fat meal or a /low-fat meal versus the fasted condition. However, in WU-KONG1A, a subgroup analysis for patients with administration under a modified fasted conditions (n=33) versus a low-fat meal (n=38) condition showed that gastrointestinal (GI) disorders are lowered with a low-fat meal (nausea/vomiting; 32% low-fat vs 67% modified fasted) compared to modified fast. For details, refer to Section 6.3.2.4.

The FDA agrees with Applicant's analyses for intrinsic factors (demographic/patient covariates and organ impairment) and QT assessment.

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 and the Applicant's Position:

Based on the assessment of intrinsic factors, no dose adjustment or change in dosing regimen is recommended based on the demographic covariates (age, sex, race, and body weight) and in specific populations (mild/moderate renal impairment and mild/moderate hepatic impairment).

The FDA's Assessment:

FDA agrees with the Applicant that no dose adjustment is needed in the intended patients based on age (19 to 96 years), sex, race (Asian 62%, White 28%, Black or African American 8%), body weight (30 to 118 kg), smoking status, mild to moderate renal impairment (CLcr 30 to 89 mL/min, estimated by Cockcroft-Gault), and mild (bilirubin ≤ ULN and AST > ULN or bilirubin >1 to 1.5x ULN and any AST) to moderate (bilirubin ≥ 1.5 to 3 x ULN and any AST) hepatic impairment. The effect of severe hepatic impairment (total bilirubin > 3 x ULN and any AST) and severe renal impairment (CLcr 15 to 29 mL/min) on the pharmacokinetics of sunvozertinib have not been studied. (b) (4)

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

Data and the Applicant's Position:

[*Source:* Module 2.7.2/Section 3.5.1]

Please see Section 6.2.2.2 for the discussion of drug-drug interactions.

The clinically relevant food-drug and drug-drug interactions with concomitant medications are described in further details below with their respective recommendation for management.

Effect of food

Of note, GI disorders were one of the most common TEAEs associated with sunvozertinib treatment. Subgroup analysis was performed to compare TEAEs in patients who received sunvozertinib under fasted and low-fat conditions. The results showed lower incidences of GI disorders, especially upper GI disorders (nausea/vomiting), in patients who took sunvozertinib with food, compared to those under fasted conditions (31.6% vs 66.7%).

There was no clinically relevant effect of food on sunvozertinib PK with the to-be-marketed tablet. The patients in the pivotal safety/efficacy studies were instructed to take sunvozertinib with food to alleviate the GI toxicities. Therefore, sunvozertinib should be taken with food.

Effect of Acid reducing agents (ARAs):

Sunvozertinib is a weak base and displays pH dependent solubility. (b) (4) Sunvozertinib exhibited rapid dissolution in biorelevant media (FeSSIF, and pH 2.5 and 4.5 buffer representing the fed stomach). Minimal food effect also suggested that sunvozertinib was not sensitive to gastric pH change. PopPK analysis also indicated that PPI use dose not impact the absorption of sunvozertinib. Taken together, the risk of the interaction between sunvozertinib and ARA is low on fed condition. As sunvozertinib should be taken with food, the concomitant use of ARA is allowed.

Effect of sunvozertinib on CYP2D6 substrate

In vitro studies showed that sunvozertinib is a weak reversible inhibitor of CYP2D6. No to weak inhibitory effect on desipramine (sensitive CYP2D6 substrate) was predicted with multiple doses of 300 mg sunvozertinib in cancer patients using PBPK modelling. Therefore, no dose adjustment for CYP2D6 substrate is necessary when sunvozertinib is coadministered.

The FDA's Assessment:

FDA agrees with recommending sunvozertinib administration with food, no restriction for concomitant use with ARAs and no dose adjustment for concomitant use with CYP2D6 substrates. Other DDI aspects have been discussed under Section 6.2.2.2 of the Assessment Aid, including sunvozertinib as an object (CYP3A inhibitor and inducers) and as a precipitant (substrate of CYP3A, P-gp, BCRP and OATP1B1). Refer to Section 6.2.2.2 of the Assessment Aid for additional details.

X	X

Siyan Zhu, PhD	Jeanne Fourie-Zirkelbach, PhD
Primary Reviewer	Team Leader

7. Sources of Clinical Data

7.1 Table of Clinical Studies

The Applicant's Description:

Data:

An overview of the clinical studies is presented in Table 18. These studies supported the efficacy and safety evaluation for sunvozertinib in treating patients with locally advanced or metastatic NSCLC with EGFR exon20ins, whose disease has progressed on or after platinum-based chemotherapy.

Table 18 Sunvozertinib Clinical Studies Relevant to the Efficacy, Safety and Clinical Pharmacology Evaluation

Study Name/ Study ID/ Status	Primary Study Objective(s)	Study Design and Population	Dosage, Regimen, Route, Duration	Sample Size	No. of Centers and Countries/Regions[#]
Efficacy and Safety Studies					
WU-KONG1A/ DZ2019E0001, Part A/ Completed	Safety and tolerability, RP2D and MTD	Open-label, multicenter, dose escalation, dose expansion and food effect study in patients with advanced NSCLC harboring EGFR or HER2 mutations	Dose levels explored included 50 mg, 100 mg, 200 mg, 300 mg, 400 mg QD, orally, continuously in 21-day cycles (except for Cycle 0 [single dose followed by 7-day washout] of dose escalation and food effect cohorts and Cycle 1 [28-day cycle] of dose escalation cohorts).	N = 113	31 centers in 7 countries (The U.S., Australia, France, Japan, South Korea, Spain, Taiwan)
WU-KONG1B/ DZ2019E0001, Part B/ Ongoing	Anti-tumor efficacy (confirmed ORR, per IRC)	Open-label, multicenter study in patients with advanced NSCLC harboring EGFR exon20ins, who had progressed on or after or been intolerant of, at least one prior line of systemic therapy	**Cohort 1**: 200 mg, QD **Cohort 2**: 300 mg, QD QD, orally, continuously in 21-day cycles.	N = 202	89 centers in 12 countries (The U.S., Argentina, Australia, Canada, China, Chile, France, Italy, Malaysia, South Korea, Spain, Taiwan)
WU-KONG2/ DZ2019E0002/ Completed	Safety and tolerability, RP2D and MTD	Open-label, multicenter, dose escalation (3+3 design) and dose expansion study in Chinese patients with advanced NSCLC harboring EGFR or HER2 mutations	Dose levels explored included 50 mg, 100 mg, 200 mg, 300 mg, 400 mg orally, QD, continuously in 21-day cycles (except for Cycle 0 [single dose followed by 7-day washout] of dose escalation cohorts).	N=48	8 centers in China

Study Name/ Study ID/ Status	Primary Study Objective(s)	Study Design and Population	Dosage, Regimen, Route, Duration	Sample Size	No. of Centers and Countries/Regions[#]
WU-KONG6/ DZ2020E0001/ Completed	Anti-tumor efficacy (confirmed ORR, per IRC)	Open-label, single arm, multicancer study in Chinese patients with advanced NSCLC harboring EGFR exon20ins, whose disease has progressed on or been intolerant of, at least one prior line of systemic therapy	300 mg, QD, orally, continuously in 21-day cycles	N=104	33 centers in China
WU-KONG28/ DZ2022E0005/ Ongoing*	Anti-tumor efficacy (PFS, per BICR)	Open-label, multicenter, randomized study in patients with locally advanced or metastatic NSCLC patients with EGFR exon20ins who are newly diagnosed or treatment naïve	DZD9008 arm: 300 mg, QD, orally, continuously in 21-day cycles	See footnote	See footnote
Clinical Pharmacology studies					
WU-KONG7/ DZ2021E0008/ Completed	Drug- Drug Interaction as CYP3A substrate	Phase 1, single-center, nonrandomized, open-label, 2-part, fixed-sequence, drug-drug interaction study in healthy adult participants	**Part A**: Single doses of 100 mg (Formulation B tablet) orally **Part B**: Single doses of 300 mg (Formulation B tablet) orally	N=40	1 center in the U.S.
WU-KONG11/ DZ2021E0003/ Completed	Human ADME Study	Phase 1, single-center, non-randomized, open-label pharmacokinetic and mass balance study of oral-administered [^{14}C]-sunvozertinib in healthy male participants	Single dose of 100 mg [^{14}C] DZD9008 suspension, orally	N=8	1 center in the U.S.

Study Name/ Study ID/ Status	Primary Study Objective(s)	Study Design and Population	Dosage, Regimen, Route, Duration	Sample Size	No. of Centers and Countries/Regions[#]
WU-KONG12/ DZ2021E0004/ Completed	Human single dose PK, food effect (low-fat, high-fat), suspension formulation PK	Phase 1 PK study in healthy participants. **Part A**: randomised, double-blind, placebo-controlled study to assess the safety, tolerability and PK of sunvozertinib following a single ascending dose. **Part B** and **D**: randomised, two-sequence studies to evaluate the effect of low-fat and high-fat meal on single oral dose PK of DZD9008. **Part C**: to evaluate the PK of sunvozertinib suspension formulation.	**Part A**: single dose, including 50, 100, 200, 300 and 400 mg (Formulation A or B tablet), orally **Part B**: single dose, 300 mg (Formulation B tablet) under fasted and low-fat fed condition, orally **Part C**: single dose, 100 mg (Formulation A tablet or suspension), orally **Part D**: single dose, 300 mg (Formulation B tablet) under fasted and high-fat fed, orally	N=78 (Including placebo N = 10) **Part A:** N=40 **Part B**: N=12 **Part C**: N=6 **Part D**: N=20	1 center in the U.S.
WU-KONG19/ DZ2021E0009/ Completed	DDI as Perpetrator of CYP3A /P-gp /BCRP /OATP1B1	Open-label, non-randomized study of sunvozertinib on the PK of the cocktail probes representative for CYP3A4, P-gp, BCRP and OATP1B1 in patients with EGFR or HER2 mutant advanced NSCLC	300 mg, a single dose, followed by 1 day washout, then 300 mg, QD, for consecutive 27 days, orally	N=25	3 centers in China
WU-KONG27/ DZ2022E0007/ Completed	PK in participants with hepatic impairment	Single-dose, non-randomized, open-label, PK study of sunvozertinib in participants with moderate hepatic impairment	200 mg, a single dose of DZD9008 (Formulation B tablet), orally	N=17	2 centers in the U.S.

BICR: blinded independent central review; DDI: drug-drug interaction; EGFR: epidermal growth factor receptor; exon20ins: exon 20 insertion mutation; HER2: human epidermal growth factor receptor 2; IRC: independent review committee; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; ORR: objective response rate; PFS: progression free survival; RP2D: recommended phase 2 dose.

[#] The center number includes all the centers that screened patient for the study.

* WU-KONG28 is a phase 3, confirmatory study. No predefined interim analysis was planned, it is not included in the pooled efficacy and safety summary.

The FDA's Assessment:

FDA agrees with the Applicant's position with the exception that the primary efficacy and safety data supporting the proposed indication was derived from the WU-KONG1/DZ2019E001, Part B clinical trial. The pooled safety data for sunvozertinib 300 mg QD included a total of 311 patients from WU-KONG1/DZ2019E001 (n=182), WU-KONG2/DZ2019E0002 (n=25), and WU-KONG6/DZ2020E001 (n=104). The pooled safety data for sunvozertinib 200 mg QD included a total of 121 patients from WU-KONG1/DZ2019E001 (n=118) and WU-KONG2/DZ2019E0002 (n=3). No data from WU-KONG28/ DZ2022E0005 was provided by the Applicant and should not have been listed in the table above.

The clinical pharmacology trials, WU-KONG7/ DZ2021E0008, WU-KONG11/ DZ2021E0003, WU-KONG12/ DZ2021E0004, WU-KONG19/ DZ2021E0009, WU-KONG27/ DZ2022E0007 listed in the table above also should not have been included in this section of the Assessment Aid. Refer to the Clinical Pharmacology (Section 6) of this Assessment Aid for additional information.

8. Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position:

The evidence of efficacy and safety for sunvozertinib as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC with EGFR exon20ins, whose disease has progressed on or after platinum-based chemotherapy, is based on data from WU-KONG studies, including WU-KONG1A, WU-KONG2, WU-KONG1B, and WU-KONG 6. A total of 363 patients were included in the integrated efficacy analysis, including 192 patients in WU-KONG1B phase 2 pivotal study.

In addition, a phase 3 study (WU-KONG28, NCT05668988) is ongoing to confirm clinical benefit by evaluating the efficacy and safety of sunvozertinib monotherapy, as compared with carboplatin-pemetrexed chemotherapy, in the first-line treatment of NSCLC patients with EGFR exon20ins. (b) (4) no data from this phase 3 confirmatory study will be included.

For efficacy analysis, as agreed with FDA at the Pre-NDA meeting, the primary efficacy analysis set was the 300 mg overall cohort (300 mg-all) in the full analysis set (FAS) of WU-KONG1B pivotal study.

- There were three analysis sets in FAS of WU-KONG1B study:
  - 300 mg overall efficacy analysis set (300 mg-all, the primary efficacy analysis set)
  - 200 mg randomized efficacy analysis set (200 mg-rand)
  - 300 mg randomized efficacy analysis set (300 mg-rand)
- In addition, supportive evidence from other clinical studies were also included:
  - WU-KONG6 Efficacy analysis set (also FAS, the primary efficacy analysis set of WU-KONG6, China phase 2 pivotal study)
  - Pooled phase 1 efficacy analysis set (WU-KONG1A and WU-KONG2)

The FDA's Assessment

The FDA generally agrees with the Applicant's position with the following clarifications:

A total of 467 patients were enrolled across the three clinical trials WU-KONG1 (Part A and B), WU-KONG2, and WU-KONG6 at various dosages (50 mg to 400 mg) with sunvozertinib, including 192 patients in the WU-KONG1B clinical trial (n=107 for sunvozertinib 300 mg QD and n=85 for sunvozertinib 200 mg QD).

FDA notes that there were 202 patients enrolled in WU-KONG1B: the first 184 patients were randomized into the two dose cohorts (n=91 to 200 mg and n=93 to 300 mg) with an additional 18 patients enrolled to the 300 mg (b) (4) Among all patients

enrolled, 10 patients did not meet the efficacy analysis criteria with respect to measurable disease at baseline, having an EGFR exon 20 insertion mutation identified from tumor tissue, or receiving prior platinum-based chemotherapy; these patients were excluded from the full analysis set.

After excluding those 10 patients, the Applicant provided the following three efficacy analysis sets for WU-KONG1B:

- 300 mg overall efficacy analysis set (n=107 patients of which 89 patients were in the randomized efficacy analysis set and 18 patients were non-randomized)
- 300 mg randomized efficacy analysis set (n=89 patients)
- 200 mg randomized efficacy analysis set (n=85 patients)

FDA agrees that WU-KONG6, a China-only trial, provided supportive data; results from this trial were not independently verified by FDA. Additionally, WU-KONG28 should not have been included in this section as no data were provided to support either the efficacy or safety of sunvozertinib, though FDA acknowledges that the Applicant intends to utilize this trial to verify clinical benefit of sunvozertinib if the current application is granted Accelerated Approval.

8.1.1 Trial Design

8.1.1.1 WU-KONG1 Study

The Applicant's Description

[*Source:* Module 5.3.5.2/WU-KONG1A CSR and WU-KONG1B CSR]

Basic study design

WU-KONG1 is a phase 1/2, open-label, multinational study of sunvozertinib in patients with locally advanced or metastatic NSCLC with EGFR or HER2 mutations. The study consists of Part A (WU-KONG1A, phase 1) and Part B (WU-KONG1B, phase 2).

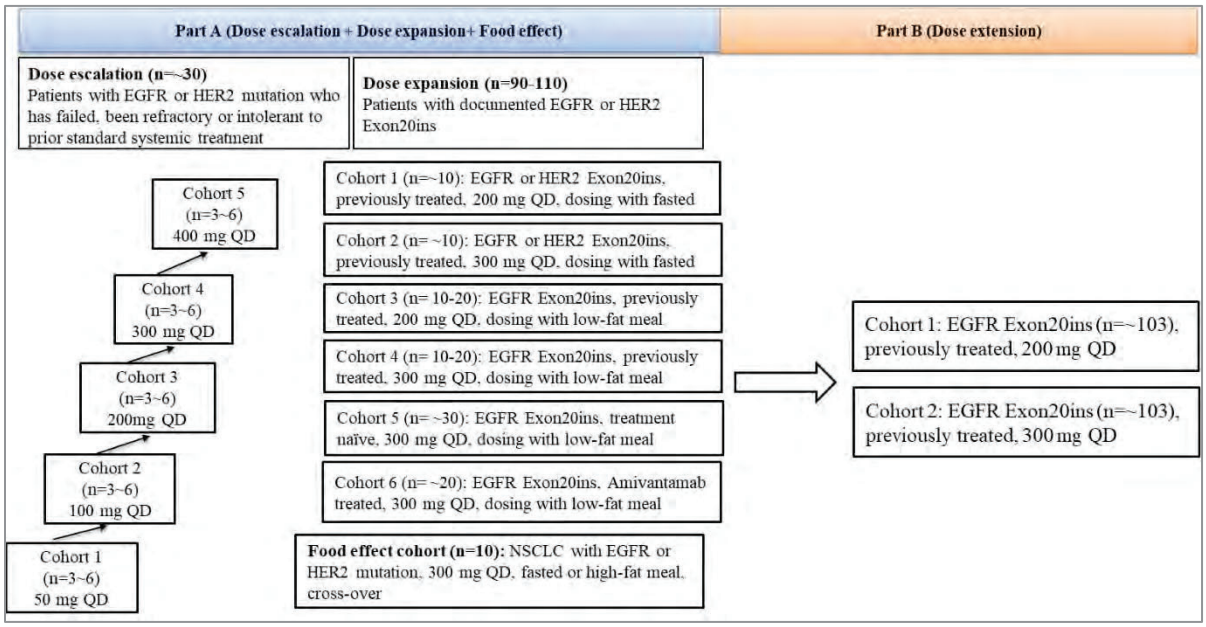
WU-KONG1A was a first-in-human study, including dose escalation, dose expansion and food effect cohorts. The primary objective was to assess safety, tolerability, PK, and anti-tumor efficacy of sunvozertinib, and to determine MTD and recommended phase 2 dose (RP2D). This study utilized a Bayesian logistic regression model (BLRM) with overdose control for dose escalation, starting from 50 mg QD, and increased in increments until MTD was defined. Decision for dose escalation upon agreement with Safety Review Committee (SRC). The dose expansion was initiated at the dose levels where anti-tumor activity (PR or CR) was observed in patients with EGFR or HER2 exon20ins. A separate cohort of ~10 patients were enrolled to assess the food effect on PK at a defined dose.

WU-KONG1B is a multinational phase 2 pivotal study in patients with advanced NSCLC with EGFR exon20ins. The primary efficacy outcome measure was confirmed ORR (cORR) as assessed by a blinded IRC. The duration of response (DoR) was the key secondary outcome measure. There were two dose randomized cohorts, 200 mg and 300 mg QD, with an interim analysis following

Simon two-stage design to check futility and inform the optimal RP2D selection for marketing application.

Figure 7 shows the study design of WU-KONG1.

Figure 7 Study Design of WU-KONG1 (Protocol Code: DZ2019E0001, Version 12.0)



The FDA's Assessment:

FDA agrees with the Applicant's description of the trial design. The trial initially planned to randomize (1:1) 206 patients stratified by brain metastasis at baseline (Yes vs No) and number of regimens of prior anti-cancer systemic therapy (<3 vs 3) to the 200 mg and 300 mg QD doses. However, based on results from an early interim analysis after a total of 52 patients were randomized into the 200 mg (n=25) or 300 mg (n=27) cohorts, among which 20 patients in each arm met the criteria of their efficacy analysis set by having at least one post-baseline assessment, the Applicant requested a Type D Written Response Only with FDA to discuss (b) (4) from WU-KONG1B. The Applicant presented the data from the 20 patients, regardless of prior platinum-based chemotherapy, reporting an ORR of 25% (95% CI: 9, 49) for the 200 mg QD dosage and an ORR of 40% (95% CI: 19, 64) for the 300 mg QD dosage. However, more adverse events were observed with the 300 mg dose, including more any Grade rash and anemia, more Grade ≥3 diarrhea, and more Grade ≥3 CPK elevation. FDA indicated that based on the provided data, (b) (4)

The Applicant continued to randomize more patients to both doses, conducting their pre-specified Simon two-stage interim analysis of the first 39 patients in each cohort who had completed at least two post-baseline tumor assessments (DCO Aug. 30, 2023). At that time, a

total of 156 patients were already randomized (n=79 to the 200 mg cohort and n=77 to the 300 mg. cohort). (b) (4) . In total, 91 patients were randomized to 200 mg and 93 patients were randomized to 300 mg, with an additional 18 patients enrolled to the 300 mg dose level in a non-randomized fashion.

Study Endpoints

The Applicant's Description

Part A

- Primary endpoints:
  - Safety endpoints: AE, serious adverse event (SAE), and dose limiting toxicity (DLT).
- Secondary endpoints:
  - PK endpoints: sunvozertinib concentrations in plasma and urine, and derived PK parameters.
  - Efficacy endpoints: ORR, best overall response (BOR), duration of response (DoR), disease control rate (DCR), tumor size change from baseline, and PFS assessed by investigator.

Part B

- Primary endpoint:
  - IRC assessed cORR according to Response Evaluation Criteria in Solid Tumor (RECIST v1.1).
- Secondary endpoints:
  - Key secondary endpoint: IRC assessed DoR
  - Other efficacy endpoints included: investigator assessed cORR and DoR; IRC and investigator assessed PFS, and tumor size change from baseline; OS
  - Other endpoints: safety and tolerability (AEs, and SAEs) and PK (plasma sunvozertinib and metabolite concentration, and derived PK parameters)

The FDA's Assessment:

FDA agrees with the Applicant's description of the study endpoints for WU-KONG1. FDA considers durable confirmed ORR evaluated by Independent Review Committee (IRC) per RECIST v1.1 as an appropriate efficacy endpoint to support accelerated approval for patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations.

FDA does not consider time to-event endpoints such as PFS and OS interpretable in the context of a single arm trial for the purposes of regulatory decision-making.

Eligibility criteria

The Applicant's Description

Key inclusion criteria:

For both Part A and Part B:Age ≥ 18

- Histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC
- Patients should have measurable disease at baseline according to RECIST v1.1
- Eastern Cooperative Oncology Group (ECOG) performance score 0-1
- Patients with brain metastasis (BM) can be enrolled under the condition that BM is previously treated and stable
- Adequate organ system functions

Part A specific

- Dose escalation and food effect cohorts: Patients should have documented EGFR or HER2 mutations
- Dose expansion cohorts: Patients should have documented EGFR or HER2 exon20ins

Part B specific:

- Patients should have documented EGFR exon20ins in tumor tissue
- Patients should have progressed on or after, or been intolerant of at least one line of platinum-based chemotherapy

Key exclusion Criteria

- Spinal cord compression or leptomeningeal metastasis
- Past medical history of or clinically active interstitial lung disease, and radiation related pneumonitis
- QTc interval > 470 msec (for France and Canada: > 470 msec for women and > 450 msec for men)
- Women of pregnancy or breastfeeding
- Previously treated with EGFR and HER2 exon20ins small molecule kinase inhibitors (only applicable for Part A expansion cohorts and Part B)

The overall study design was considered reasonable, with Part A exploring safety, PK and preliminary anti-tumor efficacy to define RP2D, and Part B further assessing anti-tumor efficacy and safety at the RP2D to support accelerated approval. The dose-randomization study design of Part B provided sufficient information for selection of the optimal dosage.

This design made it possible to explore a relatively broader patient population in Part A dose escalation cohorts, and to focus on more defined patient population in expansion cohorts with the

objective of guiding next stage of clinical development. For Part B pivotal study, the enrolled patients were representative of the intended patient population for marketing in different countries/regions. Prior amivantamab treated patients were allowed, given the unmet medical needs for this group of patients.

In single-arm pivotal studies, the primary endpoint of cORR, supported by key secondary endpoint of DoR, are acceptable surrogate endpoints for accelerated approval. These endpoints are considered to be predictive for patient survival, and thus are commonly used in clinical development for serious diseases with unmet medical needs. These efficacy endpoints for WU-KONG1B pivotal study have been agreed with FDA during the EOP1 meeting. In addition, safety and PK data were collected to enable benefit-risk assessment and dose selection.

Trial location

Part A:

A total of 31 sites across 7 countries/regions (U.S., Australia, France, Japan, South Korea, Spain, and Taiwan) enrolled 113 patients.

Part B:

A total of 89 sites across 12 countries/regions (U.S., Argentina, Australia, Canada, China, Chile, France, Italy, Malaysia, Spain, South Korea and Taiwan) enrolled 202 patients.

Choice of control group

Not applicable as this is a single-arm study.

Diagnostic criteria

Part A

Patients were required to have documented EGFR or HER2 mutations detected by the local laboratory. Retrospective mutation confirmation was conducted by the central laboratory. No companion diagnostic (CDx) was planned for Part A.

Part B:

Patients were required to have documented EGFR exon20ins in tumor tissue, which should be determined by local laboratory or sponsor designated central laboratory. EGFR exon20ins status was retrospectively confirmed via central laboratory testing. Central laboratory tissue-based CDx test was utilized in the bridging study to compare to the clinical trial assay used for patient enrollment. The *in vitro* diagnostic test, Oncomine™ Dx Express Test, is proposed as a tissue-based CDx test (via PMA M240008/M005).

Dose selection

Part A

- Dose escalation: 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg, QD
- Dose expansion: 200 mg and 300 mg, QD

- Food effect: 300 mg, QD

Part B

There were two dose cohorts: 200 mg (cohort 1) and 300 mg (cohort 2). Eligible patients were randomized into these two cohorts at a 1:1 ratio and the study allowed an interim analysis to select optimal RP2D based on the emerging data from 39 patients in each dose cohort.

Study treatment

Sunvozertinib was dosed orally.

Part A

- Dose escalation: Cycle 0 (single dose, followed by 7-day washout), then continuously daily dosing
- Dose expansion: continuously daily dosing
- Food effect: Cycle 0 (2 periods, single dose followed by 7-day washout), then continuously daily dosing

Part B

- continuously daily dosing

Assignment to treatment

The interactive response technology system was used in this study to assign each patient a unique enrollment code.

Part A: Randomization was applicable for food effect cohort (randomized to sequences of food conditions).

Part B: Blocked randomization method with stratification factors was utilized in part B. Eligible patients were randomized into 200 mg and 300 mg cohort at a 1:1 ratio, stratified by baseline brain metastasis (Yes, No) and number of prior systemic anti-cancer therapies (< 3, 3).

Blinding

Not applicable as no control arm was designed. Patients were informed which cohort and dose level were assigned.

Dose modification and discontinuation

Principles for dose modifications and discontinuation were outlined in the study protocol and summarized in the clinical study report.

Treatment related toxicities could be managed through either dose interruption or/and dose reduction. Sunvozertinib was to be interrupted in the event of grade 3 or 4 toxicity, and then resumed at the same dose or a reduced dose level following recovery of the toxicity to grade 2 or lower.

Per study protocol, sunvozertinib should be permanently discontinued in the event of ILD, ulcerative keratitis, or QTc prolongation with signs or symptoms of life-threatening arrhythmia.

Procedures and schedule

The Time and Event Schedule can be referred to Module 5.3.5.2/WU-KONG1A CSR and Module 5.3.5.2/WU-KONG1B CSR.

Dietary restriction/instruction

Part A dose escalation: sunvozertinib was administered orally under fasted conditions.

Part A dose expansion: sunvozertinib was administered under fasted condition (cohort 1, 2) or low-fat fed condition (cohort 3, 4, 5).

Part A food effect: sunvozertinib was administered under fasted conditions except for cycle 0 (2 periods under fasted or fed condition).

Part B dose extension: sunvozertinib was administered under fed condition.

Concurrent medication

Throughout the study, investigators were allowed to prescribe concomitant medications or treatment deemed necessary to provide adequate patient care except for those listed as prohibited medications (could be administered for toxicity management).

Treatment compliance

Sunvozertinib was an oral drug. It was self-administered by patients at home, except for the specific date on which patient was asked to take the drug at study site. Study drug taken was recorded by patients on patient diary for calculation of the compliance.

The FDA's Assessment:

FDA agrees with the Applicant's description of the eligibility criteria, trial location, lack of control arm, diagnostic criteria, dosage of sunvozertinib administered for Part A and Part B of the trial, study treatment, assignment to treatment, that the trial was not blinded, dose modification and discontinuation procedures, the schedule of assessments, dietary restrictions/instructions, guidance on concurrent medications, and plans to monitor treatment compliance, as reflected in the protocol.

While confirmed durable response of an appropriate magnitude can support an Accelerated Approval, FDA does not consider these endpoints as surrogate endpoints, but rather as intermediate clinical endpoints that are reasonably likely to predict clinical benefit and as such require a confirmatory pivotal trial to verify this benefit.

Protocol Amendments

The Applicant's Description

The original study protocol (dated January 16, 2019) was amended 11 times before the DCO date

of July 29, 2024. Among these, 9 amendments were related to Part B. Protocol Version 4 was the initial version created for EOP1 meeting with FDA. Following the meeting, protocol was updated with Version 9.0 as the initial version having patient enrolled. The latest version is Version 12.0. The amendments relevant to WU-KONG1B are summarized in Table 19. Amendments relevant to WU-KONG1A can be found in Module 5.3.5.2/WU-KONG1A CSR. The applicant does not believe the amendments impacted the integrity of the study or the interpretation of the results.

Table 19 Summary of Amendment to WU-KONG1B Study Protocol

Version/Date	Summary of Major Changes
Version 2.0 March 8, 2019	Following the pre-IND meeting with FDA, (b) (4) was removed from Part B. IRC review was added for Part B.
Version 3.0 September 6, 2019	Added international normalized ratio (INR) ≤ 1.5 × ULN and activated partial thromboplastin time (APTT) ≤ 1.5 × ULN; serum amylase ≤ 1.5 × ULN and serum lipase ≤ 1.5 × ULN into inclusion criteria per risk assessment based on DZD9008's activity on BTK in updated Investigator's Brochure. This amendment applied to both Part A and Part B.
Version 4.0 January 16, 2020	Added Part A expansion and changed Part B expansion to Part B extension (phase 2) study.
Version 5.0 December 17, 2020	Updated Part B extension from 4 cohorts with different EGFR or HER2 mutations to 1 cohort of EGFR exon20ins NSCLC (planned approximately 120 participants) only.
Version 8.0 April 29, 2021	Updated Part B extension cohort from only 1 cohort of 300 mg to 2 cohorts of 200 mg and 300 mg, and added Simon two-stage design, as well as updated the sample size. Updated the secondary study objectives by adding "to assess the impact of DZD9008 on patients' disease related symptoms and health related quality of life (HRQoL)".
Version 9.0* July 14, 2021	Updated exploratory endpoints by adding "collect and store plasma samples for EGFR exon20ins testing and necessary technical studies for liquid biopsy companion diagnostic development and approval" and "to collect and store blood-based samples for future exploratory research on genes/genetic aberrations that may influence response to DZD9008 treatment and/or susceptibility to DZD9008" and pharmacogenetic study.
Version 10.0 April 18, 2022	Updated the patient enrollment of Part B can be based on EGFR exon20ins confirmed in a local Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (or equivalent) or sponsor designated central laboratory.
Version 11.0 December 21, 2022	Updated the inclusion criteria by specifying that patient should have progressed on, or be intolerant of, at least one prior line with platinum-based chemotherapy.
Version 12.0 July 24, 2023	Added the description of re-screening; updated the definition of efficacy analysis set for Part B.

* The initial version for WU-KONG1B study patient enrolment.

The FDA's Assessment:

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

The Applicant implemented protocol amendment version 8 to modify the Part B extension cohort to a randomized, dose optimization to evaluate the efficacy of two doses of sunvozertinib, 200 mg QD or 300 mg QD by ORR, based on FDA feedback for dosage optimization.

FDA notes that the inclusion criteria with respect to prior response and treatment with platinum-based chemotherapy was revised with amendment 11; three patients randomized prior to this amendment had not received platinum-based chemotherapy including 2 patients in the

sunvozertinib 200 mg QD cohort and one patient in the sunvozertinib 300 mg QD cohort. Patients who had not received prior platinum-based chemotherapy were not included in the primary efficacy evaluation for this application.

These protocol amendments implemented during the trial do not appear to have had any substantial impact on trial integrity, or the evaluation of efficacy or safety of sunvozertinib.

Statistical Analysis Plan and Amendments

The Applicant's Description

The Statistical Analysis Plans (SAPs) were agreed and finalized prior to the database lock.

The draft SAP for WU-KONG1B pivotal study was submitted to FDA on April 30, 2021, together with protocol version 8.0, which reflected FDA's advice on interim futility analysis and dose selection. The SAP version 1.0 was finalized on September 6, 2023, with changes due to protocol amendments (from version 8.0 to 12.0) and optimal RP2D selection. (b) (4)

SAP amendment was made on November 16, 2023, to clarify the data presentation for randomized patients, and SAP version 2.0 was submitted to FDA on December 1, 2023.

The FDA's Assessment:

While the FDA generally agrees with the Applicant's presentation of the statistical analysis plan (SAP), (b) (4)

FDA evaluated efficacy and safety results for all dosage levels included in the trial, as presented in the review below.

When evaluating comparisons between the doses, the FDA review focused on the randomized patient populations at the two doses. When evaluating efficacy in a single cohort, the FDA review focused on the relevant patient populations enrolled at each dose regardless of randomization.

Efficacy analysis

The Applicant's Description

Efficacy analysis in WU-KONG1B was performed in FAS.

Considering two dose cohorts were planned in the study and the primary endpoint was analyzed within each cohort independently, Bonferroni method was employed to control the family-wise type I error (at one-sided 0.025). For the primary endpoint (cORR based on IRC assessment), the point estimate and its 97.5% 2-sided Confidence Interval (CI) in the primary efficacy analysis set (300 mg-all cohort) were reported based on Jung's method. P-value for the test against the null

hypothesis of cORR ≤ 17% were reported based on the Simon's two-stage method. For 200 mg-rand and 300 mg-rand cohorts, the CI for ORR was calculated based on exact (Clopper-Pearson) method. The DoR in the responders were evaluated using Kaplan-Meier method with the median value and it's 95% CI reported. PFS and OS data were analyzed using the same method as that for DoR.

No data imputation was applied for missing efficacy evaluations, except in instances of missing tumor size (WU-KONG1B only). The detailed imputation rules were specified in the SAP.

Patients with EGFR exon20ins from WU-KONG1A, who had received prior platinum-based chemotherapy and were evaluable for response, were included in the phase 1 pooled efficacy analysis set to provide supportive evidence of efficacy (using endpoints of ORR, DoR, PFS, and tumor size change) for this application.

Subgroup analysis

The cORR per IRC assessments and exact 95% CI was analyzed for the following prespecified subgroups of the FAS: age, sex, race, region, smoking history, failure reason for last line of platinum-based chemotherapy, number of prior anti-cancer lines, prior onco-immunotherapy status, prior amivantamab treatment, baseline brain metastasis, and EGFR exon20ins subtypes.

Interim analysis

An interim analysis was performed for WU-KONG1B to check futility and inform dose selection, which was planned for the primary endpoints according to the study protocol.

Safety analysis: See Section 8.2.

The FDA's Assessment:

FDA agrees with the Applicant's description of the trial design and endpoints in WU-KONG1B, noting that FDA did not assess results based on hypothesis testing or inferential assessments in the analysis of the independent cohorts. As such, while the Applicant assessed cohorts independently with statistical comparisons to historical rates and presents p-values for these assessments, FDA relied on an overall benefit:risk assessment to evaluate the outcome across primary and secondary endpoints within each cohort. This evaluation included both the magnitude of IRC-assessed confirmed ORR as well as sufficiently mature duration of response and whether the observed confirmed response rate and durability of the response outweigh any concerns over toxicity and safety in the context of other available therapies.

Confirmed ORR was assessed by FDA utilizing a 95% confidence interval.

Given that PFS and OS are time-to-event endpoints best evaluated with a comparator, these endpoints were evaluated and compared in the efficacy evaluable concurrently randomized patients from each cohort.

8.1.1.2 WU-KONG6 Study

The Applicant's Description

WU-KONG6 was a phase 2, single arm, open-label, multi-center, pivotal study to evaluate anti-tumor efficacy of sunvozertinib in Chinese patients with locally advanced or metastatic NSCLC harboring EGFR exon20ins, who had progressed on or after, or been intolerant to platinum-based chemotherapy.

Trial location

A total of 33 sites in China enrolled 104 patients.

Endpoints

The primary and secondary endpoints of WU-KONG6 were similar to those of WU-KONG1B.

Dose level

The recommended dosage is 300 mg QD, taken with food.

Key eligibility criteria

The key inclusion and exclusion criteria of WU-KONG6 study were similar to those of WU-KONG1B study.

Detailed information of protocol and protocol amendments are provided in Module 5.3.5.2/WU-KONG6 CSR.

Statistical analysis plan

The SAP for WU-KONG6 was finalized prior to the database lock. The efficacy and subgroup analysis of WU-KONG6 were similar to those of WU-KONG1B study.

The FDA's Assessment:

FDA agrees with the Applicant's description of the WU-KONG6 Study.

8.1.1.3 WU-KONG2 Study

The Applicant's Description

WU-KONG2 was a phase 1, open-label, multicenter study of sunvozertinib in Chinese patients with locally advanced or metastatic NSCLC harboring EGFR or HER2 mutations, who had failed from prior standard of treatment. The study consisted of Part A (dose escalation) and Part B (dose expansion).

Trial location

A total of 8 sites in China enrolled 48 patients.

Endpoints

The primary and secondary endpoints were similar to those of WU-KONG1A.

Dose level

Part A (Dose escalation): 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg, QD

Part B (Dose expansion): 300 mg, 400 mg, QD

Key eligibility criteria

The key eligibility criteria for Part A and Part B of the study were similar to those of WU-KONG1A dose escalation and expansion cohorts.

Detailed information of protocol and protocol amendments are provided in Module 5.3.5.2/WU-KONG2 CSR.

The FDA's Assessment:

FDA agrees with the Applicant's description of the WU-KONG2 Study.

8.1.2 Study Results

8.1.2.1 Compliance with Good Clinical Practices

The Applicant's Position:

All clinical studies were 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 obligation of clinical investigators to GCP (21 CFR 312.50 to 312.70).

The applicant confirms that studies were conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for Good Clinical Practice (GCP), and applicable regulatory requirement(s). Studies were approved by Institutional Review Boards or Independent Ethics Committees, and Informed Consent was obtained from all participants as per GCP requirements. Investigators were instructed not to deviate from the protocol except where necessary to eliminate an immediate hazard to study participants. Sites documented all protocol deviations in the participant's source documents. The applicant assessed any protocol deviation; if it was likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated, it was reported to regulatory authorities as a serious breach of GCP and the protocol.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.2.2 Financial Disclosure

Data:

Of the 937 principal investigators and sub-investigators participating in WU-KONG1B Study, 930 (99.2%) provided financial disclosure forms, and none had disclosable financial interests. A total of 7 sub-investigators did not provide financial disclosure forms, 6 were from the sites where no patients were enrolled, and another 1 did not perform any study activities.

The Applicant's Position:

The Applicant has adequately assessed clinical investigators for any financial interest/ arrangements and no disclosable financial interests were found.

The FDA's Assessment:

Appropriate financial disclosure was submitted with the application for WU-KONG1B, and no financial arrangements with the Investigator impacted the validity of the trial. Additional information regarding financial disclosure can be found in Section 19.2 Financial Disclosure of the Assessment Aid.

8.1.2.3 Patient Disposition

The Applicant's Description

Data:

[*Source:* Module 2.7.3/Section 1.4 and Section 3.2]

A total of 363 patients from WU-KONG1A, WU-KONG1B, WU-KONG2, and WU-KONG6 studies, with characteristics relevant to the intended population for marketing application, were included in the efficacy analysis sets. Results were summarized by different analysis sets.

- WU-KONG1B efficacy analysis set
    - WU-KONG1B primary efficacy analysis set (300 mg-all efficacy analysis set) (N=107):

      This is also the primary efficacy analysis set for this application. Patients who met the following criteria were included in this analysis set: 1) enrolled into cohort 2 of WU-KONG1B study; 2) with documented EGFR exon20ins in tumor tissue; 3) previously treated with platinum-based chemotherapy for advanced disease; 4) received at least one dose of sunvozertinib at 300 mg QD; 5) had measurable disease at baseline assessed by IRC.

      A total of 107 patients were included in this efficacy analysis set. As of July 29, 2024, the last patient has been followed up for at least 8 months.

    - WU-KONG1B 200 mg (N=85) and 300 mg (N=89) randomized efficacy analysis sets:

      Patients who met the following criteria were included: 1) enrolled into WU-KONG1B study under randomization; 2) with documented EGFR exon20ins in tumor tissues; 3) previously treated with platinum-based chemotherapy for advanced disease; 4) received at least one dose of sunvozertinib (200 mg or 300 mg QD); 5) had measurable disease at baseline assessed by IRC.

      A total of 174 patients were included in these two analysis sets (200 mg-rand, N=85; 300 mg-rand, N=89). The demographics and baseline disease characteristics were balanced between these two sets through stratified randomization, and thus the results

of these analysis sets were used to support the selection of optimal dosage for marketing.

- WU-KONG6 efficacy analysis set (FAS, N=97):

  Patients who met the following criteria were included: 1) enrolled into WU-KONG6 study; 2) with EGFR exon20ins confirmed by the central laboratory; 3) previously treated with platinum-based chemotherapy for advanced disease; 4) received at least one dose of sunvozertinib at 300 mg QD; 5) had measurable disease at baseline assessed by IRC.

  A total of 97 patients were included in this efficacy analysis set. The results of this analysis set, with DCO of April 3, 2023, were used to support conditional approval in China.

- Phase 1 pooled efficacy analysis set (WU-KONG1A and WU-KONG2, N=74):

  Patients who met the following criteria were included: 1) enrolled into the phase 1 studies (WU-KONG1A and WU-KONG2); 2) with documented EGFR exon20ins; 3) previously treated with platinum-based chemotherapy for advanced disease; 4) received at least one dose of sunvozertinib (dose range from 50 mg to 400 mg, QD); 5) had measurable disease at baseline and at least one post-baseline tumor assessment by investigator.

  A total of 74 patients were included in this analysis set. The results of this analysis set provided supportive evidence of anti-tumor efficacy by sunvozertinib. The DCOs for efficacy analysis of WU-KONG1A and WU-KONG2 studies were April 24, 2024, and September 27, 2021, respectively.

The Applicant's Position:

The efficacy analysis sets from WU-KONG studies could provide comprehensive efficacy analysis of sunvozertinib to support its approval. These analysis sets were previously aligned with FDA at the Pre-NDA meeting. It was agreed that results of the primary efficacy analysis set (N=107, WU-KONG1B), with the DCO of July 29, 2024, could form the basis of the NDA concerning the benefit of sunvozertinib in the intended patient population.

The FDA's Assessment:

For the WU-KONG1B clinical trial, FDA acknowledges the Applicant's position on using the 300 mg-All cohort as the primary efficacy analysis set for this application. However, there were similar overall response rates for the 200 mg QD and 300 mg QD dosages. FDA also reviewed data from the 85 patients who received sunvozertinib 200 mg QD for the proposed indication and who met the criteria for the primary efficacy analysis as described below.

FDA notes that a total of 202 patients were enrolled, with 91 patients randomly assigned to the 200 mg cohort, 93 randomly assigned to the 300 cohort, and 18 assigned to the 300 mg cohort without randomization (b) (4) A total of 10 patients (6 from the 200 mg cohort and 4 from the 300 mg cohort) were excluded from the FAS in WU-KONG 1B, as they did not meet criteria for the primary efficacy analysis as follows:

- Three (3) patients were excluded because they did not have EGFR exon20ins mutations (2 patients from the 200 mg cohort and 1 patient from the 300 mg cohort).
- Four (4) patients were excluded because they had not received prior platinum-based chemotherapy (2 patients from each cohort).
- Three (3) patients were excluded as they were assessed as not having measurable disease at baseline per IRC (2 patients from the 200 mg cohort and 1 patient from the 300 mg cohort).

Therefore, the primary efficacy population for the 200 mg cohort is based on n=85 randomized patients and the primary efficacy population for the 300 mg cohort is based on n=107 total patients (n=89 randomized patients and n=18 non-randomized patients).

Patient disposition from WU-KONG1B is shown in the table below.

FDA Table 20: Patient disposition for WU-KONG1B, FAS

	200 mg (N = 85) n (%)	**300 mg (N = 107) n (%)**
Patients Treated	85 (100)	107 (100)
Treatment status		
Treatment Ongoing	32 (38)	35 (33)
Treatment Discontinued	53 (62)	72 (67)
Primary Reason for Treatment Discontinuation		
Disease Progression	42 (49)	49 (46)
Adverse Event	7 (8)	13 (12)
Patient Decision	2 (2.4)	4 (3.7)
Non-compliance to Protocol	1 (1.2)	1 (0.9)
Other	1 (1.2)	5 (4.7)
Study Status		
Remained on Study	50 (59)	60 (56)
Discontinued from Study	35 (41)	47 (44)
Primary Reason for Study Discontinuation		
Death	31 (36)	37 (35)
Withdrawal by Patient	3 (3.5)	9 (8)
Lost to Follow-up	1 (1.2)	1 (0.9)

As of the data-cutoff date of July 29, 2024, treatment discontinuations occurred in 62% of patients for the sunvozertinib 200 mg cohort and 67% of patients for the sunvozertinib 300 mg cohort, treatment discontinuations due to disease progression occurred in 49% of patients for the sunvozertinib 200 mg cohort and 46% of patients for the sunvozertinib 300 mg cohort.

8.1.2.4 Protocol Violations/Deviations

The Applicant's Description

Data:

Among the 111 patients enrolled into 300 mg-all cohort of WU-KONG1B study, a total of 30 patients (27.0%) experienced at least one important protocol deviation. The most frequently occurred important protocol deviations were related to study conduct or procedures (including missing visits or missing testing required by protocol), followed by informed consent (incomplete informed consent process or using suspended consent form). Important protocol deviations are summarized in Table 21.

Table 21 Important Protocol Deviations (300 mg-All, WU-KONG1B)

Deviation Category **Deviation Subcategory**	**300 mg-All*** **(N = 111)** **n (%)**
Patients with at least 1 Important Protocol Deviation	30 (27.0)
Study Conduct/Procedures	22 (19.8)
Study Assessment	10 (9.0)
Sample Collection	6 (5.4)
Inclusion/Exclusion Criteria	4 (3.6)
Screening	7 (6.3)
Study Restrictions/Withdrawal Criteria	3 (2.7)
Informed Consent	13 (11.7)
Presence/Absence	10 (9.0)
Process	2 (1.8)
Signature/Date	1 (0.9)
Version	1 (0.9)
Safety	4 (3.6)
Recording	3 (2.7)
Reporting/Follow-up	1 (0.9)
Investigational Product	2 (1.8)
Handling/Storage/Retention	2 (1.8)

Source: Applicant Table. Module 5.3.5.2/WU-KONG1B CSR/Table 9. Data cut-off: July 29, 2024.
*All treated patients in 300 mg-all cohort, including the 107 patients in primary efficacy analysis set.

Important protocol deviation of WU-KONG1A, WU-KONG2 and WU-KONG6 studies can be found in the CSR of each individual studies in Module 5.3.5.2.

The Applicant's Position:

The applicant examined and investigated each and every important protocol deviation identified in WU-KONG1B study, as well as those identified in other studies relevant to the analysis. Similar in pattern and nature to other clinical studies, these deviations are considered not to impact the overall efficacy or safety conclusions of this NDA (Module 5.3.5.2/ WU-KONG1B CSR).

The FDA's Assessment:

On May 8, 2025, the Applicant responded to a May 2, 2025, Information Request from the FDA and provided the following additional data shown below.

Table 22: Important Protocol Deviations (WU-KONG1B) – Applicant Table

Deviation Category Deviation Subcategory	200 mg (N = 91) n (%)	300 mg-All (N = 111) n (%)
Patients with at least 1 Important Protocol Deviation	28 (30.8)	30 (27.0)
Study Conduct/Procedures	20 (22.0)	22 (19.8)
Study Assessment	5 (5.5)	10 (9.0)
Sample Collection	7 (7.7)	6 (5.4)
Inclusion/Exclusion Criteria	5 (5.5)	4 (3.6)
Screening	1 (1.1)	7 (6.3)
Dose Formulation/Dose Administration	3 (3.3)	0 (0.0)
Study Restrictions/Withdrawal Criteria	0 (0.0)	3 (2.7)
Informed Consent	7 (7.7)	13 (11.7)
Presence/Absence	4 (4.4)	10 (9.0)
Process	1 (1.1)	2 (1.8)
Signature/Date	2 (2.2)	1 (0.9)
Version	1 (1.1)	1 (0.9)
Safety	3 (3.3)	4 (3.6)
Recording	1 (1.1)	3 (2.7)
Reporting/Follow-up	2 (2.2)	1 (0.9)
Investigational Product	0 (0.0)	2 (1.8)
Handling/Storage/Retention	0 (0.0)	2 (1.8)
Other	1 (1.1)	0 (0.0)
Other	1 (1.1)	0 (0.0)

Source: ADSL, ADDV. Data extraction: 27Sep2024, Data cut-off: 29Jul2024.
N: Number of patients in the analysis set for each treatment group; The percentage was calculated based on N as denominator.
A patient was counted once only within each category or subcategory of important protocol deviation.

The FDA's Assessment

Protocol deviations occurred in 31% of patients for the sunvozertinib 200 mg cohort and 27% of patients for the sunvozertinib 300 mg cohort in the WU-KONG1B clinical trial. The protocol deviations were categorized into study conduct/procedure (22% for the 200 mg cohort vs 20% for the 300 mg cohort), informed consent (8% for 200 mg cohort vs 12% for 300 mg cohort), safety (3.3% for the 200 mg cohort vs 3.6% for the 300 mg cohort), investigational product (0% for 200 mg cohort vs 1.8% for 300 mg cohort) and other (1.1% for the 200 mg cohort vs 0% for

the 300 mg cohort). For clarification, the other category included a patient in the 200 mg cohort who did not return to the site within the specific visit window. For the Cycle 4 Day 1 and Cycle 6 Day 1 assessment visits, the patient was unable to return to the site due to hospitalization related to symptoms of nausea for Cycle 4 and hospitalization due to lumbar fracture for Cycle 6. The relevant assessments were performed one week later than the window period specified in the protocol.

These deviations do not impact the integrity of the study or interpretation of the trial results.

8.1.2.5 Table of Demographic Characteristics

The Applicant's Description

Data:

[*Source:* Module 2.7.3/Section 3.2]

There were 107, 97 and 74 patients included in WU-KONG1B primary efficacy analysis set, WU-KONG6 primary efficacy analysis set and phase 1 pooled efficacy analysis set, separately. The demographic characteristics of the patient population are provided in Table 23.

Of the 107 patients in WU-KONG1B primary efficacy analysis set, median age was 64 years (range: 37 to 85), 47.7% were ≥ 65 years of age; more than half were female (56.1%); 42.1% were non-Asian (including 40.2% of White and 1.9% of Black or African American); 45.8% were from non-Asia countries/regions; 64.5% were never smoker; 64.5% had ECOG performance score of 1 at study entry.

The demographics of the three efficacy analysis sets were in general comparable, except that the median age was older in WU-KONG1B study, and all patients were from China in WU-KONG6 study.

The Applicant's Position:

The demographic characteristics of patient population in the efficacy analysis sets were considered representative for the intended patient population.

Table 23 Demographic Characteristics (Efficacy Analysis Sets)

	Primary (N=107)	WU-KONG6 (N=97)	Phase 1 Pooled (N=74)
Age (Years)			
Median (Min, Max)	64.0 (37, 85)	58.0 (29, 79)	59.0 (32, 85)
Age Group, n (%)			
< 65/≥ 65	56 (52.3)/51 (47.7)	69 (71.1)/28 (28.9)	52 (70.3)/22 (29.7)
Sex, n (%)			
Female/Male	60 (56.1)/47 (43.9)	58 (59.8)/39 (40.2)	44 (59.5)/30 (40.5)
Race, n (%)			
Asian	62 (57.9)	97 (100.0)	61 (82.4)
White	43 (40.2)	0 (0.0)	13 (17.6)
Black or African American	2 (1.9)	0 (0.0)	0 (0.0)

	Primary (N=107)	WU-KONG6 (N=97)	Phase 1 Pooled (N=74)
Region, n (%)			
Asia/Non-Asia	58 (54.2)/49 (45.8)	97 (100.0)/0 (0.0)	52 (70.3)/22 (29.7)
Smoking History, n (%)			
Never/Ever	69 (64.5)/38 (35.5)	65 (67.0)/32 (33.0)	49 (66.2)/25 (33.8)
Baseline ECOG Performance Status, n (%)			
0/≥ 1/Missing	38 (35.5)/69 (64.5)/0 (0)	29 (29.9)/67 (69.1)/1 (1.0)	27 (36.5)/47 (63.5)/0 (0)

Source: Applicant Table. Module 2.7.3/Table 5, Table 7 and Table 9.
ECOG: Eastern Cooperative Oncology Group; Max: Maximum; Min: Minimum.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to a May 2, 2025, Information Request from the FDA and provided the following additional data shown below.

Table 24: Demographic Characteristics (Efficacy Analysis Sets, WU-KONG1B) – Applicant Table

	200 mg (N=85)	300 mg-All (N=107)
Age (Years)		
Median (Min, Max)	61.0 (35, 88)	64.0 (37, 85)
Age Group, n (%)		
<65/≥65	46 (54.1)/39 (45.9)	56 (52.3)/51 (47.7)
Sex, n (%)		
Female/Male	57 (67.1)/28 (32.9)	60 (56.1)/47 (43.9)
Race, n (%)		
Asian	55 (64.7)	62 (57.9)
White	28 (32.9)	43 (40.2)
Black or African American	0 (0.0)	2 (1.9)
Other	1 (1.2)	0 (0.0)
Not Reported	1 (1.2)	0 (0.0)
Region, n (%)		
Asia/Non-Asia	55 (64.7)/30 (35.3)	58 (54.2)/49 (45.8)
Smoking History, n (%)		
Never/Ever	60 (70.6)/25 (29.4)	69 (64.5)/38 (35.5)
Baseline ECOG Performance Status, n (%)		
0/1	33 (38.8)/52 (61.2)	38 (35.5)/69 (64.5)

Source: Applicant Table. Module 2.7.3/Table 5, Table 7 and Table 9.
ECOG: Eastern Cooperative Oncology Group; Max: Maximum; Min: Minimum.

Additional demographic and baseline characteristics are provided for the primary efficacy analysis population in WU-KONG1B in the table below.

FDA Table 25: Demographics and Baseline Characteristics, FAS

	200 mg (N=85)	300 mg-All (N=107)
Ethnicity, n (%)		
Not Hispanic or Latino	83 (98)	97 (91)
Hispanic or Latino	2 (2.4)	10 (9)
Stage of disease at study entry, n (%)		
Metastatic	82 (96)	104 (97)
Locally Advanced	3 (3.5)	3 (2.8)
Age Group, n (%)		
<75/≥75	29 (74)/10 (26)	37 (73)/14 (27)
Country of Enrollment		
China	43 (51)	45 (42)
France	9 (11)	19 (18)
Spain	7 (8)	16 (15)
Taiwan	7 (8)	8 (7)
U.S.A.	5 (6)	6 (6)
Italy	6 (7)	5 (4.7)
South Korea	5 (6)	3 (2.8)
Argentina	1 (1.2)	2 (1.9)
Malysia	0	2 (1.9)
Australia	1 (1.2)	1 (0.9)
Canada	1 (1.2)	0

For the sunvozertinib 200 mg cohort, the median age was 61 years (range: 35, 88 years); 67% were female; 65% were Asian; 33% were White; 2.4% were Hispanic or Latino; and 71% never smoked. At baseline, 61% had an ECOG PS of 1 and 96% had metastatic disease.

For the sunvozertinib 300 mg cohort, the median age was 64 years (range: 37, 85); 56% were female; 58% Asian; 40% White; 1.9% Black or African American; 9% Hispanic or Latino; and 64% never smoked. At baseline, 64% had an ECOG PS of 1 and 97% had metastatic disease.

The WU-KONG1B clinical trial was a multinational trial and the demographic and baseline characteristics of the patients were generally representative of the U.S. population, with the exception that the majority of patients were Asian or White and non-Hispanic/non-Latino. The trial did not include other racial and ethnic demographic groups to be entirely representative of the racial and ethnic diversity of the U.S. population. Please see Section 13 of the Assessment Aid describing the expectation that additional data, potentially in additional subgroups of patients, will be obtained from the ongoing WU-KONG28 confirmatory trial for sunvozertinib.

FDA did not independently verify data from WU-KONG6 as the trial was considered supportive only.

8.1.2.6 Other Baseline Characteristics

The Applicant's Description

Data:

[Source: Module 2.7.3/Section 3.2 and 3.3]

Other baseline characteristics, including disease characteristics and prior anti-cancer therapy, were summarized in and Table 27.

The baseline disease characteristics of the three analysis sets were in general comparable, except that higher percentage of patients in phase 1 pooled set had brain metastasis at the study entry. All patients (100%) had prior treatment with platinum-based chemotherapy for advanced NSCLC. Other treatments included onco-immunotherapy, antiangiogenic therapy, amivantamab, and first to third generations of EGFR TKIs. Patients in the phase 1 pooled analysis set were more heavily pretreated with prior anti-cancer therapy.

The Applicant's Position:

The baseline disease characteristics of the three efficacy analysis sets were representative for the intended patient population. The majority of patients were adenocarcinoma of histology, and at metastatic stage upon study entry. In these three analysis sets, at least 55 EGFR exon20ins subtypes were included, with 769_ASV and 770_SVD as the most predominant subtypes, consistent with published epidemiology reports (Riess JW, et al., 2018).

All patients received prior platinum-based chemotherapy, aligned with the prescribing populations. Primary efficacy analysis set comprised more patients with prior amivantamab treatment from U.S. and EU reflecting the changes of clinical practice in these regions. More patients in WU-KONG6 and phase 1 studies received first to third generations of EGFR TKIs, and fewer patients received prior onco-immunotherapy.

Table 26 Baseline Disease Characteristics (Efficacy Analysis Sets)

	Primary (N=107)	WU-KONG6 (N=97)	Phase 1 Pooled (N=74)
Histology Type, n (%)			
Adenocarcinoma	104 (97.2)	93 (95.9)	70 (94.6)
Squamous Cell Carcinoma	0 (0.0)	3 (3.1)	2 (2.7)
Adenosquamous Carcinoma	1 (0.9)	1 (1.0)	1 (1.4)
Other	2 (1.9)	0 (0.0)	1 (1.4)
Extent of Disease upon Study Entry, n (%)			
Locally Advanced/Metastatic	3 (2.8)/104 (97.2)	4 (4.1)/93 (95.9)	5 (6.8)/69 (93.2)
Brain Metastasis at Baseline, n (%)			
Yes/No	27 (25.2)/80 (74.8)	31 (32.0)/66 (68.0)	31 (41.9)/43 (58.1)
EGFR Exon20ins Subtype, n (%)*			
769_ASV	23 (21.5)	38 (39.2)	26 (35.1)
770_SVD	22 (20.6)	17 (17.5)	11 (14.9)

	Primary (N=107)	WU-KONG6 (N=97)	Phase 1 Pooled (N=74)
Others	57 (53.3)	42 (43.3)	31 (41.9)
Unknown	5 (4.7)	0 (0.0)	6 (8.1)

Source: Applicant Table. Module 2.7.3/Table 6, Table 8 and Table 10.
* EGFR exon20ins subtypes are presented in abbreviated term in this document. A summary of EGFR exon20ins subtypes by different format can be found in Module 2.5/Table 2.

Table 27 Previous Anti-cancer Therapies (Efficacy Analysis Sets)

	Primary (N = 107)	WU-KONG6 (N=97)	Phase 1 Pooled (N=74)
Patients with Any Prior Systemic Anti-Cancer Therapy, n (%)	107 (100.0)	97 (100.0)	74 (100.0)
Lines of Prior Anti-Cancer Therapy, n (%)			
1	69 (64.5)	47 (48.5)	24 (32.4)
2	29 (27.1)	34 (35.1)	18 (24.3)
≥ 3	9 (8.4)	16 (16.5)	32 (43.2)
Categories of Prior Anti-Cancer Therapy, n (%)			
Chemotherapy	107 (100.0)	97 (100.0)	74 (100.0)
Platinum-based Chemotherapy	107 (100.0)	97 (100.0)	74 (100.0)
Onco-immunotherapy [a]	52 (48.6)	34 (35.1)	31 (41.9)
Antiangiogenic Therapy [b]	30 (28.0)	58 (59.8)	33 (44.6)
Amivantamab	14 (13.1)	3 (3.1)	5 (6.8)
EGFR TKI [c]	14 (13.1)	26 (26.8)	28 (37.8)
Others	5 (4.7)	16 (16.5)	12 (16.2)

Source: Applicant Table. Module 2.7.3/Table 11, Table 12 and Table 13.
[a] Onco-immunotherapy includes anti-PD(L)-1 and anti-CTLA-4 monoclonal antibodies. [b] Antiangiogenic therapy only refers to anti-VEGF/VEGFR antibody, such as bevacizumab and its similar biological medicinal products. [c] EGFR TKI includes the first-, second- and third-generation EGFR TKIs.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to a May 2, 2025, Information Request from the FDA and provided the following additional data as shown below.

Table 28: Baseline Disease Characteristics (Efficacy Analysis Sets, WU-KONG1B) – Applicant Table

	200 mg (N=85)	300 mg-All (N=107)
Histology Type, n (%)		
Adenocarcinoma	80 (94.1)	104 (97.2)
Squamous Cell Carcinoma	3 (3.5)	0 (0.0)
Adenosquamous Carcinoma	1 (1.2)	1 (0.9)
Other	1 (1.2)	2 (1.9)
Extent of Disease upon Study Entry, n (%)		

	200 mg (N=85)	300 mg-All (N=107)
Locally Advanced/Metastatic	3 (3.5)/82 (96.5)	3 (2.8)/104 (97.2)
Brain Metastasis at Baseline, n (%)		
Yes/No	21 (24.7)/64 (75.3)	27 (25.2)/80 (74.8)
EGFR Exon20ins Subtype, n (%)*		
769_ASV	18 (21.2)	23 (21.5)
770_SVD	21 (24.7)	22 (20.6)
Others	41 (48.2)	57 (53.3)
Unknown	5 (5.9)	5 (4.7)

Source: Applicant Table. Module 2.7.3/Table 6

Table 29: Previous Anti-Cancer Therapies (Efficacy Analysis Sets, WU-KONG1B) – Applicant able

	200 mg (N=85)	300 mg-All (N=107)
Patients with Any Prior Systemic Anti-Cancer Therapy, n (%)	85 (100.0)	107 (100.0)
Lines of Prior Anti-Cancer Therapy, n (%)		
1	54 (63.5)	69 (64.5)
2	25 (29.4)	29 (27.1)
3	6 (7.1)	9 (8.4)
Categories of Prior Anti-Cancer Therapy, n (%)		
Chemotherapy	85 (100.0)	107 (100.0)
Platinum-based Chemotherapy	85 (100.0)	107 (100.0)
Onco-immunotherapy [a]	36 (42.4)	52 (48.6)
Antiangiogenic Therapy [b]	24 (28.2)	30 (28.0)
Amivantamab	12 (14.1)	14 (13.1)
EGFR TKI [c]	5 (5.9)	14 (13.1)
Others	5 (5.9)	5 (4.7)

Source: Applicant Table. Module 2.7.3/Table 11.

[a] Onco-immunotherapy includes anti-PD(L)-1 and anti-CTLA-4 monoclonal antibodies. [b] Antiangiogenic therapy only refers to anti-VEGF/VEGFR antibody, such as bevacizumab and its similar biological medicinal products. [c] EGFR TKI includes the first-, second- and third-generation EGFR TKIs.

The FDA's Assessment

For the sunvozertinib 200 mg cohort, at baseline, 94% had adenocarcinoma histology, 25% had brain metastasis, 42% received prior anti-PD-(L)1 antibody therapy, and 14% received prior amivantamab therapy.

For the sunvozertinib 300 mg cohort, at baseline, 97% had adenocarcinoma histology, 25% had brain metastasis, 49% received prior anti-PD-(L)1 antibody therapy, and 13% received prior amivantamab therapy.

FDA did not independently verify the data from the WU-KONG6 trial, which was considered supportive only.

8.1.2.7 Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Description

Data and Applicant's Position:

Treatment Compliance: Sunvozertinib is an oral drug and was self-administered. In WU-KONG studies, a diary card was provided to patient, where the study drug administration was recorded. Overall treatment compliance was assessed as a reflection of exposure to the study drug. Median relative dose intensity (RDI) for pooled 300 mg safety analysis set was 92% (Section 8.2.2)

Concomitant Medications: The concomitant medications were predominately used for the management of comorbidities and toxicities.

Rescue Medication: Not appliable.

The FDA's Assessment:

FDA generally agrees that treatment compliance was captured from the diary cards provided to each patient. The median relative dose intensity for the sunvozertinib 200 mg cohort was 99% and 85% for the sunvozertinib 300 mg cohort.

8.1.2.8 Efficacy Results – Primary Endpoint

The Applicant's Description

The primary efficacy endpoint of phase 2 pivotal studies, WU-KONG1B and WU-KONG6, was IRC assessed cORR. For phase 1 pooled efficacy analysis set, efficacy response (cORR) was assessed by investigators.

Data:

[*Source:* Module 2.7.3/Section 3.4.1, Section 3.4.2 and Section 3.4.3]

Primary efficacy analysis set

As shown in Table 30, the IRC assessed cORR was 45.8% (97.5% CI: 34.8%, 56.1%) based on Jung's method, which met its predefined target with statistical significance ($p<0.0001$). The confirmed response included 1.9% CR and 43.9% PR. The cORR by investigator assessment was 37.4%. The concordance between IRC and investigator assessed responder or non-responder was 76.6% (Module 2.7.3/Section 3.4.1).

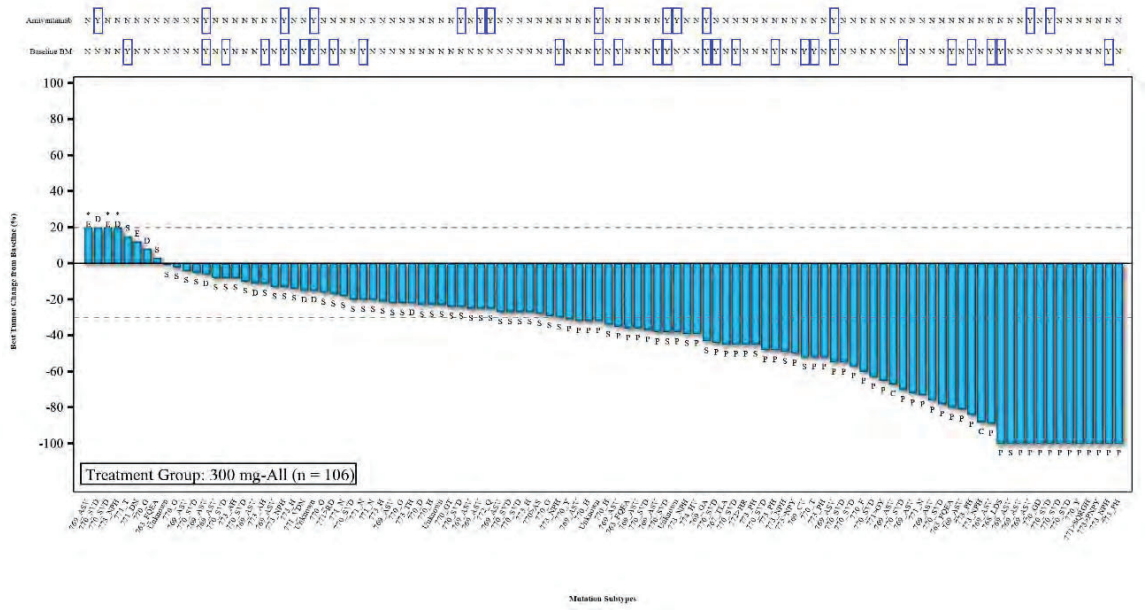
Table 30 cORR of Primary Efficacy Analysis Set (WU-KONG1B)

	300 mg-All (N=107)	
	IRC	INV
Objective Response Rate, n (%)	49 (45.8)	40 (37.4)
97.5% CI [a]	(34.8, 57.0)	(27.0, 48.6)
UMVUE of cORR with 97.5% CI [b]	45.8 (34.8, 56.1)	37.4 (27.0, 47.7)
p-value [c]	< 0.0001	< 0.0001
Disease Control Rate, n (%)	95 (88.8)	95 (88.8)
97.5% CI [a]	(80.1, 94.6)	(80.1, 94.6)

Source: Applicant Table. Module 2.7.3/Table 14. Data cut-off: 29Jul2024.
CI: Confidence Interval; cORR: confirmed Objective Response Rate; IRC: Independent Review Committee; INV: Investigator; UMVUE: Uniformly Minimum Variance Unbiased Estimator. [a] Based on the Clopper-Pearson exact CI method for a single binomial proportion. [b] UMVUE of ORR and two-sided 97.5% CI were calculated based on Jung's method. [c] The one-sided p-value against a null hypothesis of cORR ≤ 17% was calculated based on Simon's two-stage method.

Figure 8 shows the waterfall plot of the best percentage change in target tumor lesion. Anti-tumor efficacy of sunvozertinib was observed in patients with baseline brain metastasis, with prior amivantamab treatment, and independent of EGFR exon20ins subtypes.

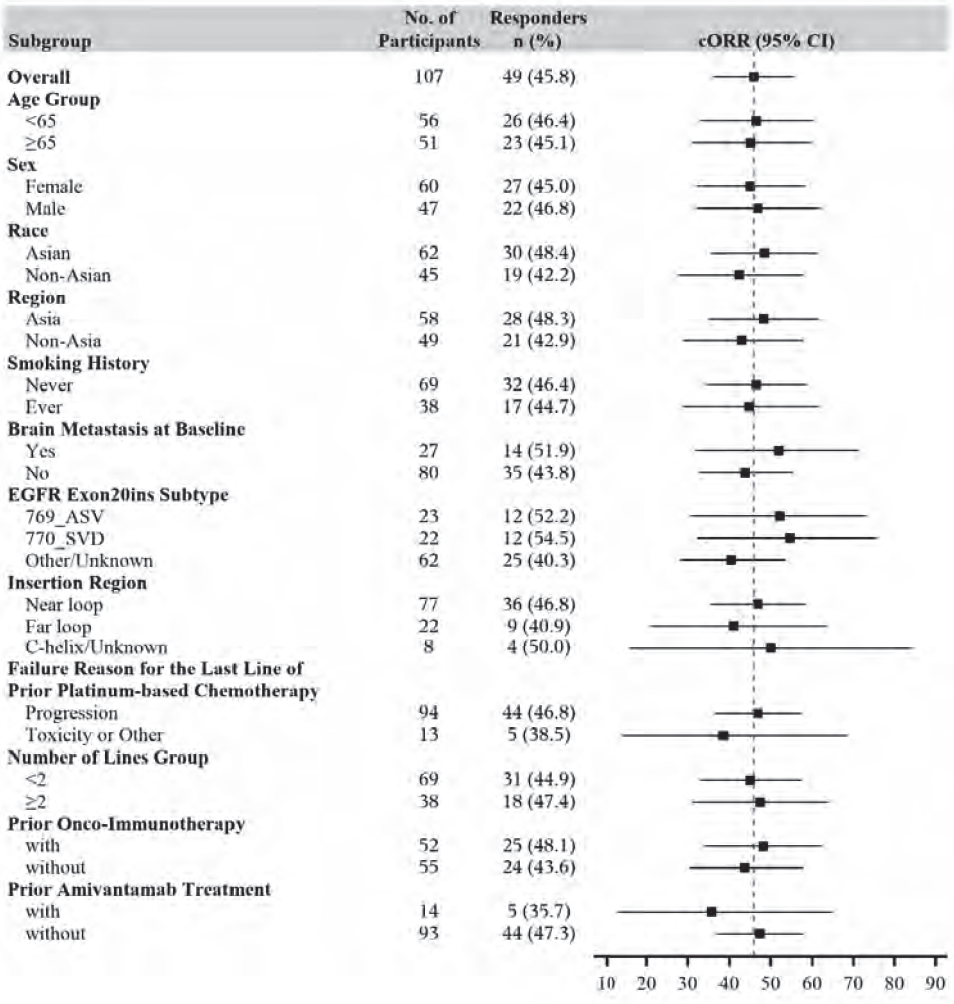
Figure 8 Waterfall Plot of Best Percentage Change from Baseline of Target Lesions Assessed by IRC (Primary Efficacy Analysis Set, WU-KONG1B)



Source: Applicant Figure. Module 2.7.3/Figure 6. Data cut-off: 29Jul2024.
BM: Brain Metastasis. Confirmed best overall response was displayed in the plot (C: Complete Response; P: Partial Response; S: Stable Disease [Non-CR/Non-PD]; D: Progressive Disease; E: Not Evaluable).

The prespecified subgroup analysis of IRC assessed cORR demonstrated that clinical efficacy of sunvozertinib monotherapy was observed across all clinically relevant subgroups (Figure 9).

Figure 9 Forest Plot of Subgroup Analysis of IRC Assessed cORR (Primary Efficacy Analysis Set, WU-KONG1B)



Source: Applicant Figure. Module 2.7.3/Figure 4. Data cut-off: 29Jul2024.
The dashed line represented the overall ORR regardless of subgroup.

WU-KONG6 efficacy analysis set

The cORR per IRC assessment was 60.8% (95% CI: 50.4%, 70.6%), which met its predefined target with statistical significance (P<0.0001). All 59 confirmed responders were PRs. Investigator assessed cORR was 47.4%.

Phase 1 pooled efficacy analysis set

Across 50 mg to 400 mg, the cORR per investigator assessment was 36.5%. At 300 mg, the cORR was 45.0%.

The Applicant's Position:

Results from different analysis sets revealed robust anti-tumor efficacy of sunvozertinib at 300 mg QD in treating patients with EGFR exon20ins NSCLC, whose disease had progressed on or after platinum-based chemotherapy:

- In view of median time on treatment in WU-KONG1B study (~8.3 months) at the DCO of July 29, 2024, and considering the time to response, the primary endpoint of cORR is considered mature.
- Across different efficacy analysis sets, the cORR was consistently higher than 45%, suggesting the efficacy was robust.
- Sunvozertinib monotherapy at 300 mg QD delivered consistent clinical benefit across different clinically relevant subgroups, including demographic factors, baseline brain metastasis, EGFR exon20ins subtypes, lines and types of prior anti-cancer therapy.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to a May 2, 2025, Information Request from FDA and provided the following results including response rates in patients receiving the 200 mg dose.

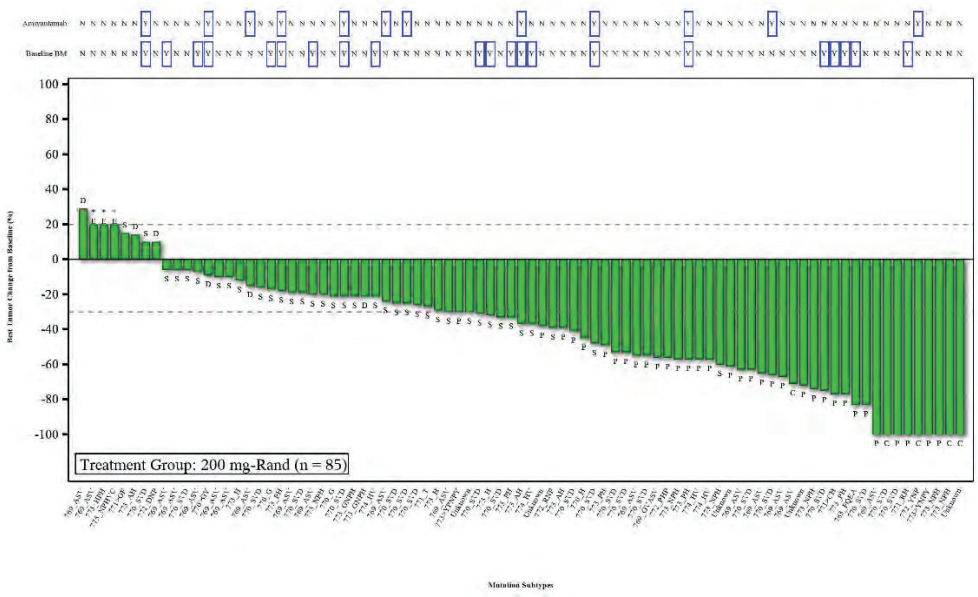
Table 31: cORR of Efficacy Analysis Sets (WU-KONG1B) – Applicant Table

	200 mg (N=85)		300 mg-All (N=107)	
	IRC	**INV**	**IRC**	**INV**
Objective Response Rate, n (%)	39 (45.9)	32 (37.6)	49 (45.8)	40 (37.4)
95% CI [a]	(35.0, 57.0)	(27.4, 48.8)	(36.1, 55.7)	(28.2, 47.3)
UMVUE of cORR with 95% CI [b]	NA	NA	45.8 (36.1, 54.8)	37.4 (28.2, 46.3)

Data cut-off: 29Jul2024.
CI: Confidence Interval; cORR: confirmed Objective Response Rate; IRC: Independent Review Committee; INV: Investigator; NA: Not Applicable; UMVUE: Uniformly Minimum Variance Unbiased Estimator. [a] Based on the Clopper-Pearson exact CI method for a single binomial proportion. [b] UMVUE of ORR and two-sided 95% CI were calculated based on Jung's method. [c] The one-sided p-value against a null hypothesis of cORR ≤ 17% was calculated based on binomial exact test.

Figure 10: Waterfall Plot of Best Percentage Change from Baseline of Target Lesions Assessed by IRC (Efficacy Analysis Sets, WU-KONG1B)

A. 200 mg efficacy set



The FDA's Assessment:

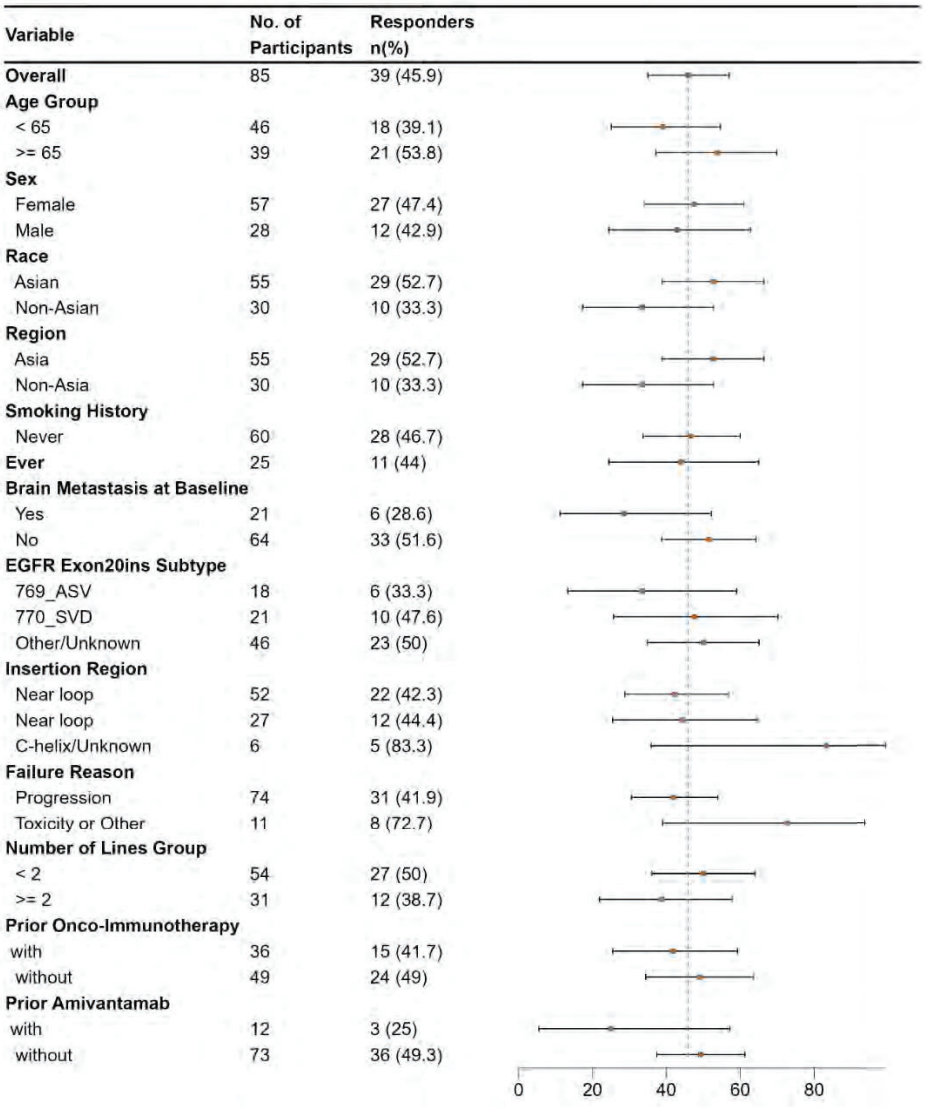
FDA agrees with the Applicant's presentation of primary efficacy results for ORR, noting that as single arm dose cohorts with no control for multiplicity in any of the hypothesis tests presented in Table 30 the p-values reported by the Applicant should be interpreted with caution. Additionally, FDA evaluated ORR with its associated 95% confidence interval as opposed to the 97.5% level presented by the Applicant.

Efficacy in terms of durable confirmed ORR was demonstrated at both dosage levels of 200 mg and 300 mg QD.

FDA observed a difference between IRC and investigator assessed ORR in both cohorts. The overall concordance of IRC and investigator assessed responders/non-responders was 77.6% and 76.6% in the 200 mg and 300 mg-All cohort, respectively. The Applicant responded to an information request from FDA providing clarification on this discrepancy noting that the majority of discrepancies were the result of target lesion selection and measurement differences between IRC and the investigator. In general, this level of discordance between IRC and investigator assessments is not unusual.

FDA performed subgroup analyses of ORR for patients who received sunvozertinib 200 mg in WU-KONG1B across major demographic and clinical characteristics as shown below.

FDA Figure 11: Forest Plot of Subgroup Analysis of IRC Assessed cORR (200 mg cohort, WU-KONG1B



Source: FDA reviewer generated [adtte.xpt]

In general, sunvozertinib 200 mg QD demonstrated anti-tumor activity across subgroups. Due to small sample sizes, differential effects in ORR should be interpreted with caution.

FDA further reviewed subgroup analyses in the 200 mg and 300 mg cohorts (b) (4)

Subgroup Analysis for Patients who Received Prior Amivantamab – 200 mg vs 300 mg doses

There were 12 patients (n=12/85; 14%) who received sunvozertinib 200 mg QD and 14 patients (n=14/107; 13%) who received sunvozertinib 300 mg QD who had received prior amivantamab therapy. The ORR was 25% (95% CI: 5, 27) and 36% (95% CI: 13, 65) for the sunvozertinib 200 mg and 300 mg cohorts, respectively. While the point estimate for ORR is higher for the 300 mg dose, the confidence interval for the ORRs overlap. Given the small sample sizes, these results are inconclusive (b) (4)

Subgroup Analysis for Patients with Baseline Brain Metastases – 200 mg vs 300 mg doses

In total, for patients determined to have baseline brain metastases (both measurable and non-measurable lesions per RECIST) by the investigator, there were 21 patients (n=21/85; 25%) who received sunvozertinib 200 mg QD and 27 patients (n=27/107; 25%) who received 300 mg QD. In patients with baseline brain metastasis, the ORR was 29% (95% CI: 11, 52) and 52% (95% CI: 32, 71) for the 200 mg and 300 mg cohorts, respectively.

However, FDA notes (b) (4) for several reasons. First, only patients with stable, treated brain metastases were eligible to enroll to the trial. Patients had a mix of both measurable and non-measurable brain metastases at baseline. Second, brain imaging was not required at regular intervals and the Applicant confirmed on January 31, 2025, in a response to an FDA information request, that brain metastases were not included as target lesions when performing RECIST assessments of ORR.

While the protocol did not include intracranial ORR as a prespecified exploratory endpoint, FDA sent multiple Information Requests to determine if intracranial ORR may be evaluated in a post-hoc analysis for patients with measurable brain lesions at baseline. On April 11, 2025, the Applicant provided additional data to better assess intracranial response with sunvozertinib in an exploratory analysis. Given that recent radiation therapy may impact an assessment of intracranial response, as described in the FDA Guidance: Evaluating Cancer Drugs in Patients with Central Nervous System Metastases, the Applicant provided response data based on receipt of intracranial radiation ≥60 days before initiating study therapy with sunvozertinib and <60 days before initiating treatment with sunvozertinib. Data from the Applicant's response to the Information Request are presented in the FDA-generated table below. Importantly, the table below includes data from additional patients who were assessed to have baseline brain metastases by IRC compared to baseline brain metastases identified by the investigators.

FDA Table 32: Exploratory Intracranial ORR (FAS, WU-KONG1B)

	WU-KONG 1B	
	200 mg (n=85)	**300 mg (n=107)**
Brain Radiotherapy < 60 days before treatment, n	12	14
Patients with measurable brain lesions at baseline, n	3	8
Intracranial ORR (for patients with measurable lesions at baseline), % (95% CI)	0% (0, 71)	63% (25, 91)
Brain Radiotherapy ≥ 60 days before treatment, n	13	14
Patients with measurable brain lesions at baseline, n	2	4
Intracranial ORR (for patients with measurable lesions at baseline), % (95% CI)	0% (0, 84)	25% (0.6, 81)
No Prior Brain Radiotherapy, n	60	79
Patients with measurable brain lesions at baseline, n	0	2
Intracranial ORR (for patients with measurable lesions at baseline), % (95% CI)	-	0% (0, 84)

Results from patients who recently received brain irradiation (e.g., <60 days before treatment) should be interpreted with caution as the observed intracranial response may reflect a treatment response to radiation, sunvozertinib, or a combination of both. A more informative assessment may be in patients who received brain radiotherapy ≥60 days before initiation of treatment with sunvozertinib or who did not receive brain radiotherapy at all.

For patients who received radiotherapy ≥60 days before initiation of treatment, there were only 13 patients who received sunvozertinib 200 mg QD of whom only 2 patients had measurable brain lesions at baseline; the intracranial ORR was 0% (95% CI: 0, 84) in these 2 patients. For patients who received radiotherapy ≥60 days before initiation of treatment, there were only 14 patients who received sunvozertinib 300 mg QD of whom only 4 patients had measurable brain lesions at baseline; 1 patient with measurable disease at baseline had an intracranial response for an intracranial ORR of 25% (95% CI: 0.6, 81).

There were no patients in the 200 mg QD cohort with measurable brain lesions at baseline who did not receive brain radiotherapy. In the 2 patients in the 300 mg QD cohort with measurable brain lesions at baseline who did not receive brain radiotherapy, neither patient had an intracranial response with sunvozertinib.

Given very limited sample sizes for each dose level, the subgroup analysis results are inconclusive; (b) (4)

Data Quality and Integrity

Data and Applicant's Position

Quality control and quality assurance of the study data were implemented per the applicant's GCP Standard Operating Procedures (SOPs). The contract research organizations (CROs) and central laboratories implemented data quality control activities based on their relevant in-house SOPs. Before the first patient was enrolled, a representative of Dizal visited the study site to review and discuss the requirements of the protocol and related documents with the investigational site staff, and to train them in any study-specific procedures, including the collection of samples and the Web Based Data Capture (WBDC) system utilized. During the study, a representative of Dizal conducted monitoring activities to ensure compliance of the investigators and other site staff members involved in this study. There were no issues identified that could potentially impact data quality and integrity.

The FDA's Assessment:

The submission contained all the required components of the electronic Common Technical Document (eCTD) and was of the quality and integrity to allow for FDA review of the clinical trial data from WU-KONG1B. Overall, there were no significant data quality or integrity issues identified during the review of this NDA.

8.1.2.9 Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position

The key secondary endpoint of the two phase 2 pivotal studies, WU-KONG1B and WU-KONG6, was IRC assessed DoR. Other secondary endpoints included investigator assessed cORR and DoR, IRC and investigator assessed PFS, and OS.

Data:

[*Source:* Module 2.7.3/Section 3.4.1, Section 3.4.2 and Section 3.4.3]

Primary efficacy analysis set

The DoR based on IRC and investigator assessments are summarized in Table 33.

In WU-KONG1B, among the 49 IRC confirmed responders, with median follow-up of 9.7 months, DoR data were not mature, and 59.2% of responders were still responding. The estimated 9-month and 12-month durable response rates were 59.3% and 50.1%, respectively. Among 40 responders assessed by investigator, with median follow-up of 9.6 months, the estimated median DoR was 8.8 months, with 45.0% of responders still responding.

With median follow-up of 11.0 and 12.3 months, the estimated median PFS based on IRC and investigator assessment were 6.9 months and 6.8 months, respectively.

With median follow-up of 12.8 months, there were 65.4% of patients censored, and the OS data were not mature. The estimated 12-month rate was 70.5%.

Table 33 DoR of Primary Efficacy Analysis Set (WU-KONG1B)

	300 mg-All (N = 107)	
	IRC	**INV**
Number of Responders	49	40
Number of Responders Censored, n (%)	29 (59.2)	18 (45.0)
Duration of Response (months)		
Median (95% CI) [a]	NE (6.7, NE)	8.8 (5.3, 18.0)
Min, Max	2.0, 19.4 +	1.1 +, 18.0
Durable Response Rate (%) (95% CI) [a] at		
6 months	72.7 (57.6, 83.2)	59.6 (42.1, 73.5)
9 months	59.3 (42.9, 72.5)	46.5 (29.1, 62.2)
12 months	50.1 (31.8, 65.9)	33.9 (15.9, 52.9)
Follow-up Time (months)		
Median (95% CI) [b]	9.7 (8.3, 11.1)	9.6 (8.1, 12.5)

Source: Applicant Table. Module 2.7.3/Table 16. Data cut-off: 29Jul2024.
DoR: Duration of Response; NE: Not Estimable. Percentage was calculated based on the number of responders as denominator. [a] Estimated by Kaplan-Meier method. [b] Estimated by reverse Kaplan-Meier method.

WU-KONG6 efficacy analysis set

Among 59 responders assessed by IRC, the median follow-up time was 9.8 months. The estimated median DoR was 8.3 months (95% CI: 5.6, 10.4), with 6-month and 9-month durable response rates of 59.5% and 43.2%, separately. For 46 responders assessed by investigator, the estimated median DoR was 9.2 months.

The Applicant's Position:

In the primary efficacy analysis set, the DoR data demonstrated durable clinical efficacy of sunvozertinib in advanced NSCLC patients with EGFR exon20ins, post prior platinum-based chemotherapy. With median follow-up of 9.7 months for IRC confirmed responders, median DoR was not reached, and 59.2% of responders were still responding. The DoR results of other studies provided additional supportive evidence of the durable anti-tumor efficacy.

The FDA's Assessment:

FDA agrees with the Applicant's presentation of secondary endpoints.

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following additional data provided below (Table 34), which presents confirmed ORR and DoR by investigator and IRC assessment for each dose based on data from the 120-day safety update. With a DCO date of December 2, 2024, and an approximate 4 additional months of follow-up, the estimated median DoR was now reached and was 11.1 (95% CI: 8.2, NE) and 9.8 (8.3, 13.9) months as assessed by IRC in the 200 mg and 300 mg cohorts, respectively. It is noted that additional patients were enrolled in the 300 mg cohort (b) (4) potentially contributing to the numerical differences in median estimates

given differential follow-up, which was not observed in the concurrently randomized patients. In general, DoR is a responder analysis based on a post-randomization outcome, thereby precluding a direct comparison of DoR between the two arms.

Table 34: cORR and DoR of Efficacy Analysis Sets, WU-KONG1B – Applicant Table

	200 mg (N = 85)		300 mg-All (N = 107)	
	IRC	**INV**	**IRC**	**INV**
Objective Response Rate, n (%)	39 (45.9)	32 (37.6)	49 (45.8)	41 (38.3)
95% CI [a]	(35.0, 57.0)	(27.4, 48.8)	(36.1, 55.7)	(29.1, 48.2)
Number of Responders Censored, n (%) [b]	20 (51.3)	11 (34.4)	22 (44.9)	10 (24.4)
Duration of Response (months)				
Median (95% CI) [c]	11.1 (8.2, NE)	8.5 (7.0, 13.4)	9.8 (8.3, 13.9)	6.9 (5.3, 10.9)
Min, Max	1.4 +, 24.8 +	2.7, 23.1 +	2.0, 21.0 +	1.1 +, 18.0
Durable Response Rate (%) (95% CI) [c] at				
6 months	78.4 (61.3, 88.6)	78.1 (59.5, 88.9)	72.7 (57.6, 83.2)	61.1 (43.8, 74.5)
9 months	63.5 (45.4, 77.0)	49.1 (30.8, 65.1)	54.1 (38.6, 67.3)	44.1 (27.8, 59.2)
12 months	49.8 (31.6, 65.5)	35.1 (18.8, 51.8)	46.2 (30.9, 60.2)	29.1 (15.3, 44.4)
Follow-up Time (months)				
Median (95% CI) [d]	15.2 (11.0, 16.6)	15.4 (12.4, 17.8)	12.5 (11.1, 15.0)	15.2 (13.7, NE)

Source: 0024\m5\datasets\dz2019e0001-partb\analysis\adam\datasets\ADRS, ADTTE, ADSL. Data cut-off: 02Dec2024.
CI: Confidence Interval; cORR: confirmed Objective Response Rate; DoR: Duration of Response; IRC: Independent Review Committee; INV: Investigator; NE: Not Estimable. [a] Calculated based on the Clopper-Pearson exact CI method for a single binomial proportion. [b] Percentage was calculated based on the number of responders as denominator. [c] Estimated by Kaplan-Meier method. [d] Estimated by reverse Kaplan-Meier method.

In addition to evaluating durability through Kaplan-Meier estimates as presented above, FDA additionally considers a more conservative metric of the observed percentage of responders maintaining response at relevant landmark timepoints in assessing durability (Table 36).

FDA Table 35: Observed DoR of Efficacy Analysis Sets, WUKONG1B

	200 mg (N=85)	300 mg (N=107)

	IRC	INV	IRC	INV
Number of responders	39	32	49	41
DoR > 6 months, n (%)	28 (72%)	25 (78%)	32 (65%)	22 (54%)
DoR > 9 months, n (%)	21 (54%)	14 (44%)	23 (47%)	15 (37%)
DoR > 12 months, n (%)	11 (28%)	10 (31%)	13 (27%)	9 (22%)

Source: FDA reviewer generated analysis [adrs.xpt]

Durability of response was observed, with 72% of responders in the 200 mg cohort and 65% of responders in the 300 mg cohort experiencing a response of at least 6 months.

PFS by IRC was evaluated using this same safety DCO date among patients concurrently randomized to 200 mg (n=85) and 300 mg (n=89) doses and the medians were 8.4 (95% CI: 6.8, 13.9) months and 7.7 (95% CI: 6.0, 9.8) months, respectively.

Dose/Dose Response

Data and the Applicant's Position:

[*Source:* Module 2.7.2/Section 3.8]

The dose optimization of sunvozertinib was firstly informed by PK, tolerability/safety and anti-tumor efficacy data in dose escalation/expansion cohorts of early phase trials, and then using dose-randomization design in WU-KONG1B study to compare efficacy and safety between the selected two dosages (200 mg and 300 mg QD). The dose selection was also supported by exposure-response analysis for efficacy and safety, summarized in Section 6.2.2.1.

In phase 1 studies, the dose range of 50 mg to 400 mg was explored in dose escalation to identify MTD, and the dose range of 200 mg to 400 mg was further evaluated in dose expansion to narrow down 200 mg and 300 mg dose levels for phase 2 pivotal trial.

- Anti-tumor efficacy was observed at the dose levels ≥ 100 mg. Sunvozertinib at 400 mg showed less optimal efficacy, compared to 200 mg and 300 mg. Hence, these two dosages were further evaluated in phase 2 pivotal study.

In phase 2 pivotal study, the dosages of 200 mg (N = 85) and 300 mg QD (N = 89) were evaluated following a dose-randomization study design.

- The IRC assessed cORRs were 45.9% and 47.2%, respectively, which is supported by flat exposure-response relationship for ORR.
- Pre-defined subgroup analysis showed less variabilities of cORR at 300 mg than that of

200 mg.

- The comprehensive efficacy assessments suggested more favorable efficacy profiles at 300 mg QD than that of 200 mg QD, in consideration of more complexed population in clinical practice, including different races, patients from different countries or regions, having high risk factor (i.e., brain metastasis), and prior treated with amivantamab.

The dosage of 300 mg QD has been further assessed in the ongoing phase 3 study (WU-KONG28).

More detailed description of dose/dose response and justification for the to-be-marketed dosage can be found in Section 6.2.2.

The FDA's Assessment:

FDA acknowledges the dose randomization of two dose levels (sunvozertinib 200 mg and 300 mg QD) in WU-KONG1B. The IRC assessed cORR was consistent across dose levels, at 46% (95% CI: 35, 57) for sunvozertinib 200 mg QD and 46% (95% CI: 36, 56) for sunvozertinib 300 mg QD. There were no clinically significant differences in the E-R relationships for ORR observed over the dose range of 200 to 300 mg. Refer to FDA's assessment in Section 6.2.2 of the Assessment Aid for additional details.

Durability of Response

Data and the Applicant's Position:

See discussion of DoR under Secondary and other relevant endpoints.

The FDA's Assessment:

Refer to FDA's Assessment in Section 8.1.2.9 of the Assessment Aid.

Persistence of Effect

Data and the Applicant's Position:

As defined in the study protocol and also with the common practice for anti-cancer therapies treating locally advanced or metastatic disease, patients in WU-KONG1, WU-KONG2 and WU-KONG6 studies received sunvozertinib treatment until there was loss of clinical benefit as assessed by investigator.

The FDA's Assessment:

Refer to FDA's Assessment on Durability of Response in Section 8.1.2.9 of the Assessment Aid.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data and the Applicant's Position:

[*Source:* Module 2.7.3/Section 3.4.1].

In the primary efficacy analysis set of WU-KONG1B, the percentage of patients treated with sunvozertinib 300 mg QD who reported no pain or discomfort increased starting as early as week

6, and sustained during the study treatment, suggesting the treatment effect of sunvozertinib on improvement of pain or discomfort, which could be cancer related.

The FDA's Assessment:

In the WU-KONG1B study, data of EQ-5D-5L were collected for exploratory analysis. In general, FDA does not accept results from the EQ-5D for benefit-risk assessment, as this measure is a generic health preference measure used for health technology assessment.

Additional Analyses Conducted on the Individual Trial

Data and the Applicant's Position:

Not applicable.

The FDA's Assessment

FDA agrees with the Applicant's position.

8.1.3 Integrated Review of Effectiveness

Data and the Applicant's Position:

Not applicable. See efficacy across studies in below Section 8.1.4.

The FDA's Assessment:

FDA agrees.

8.1.4 Assessment of Efficacy Across Trials

[*Source:* Module 2.7.3/Section 3]

Primary Endpoints

Data and the Applicant's Position:

From phase 1 to phase 2 studies, sunvozertinib consistently demonstrated anti-tumor efficacy in patients with NSCLC with EGFR exon20ins who had progressed on or after prior platinum-based chemotherapy, with cORR from 45% to 60.8% at the dosage of 300 mg QD in multiple trials.

The FDA's Assessment:

This section is not applicable as there is only one clinical trial assessing efficacy.

Secondary and Other Endpoints

Data and the Applicant's Position:

From phase 1 to phase 2 studies, sunvozertinib demonstrated durable response in the target patient population. In WU-KONG1B pivotal study, with median 9.7-month follow-up, the DoR was not mature, with 59.2% of responders still responding. In another phase 2 pivotal study WU-KONG6, the estimated median DoR was 8.3 months with median 9.8-month follow-up. It should be pointed out that WU-KONG6 was conducted in the middle of COVID-19 pandemic, and patients might be

negatively affected by not being able to have access to sunvozertinib timely or meet investigators for regular check-up.

The FDA's Assessment:

This section is not applicable as there is only one clinical trial assessing efficacy.

Subpopulations

Data and the Applicant's Position:

Across the 3 different efficacy analysis sets, the anti-tumor efficacy of sunvozertinib in NSCLC patients with EGFR exon20ins was observed irrespective of age, sex, race and region, smoking history, lines of prior anti-cancer therapy, prior IO treatment, prior amivantamab treatment, baseline brain metastasis and EGFR exon20ins subtypes.

The FDA's Assessment:

This section is not applicable as there is only one clinical trial assessing efficacy.

Additional Efficacy Considerations

Data and the Applicant's position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.5 Integrated Assessment of Effectiveness

Data and the Applicant's Position:

[*Source:* Module 2.7.3/Section 3, Section 4 and Section 5]

NSCLC with EGFR exon20ins is a serious disease with unmet medical needs. Even with regular approval of amivantamab in both first- and ≥ second-line settings, its anti-tumor efficacy was not optimal with cORR of 40% in patients with prior platinum-based chemotherapy. In addition, treatment options are still lacking post amivantamab failure. Moreover, monotherapy with oral administration should bring better clinical compliance.

With integrated efficacy analysis, sunvozertinib demonstrated as an emerging oral, effective, monotherapy treatment option for this patient population based on the following evidence:

- In WU-KONG1B multinational phase 2 pivotal study, sunvozertinib demonstrated remarkable and durable anti-tumor efficacy in patients with locally advanced or metastatic NSCLC with EGFR exon20ins whose disease has progressed on or after platinum-based chemotherapy.
    - The primary endpoint, IRC assessed cORR was 45.8% in the primary efficacy analysis set, which met its predefined target with statistical significance. In addition, subgroup analysis indicated that the anti-tumor efficacy was irrespective of different

demographics (age, sex, smoking status, race, and region), disease characteristics (baseline brain metastasis, and mutation subtypes) and prior treatment background.

- The anti-tumor efficacy of sunvozertinib was durable. With median 9.7-month follow-up, the median DoR was not mature. The PFS and OS results suggested a trend of improvement of patient survival, better than historical data of available therapies in similar patient population.
- Sunvozertinib achieved better anti-tumor efficacy than amivantamab in similar patient population, those without prior amivantamab treatment (cORR of 47.3% vs. 40%). Sunvozertinib also demonstrated anti-tumor efficacy in patients who failed prior amivantamab treatment.
- The patient population in WU-KONG1B study were diversified with patients of different races and from different countries/regions. Taken together with subgroup analysis results, the anti-tumor efficacy of sunvozertinib in this study could be generalized for the U.S patient population.

- The results of another phase 2 pivotal study, WU-KONG6 conducted in a similar patient population to that of WU-KONG1B, also demonstrated robust and durable anti-tumor efficacy by sunvozertinib, providing additional independent evidence to support the application of sunvozertinib in the intended patient population.
- The pooled analysis of phase 1 studies provided supportive evidence of anti-tumor efficacy of sunvozertinib in patients with more complex diseases and prior treatment background.

At the time of initiation of phase 2 pivotal study WU-KONG1B, there was no approved targeted therapy for the treatment of NSCLC with EGFR exon20ins. Platinum-based chemotherapy was commonly used in the clinic. Following disease progressed on or after platinum-based chemotherapy, onco-immunotherapy, other EGFR TKIs, and other chemotherapies were treatment choices, but the clinical outcome was not satisfactory. In comparison with the above-mentioned available therapies in ≥ second-line settings, sunvozertinib offers cORR of 45.8%, which already more than doubled the ORRs by chemotherapy (17.6%), other EGFR TKIs (10.0%), and onco-immunotherapy (5%) based on real-world data. In addition, the durability was further evidenced by the long DoR.

In comparison with emerging treatment of amivantamab, sunvozertinib also demonstrated superior anti-tumor efficacy. In WU-KONG1B overall population where diversified EGFR exon20ins subtypes (≥ 47 variants) and patients with and without prior amivantamab treatment were enrolled, sunvozertinib showed higher cORR (45.8% vs 40%) than amivantamab in CHYSALIS study (≥ 25 EGFR exon20ins variants). In patient population without amivantamab treatment (similar to that of CHYSALIS study), even higher cORR was observed (47.3% vs 40%). In addition, sunvozertinib also demonstrated anti-tumor efficacy in patients who failed amivantamab treatment, suggesting its potential to overcome amivantamab resistance. More importantly, with 9.7-month follow-up, the DoR was still not mature, suggesting the durability of anti-tumor efficacy by sunvozertinib. Also, a single agent with oral administration could favor better compliance in the clinic.

Thus, it is the Applicant's position that the current efficacy data from WU-KONG1B, together with the supportive evidence from other WU-KONG studies, demonstrated that sunvozertinib, if approved, would provide a significant improvement over the available chemotherapy for patients with locally advanced or metastatic NSCLC with EGFR exon20ins whose disease has progressed on or after platinum-based chemotherapy. With the approval of the emerging treatment of amivantamab, sunvozertinib monotherapy with oral route of administration could potentially provide a treatment option with better efficacy and compliance. More importantly, through different mechanisms of action from amivantamab, sunvozertinib could provide a treatment option to overcome resistance to amivantamab.

The FDA's Assessment:

Based on the results from WU-KONG1B, the review team concluded that the Applicant provided substantial evidence of effectiveness for sunvozertinib in adult patients with locally advanced or metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy.

The efficacy evaluation for this submission is primarily based on the analysis of the dose randomization part of WU-KONG1B for sunvozertinib 200 mg QD (N=85 patients) and sunvozertinib 300 mg QD (N=107 total patients, with 89 patients randomized and 18 patients non-randomized at this dose level). The ORR was 46% (95% CI:35, 57) for patients who received sunvozertinib 200 mg QD and the ORR was 46% (95% CI: 36, 56) for patients who received sunvozertinib 300 mg QD. Based on a data cutoff date of December 2, 2024, the median duration of response was 11.1 months (95% CI: 8.3, NE) for patients on the sunvozertinib 200 mg QD arm and 9.8 months (95% CI: 8.3, 13.9) for patients on the sunvozertinib 300 mg QD arm.

(b) (4)

8.2 Review of Safety

Data and the Applicant's Position:

[*Source:* Module 2.7.4]

The integrated safety analysis was based on data from WU-KONG1, WU-KONG2 and WU-KONG6 studies.

There were three safety analysis sets:

- Pooled 300 mg safety analysis set (all patients included in WU-KONG studies, received sunvozertinib 300 mg QD, N = 311)
- Primary safety analysis set (patients enrolled in cohort 2 of WU-KONG1B, received at least one dose of sunvozertinib 300 mg QD, N = 111)
- Overall safety analysis set (all patients included in WU-KONG studies, received at least one dose of sunvozertinib, doses ranged from 50 mg to 400 mg QD, N = 467)

It should be noted that there was overlap of safety populations across the 3 safety analysis sets. For example, within the 467 patients in the overall safety analysis set, 311 of the pooled 300 mg safety analysis set were also included; all patients in the primary safety analysis set were included in both pooled 300 mg and overall safety analysis sets. By defining different analysis sets, the safety profiles of sunvozertinib could be comprehensively analyzed.

As agreed with FDA during the pre-NDA meeting, a total of 311 patients in the pooled 300 mg safety analysis set were the primary population for adverse drug reaction (ADR) (b) (4) In this safety analysis set, the majority of patients (93.2%) carried EGFR exon20ins.

Across different studies, patients were treated with sunvozertinib until disease progression, intolerable toxicity, or met other discontinuation criteria. Sunvozertinib treatment could continue after disease progression if, in the opinion of the investigator, the patient continued benefiting from the treatment.

The FDA's Assessment:

(b) (4) FDA's primary safety review involved evaluating safety (and efficacy) of patients randomized to both the 200 mg QD and 300 mg QD dosages in the WU-KONG1B dose randomization trial. On May 2, 2025, FDA issued an information request for the Applicant to provide updated safety analyses with side-by-side comparisons of adverse events observed for the 200 mg QD and 300 mg QD dosages in WU-KONG1B.

FDA did not agree with the Applicant's pooling of data across multiple dose levels for sunvozertinib to evaluate safety. The primary safety populations evaluated by FDA consisted of the 91 patients in the 200 mg QD cohort and the 111 patients in the sunvozertinib 300 mg QD cohort in WU-KONG1B who received at least one dose of study therapy. FDA reviewed pooled safety data of sunvozertinib 200 mg QD in a total of 121 patients with NSCLC who received at least one dose of sunvozertinib 200 mg QD in n=91 patients from WU-KONG1B (the primary safety population), n=27 patients from WU-KONG1A, and n=3 patients from WU-KONG2. FDA also evaluated pooled safety data in a total of 311 patients with NSCLC who received at least one dose of sunvozertinib 300 mg QD in n=182 patients from WU-KONG1, n=25 patients from WU-KONG2, and n=104 patients from WU-KONG6.

8.2.1 Safety Review Approach

The Applicant's Position:

The summary of safety includes information on study drug exposure; analyses of safety results including TEAEs and treatment-related adverse events (TRAEs); any TEAEs or TRAEs of grade 3 or higher; on-study deaths; SAEs; TEAEs leading to dose interruption, dose reduction, or treatment discontinuation; AEs of special interest (AESI); clinical laboratory evaluations, ECG, left ventricular ejection fraction (LVEF), and vital signs.

In addition, the safety summary also includes subgroup analyses of TEAEs (pooled 300 mg and primary safety analysis sets) for age (18 to < 65 years; 65 to < 75 years; ≥ 75 years), sex (male; female), race (non-Asian; Asian), region (non-Asia, Asia), smoking status (ever, never), prior lines of anti-cancer therapy (< 2, ≥ 2), prior onco-immunotherapy (Yes, No), and ECOG score at baseline (0, ≥ 1).

The FDA's Assessment:

FDA agrees.

8.2.2 Review of the Safety Database

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 1.2]

The drug exposure was summarized by safety analysis sets and presented in Table 36Table 37.

- Pooled 300 mg safety analysis set: By the DCO date, 75.9% discontinued treatment. The main reason for treatment discontinuation was disease progression. The median duration of exposure was 6.9 months. The median RDI was 92.0%.
- Primary safety analysis set: By the DCO date, 67.6% discontinued treatment. The main reason for treatment discontinuation was disease progression The median duration of exposure was 8.2 months. The median RDI was 85.2%.
- Overall safety analysis set: By the DCO date, 75.8% discontinued treatment. The median duration of exposure was 6.9 months. The median RDI was 93.5%.

There was no clear correlation of treatment duration with dose levels, while the median treatment duration of 200 mg and 300 mg were longer than that of other dose levels.

Treatment durations were considered sufficient for the characterization of safety profile of sunvozertinib in the target patient population, given the median time to onset of common TEAEs was within the first month. At (b) (4) 300 mg QD, the median RDI was 92.0%, suggesting the acceptable tolerability.

Table 36 Extent of Overall Exposure of Sunvozertinib (Safety Analysis Sets)

	Primary (N = 111)	Pooled 300 mg (N = 311)	Overall (N = 467)
Total Duration of Exposure (months)			
Median (Min, Max)	8.2 (0.4, 23.9)	6.9 (0.2, 44.2)	6.9 (0.03, 51.4)
Total Duration (months) Categories, n (%)			
≥ 3 - < 6	29 (26.1)	72 (23.2)	108 (23.1)
≥ 6 - < 9	15 (13.5)	44 (14.1)	62 (13.3)
≥ 9 - < 12	24 (21.6)	53 (17.0)	76 (16.3)
≥ 12	26 (23.4)	68 (21.9)	107 (22.9)
Missing	0 (0.0)	2 (0.6)	2 (0.4)
Relative Dose Intensity (%)			
Median (Min, Max)	85.2 (37.1, 100.0)	92.0 (37.0, 100.7)	93.5 (37.0, 179.6)

Source: Applicant Table. Module 2.7.4/Table 5. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information below.

Table 37: Extent of Overall Exposure of Sunvozertinib (Safety Analysis Sets) – Applicant Table

	Pooled 200 mg (N = 121)	Primary 200 mg (N = 91)	Primary 300 mg (N = 111)
Total Duration of Exposure (months)			
Median (Min, Max)	8.3 (0.2, 51.4)	8.5 (0.2, 32.0)	8.2 (0.4, 23.9)
Total Duration (months) Categories, n (%)			
≥ 3 - < 6	26 (21.5)	20 (22.0)	29 (26.1)
≥ 6 - < 9	14 (11.6)	11 (12.1)	15 (13.5)
≥ 9 - < 12	20 (16.5)	17 (18.7)	24 (21.6)
≥ 12	34 (28.1)	26 (28.6)	26 (23.4)
Relative Dose Intensity (%)			
Median (Min, Max)	98.0 (46.1, 140.7)	99.2 (46.1, 140.7)	85.2 (37.1, 100.0)

Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.

The FDA's Assessment:

FDA agrees with the information provided in the above table. In the 91 patients from the primary safety population who received sunvozertinib 200 mg QD, 59% of patients were exposed for 6 months or longer and 29% were exposed for greater than one year. Among the 111 patients who received sunvozertinib 300 mg QD in the primary safety population, 59% were exposed for 6 months or longer and 23% were exposed for greater than one year.

8.2.3 Relevant Characteristics of the Safety Population

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 1.3 and Section 1.4]

The demographics and baseline disease characteristics of the three safety analysis sets are summarized in Table 38 In pooled 300 mg safety analysis set, the median age was 61 years old. The majority of patients were female, never smoker, with ECOG performance score ≥ 1. Approximately 23.2% of patients were non-Asian. The majority of patients (93.2%) had EGFR exon20ins NSCLC, and 30.9% of patients had baseline brain metastasis. The majority of patients (88.7%) had prior platinum-based chemotherapy, and 7.4% of patients had prior amivantamab treatment, consistent with amivantamab as an emerging treatment during the study conduct.

Overall, patients included in the three safety analysis sets had comparable demographics and baseline disease characteristics. In addition, more patients of primary safety analysis sets were non-Asian (41.4%), and more patients had prior-amivantamab treatment (15.3%), compared to the pooled 300 mg and overall safety analysis set.

Table 38 Demographics and Baseline Disease Characteristics (Safety Analysis Sets)

	Primary (N = 111)	Pooled 300 mg (N = 311)	Overall (N = 467)
Age (Years)			
Median (Min, Max)	64.0 (37, 89)	61.0 (29, 96)	61.0 (29, 96)
Age Group, n (%)			
< 65/≥ 65	57 (51.4)/54 (48.6)	189 (60.8)/122 (39.2)	286 (61.2)/181 (38.8)
Sex, n (%)			
Female/Male	63 (56.8)/48 (43.2)	169 (54.3)/142 (45.7)	270 (57.8)/197 (42.2)
Race, n (%)			
Asian	65 (58.6)	239 (76.8)	356 (76.2)
White	44 (39.6)	66 (21.2)	103 (22.1)
Black or African American	2 (1.8)	3 (1.0)	3 (0.6)
Others	0 (0.0)	2 (0.6)	3 (0.6)
Not Reported	0 (0.0)	1 (0.3)	2 (0.4)
Smoking History, n (%)			
Never/ever	72 (64.9)/39 (35.1)	197 (63.3)/114 (36.7)	309 (66.2)/158 (33.8)
Region, n (%)			
Asia/Non-Asia	60 (54.1)/51 (45.9)	225 (72.3)/86 (27.7)	333 (71.3)/134 (28.7)
Baseline ECOG Performance Status, n (%)			
0/≥1/Missing	38 (34.2)/73 (65.8)/0 (0.0)	102 (32.8)/208 (66.9)/1 (0.3)	166 (35.5)/300 (64.2)/1 (0.2)
Extent of Disease upon Study Entry, n (%)			
Locally Advanced/Metastatic	3 (2.7)/ 108 (97.3)	14 (4.5)/ 297 (95.5)	18 (3.9)/ 449 (96.1)
Brain Metastasis at Baseline, n (%)			
Yes/No	28 (25.2)/ 83 (74.8)	96 (30.9)/ 215 (69.1)	145 (31.0)/ 322 (69.0)

	Primary (N = 111)	Pooled 300 mg (N = 311)	Overall (N = 467)
Mutation Type, n (%)			
EGFR Exon20ins	110 (99.1)	290 (93.2)	420 (89.9)
Other EGFR/HER2 Mutation	1 (0.9)	21 (6.8)	47 (10.1)

Source: Applicant Table. Module 2.7.4/Table 7 and Table 8. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.
ECOG: Eastern Cooperative Oncology Group. Other EGFR or HER2 mutations include EGFR sensitizing, T790M and uncommon mutations, and HER2 mutations.

The FDA's Assessment:

FDA does not agree with the Applicant's presentation of the overall safety population (N=467) across all doses for sunvozertinib in the above table. Therefore, FDA sent an information request on May 2, 2025, and the Applicant responded on May 8, 2025, providing the following information below, with demographics presented in the safety populations at specific dose levels.

Table 39: Demographics and Baseline Disease Characteristics (Safety Analysis Sets) – Applicant Table

	Pooled 200 mg (N = 121)	Primary 200 mg (N = 91)	Primary 300 mg (N = 111)
Age (Years)			
Median (Min, Max)	61.0 (34, 88)	62.0 (35, 88)	64.0 (37, 89)
Age Group, n (%)			
<65/≥65	69 (57.0)/ 52 (43.0)	48 (52.7)/43 (47.3)	57 (51.4)/54 (48.6)
Sex, n (%)			
Female/Male	81 (66.9)/40 (33.1)	61 (67.0)/30 (33.0)	63 (56.8)/48 (43.2)
Race, n (%)			
Asian	87 (71.9)	59 (64.8)	65 (58.6)
White	32 (26.4)	30 (33.0)	44 (39.6)
Black or African American	0 (0.0)	0 (0.0)	2 (1.8)
Others	1 (0.8)	1 (1.1)	0 (0.0)
Not Reported	1 (0.8)	1 (1.1)	0 (0.0)
Smoking History, n (%)			
Never/ever	86 (71.1)/35 (28.9)	64 (70.3)/27 (29.7)	72 (64.9)/39 (35.1)
Region, n (%)			
Asia/Non-Asia	83 (68.6)/38 (31.4)	59 (64.8)/32 (35.2)	60 (54.1)/51 (45.9)
Baseline ECOG Performance Status, n (%)			
0/1	52 (43.0)/69 (57.0)	35 (38.5)/56 (61.5)	38 (34.2)/73 (65.8)
Extent of Disease upon Study Entry, n (%)			
Locally Advanced/Metastatic	4 (3.3)/117 (96.7)	3 (3.3)/88 (96.7)	3 (2.7)/ 108 (97.3)
Brain Metastasis at Baseline, n (%)			
Yes/No	33 (27.3)/88 (72.7)	22 (24.2)/69 (75.8)	28 (25.2)/ 83 (74.8)

	Pooled 200 mg (N = 121)	Primary 200 mg (N = 91)	Primary 300 mg (N = 111)
Mutation Type, n (%)			
EGFR Exon20ins	115 (95.0)	90 (98.9)	110 (99.1)
Other EGFR/HER2 Mutation	6 (5.0)	1 (1.1)	1 (0.9)

Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.

The FDA's Assessment:

FDA agrees the baseline demographics and disease characteristics between the 200 mg and 300 mg sunvozertinib cohorts appear similar.

8.2.4 Adequacy of the Safety Database

Data and the Applicant's Position:

The pooled 300 mg, primary and overall safety analysis sets included 311, 111 and 467 patients respectively. The majority of patients harbored EGFR exon20ins and prior treatment with platinum-based chemotherapy. The applicant considers that the safety databases are adequate to assess the safety of sunvozertinib monotherapy for the treatment of patients with advanced NSCLC, to provide guidance regarding the management of toxicity, and to assess the benefit-risk profile of sunvozertinib in the target population.

The FDA's Assessment:

FDA pooled data from patients who received sunvozertinib 200 mg QD in WU-KONG1 (n=118) and WU-KONG2 (n=3) for a total of 121 patients; data from patients who received sunvozertinib 300 mg QD was pooled from patients treated in WU-KONG1 (n=182), WU-KONG2 (n=25), and WU-KONG6 (n=104) for a total of 311 patients.

8.2.5 Adequacy of Applicant's Clinical Safety Assessments

8.2.5.1 Issues Regarding Data Integrity and Submission Quality

Data and the Applicant's Position:

[*Source:* Module 2.5/Section 1.4.3]

This submission was of adequate quality for clinical review. Each study was conducted following GCP. There are no concerns regarding the integrity of the submission.

There were no issues regarding data quality identified by the Applicant, and thus, the Applicant does not anticipate any issues with the safety review or the quality of the overall submission that would affect the agency's ability to perform the review.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.5.2 Categorization of Adverse Event

Data and the Applicant's Position:

In WU-KONG studies relevant to this safety analysis, AEs were collected from the first dosing, and SAEs were collected from the time a signed and dated informed consent form was obtained, until 28 days after the last dose of study treatment.

AEs were graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 for consistency. AE causality was upon investigator assessment. The AE summaries are presented by system organ class (SOC) and/or preferred term (PT), and by maximum grades when needed. Patients with multiple episodes were counted only once per event.

Summaries of reported AEs in this application were based on TEAEs, defined as any AE that occurs from the first dose of study drug and through the end of treatment until 28 days after the last dose of study drug, or any drug-related AE as assessed by investigator.

AESIs were selected based on the expected profiles of sunvozertinib which took into account the safety profiles of other approved EGFR inhibitors.

On-study death, which is defined as a death that occurs between the first dose of study drug and within 28 days after the last dose of study drug, were analyzed.

As agreed with FDA at the pre-NDA meeting, patient narratives are provided for the following events in WU-KONG studies: death within 30 days of the last dose of study treatment; discontinuation of study drug due to an AE, SAE, AESIs including all ILD/pneumonitis, other AESIs of grade 3 or 4, overdose and pregnancy (if applicable). Narratives of SAE and death are provided as an appendix to the CSR. Narratives of AESIs or AEs leading to treatment discontinuation and overdose are provided in Module 5.3.5.3/ISS/Section 2.

The AE collection, coding, categorization and summary are considered by the applicant to be reasonable and appropriate, and are consistent with the typical clinical development practice for oncology study.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.5.3 Routine Clinical Tests

Data:

[*Source:* Module 2.7.4/Section 1.1.7]

In addition to monitoring of AEs, safety evaluations in WU-KONG studies also include laboratory data (hematology, clinical chemistry, urinalysis, and coagulation function), vital signs (pulse rate and blood pressure), body weight, 12-lead ECG, physical examination, pulmonary function test, cardiac function (MUGA/ECHO). Hematology, clinical chemistry, urinalysis, and coagulation function were tested in local laboratories, and ECGs were tested locally and centrally reviewed (WU-KONG1B and WU-KONG6).

The Applicant's Position:

The assessment method, time points for collection of safety measurement are appropriate for the disease and indication investigated in WU-KONG studies.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.6 Safety Results

8.2.6.1 Deaths

Data:

[*Source:* Module 2.7.4/Section 2.4]

Overall survival was a secondary endpoint in WU-KONG1B and WU-KONG6 studies, and survival data continued to be collected on all patients until death or loss of follow-up. For WU-KONG1A and WU-KONG2 studies, no survival follow-up was required per study protocol, safety follow-up period was 28 days post the last dose of sunvozertinib. For all deaths that occurred during the study defined collection period, the primary and secondary causes of death were required to be collected, and coded by MedDRA 27.0.

Table 41 summarizes the on-study death that occurred during the study treatment period until 28 days post the last dose of study drug by primary cause of death, through the clinical cut-off date of each study. and Table 43 summarizes TEAEs and drug-related TEAEs with fatal outcome.

Progressive disease or disease under investigation (lung neoplasm malignant, lung adenocarcinoma, NSCLC metastasis, and malignant neoplasm progression, etc.) were the most common causes of death.

Pneumonia and sepsis were the most common TEAEs with fatal outcomes in all safety analysis sets. No patient had any drug-related TEAEs with fatal outcomes in WU-KONG1B study. Among 467 patients in the overall safety analysis set, 3 patients died with death reasons could not be collected, and another 2 patients died with pneumonia for which causality with sunvozertinib could not be fully excluded by investigators. These 5 events were summarized as drug-related TEAEs with fatal outcomes for conservative consideration. A full listing of TEAEs with fatal outcomes can be found in Module 2.7.4/Table 19.

Table 40 Summary of On-study Death (Safety Analysis Sets)

Death Category Primary Cause of Death	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
All Deaths	40 (36.0)	91 (29.3)	132 (28.3)
Deaths from First Dose until 28 Days after Last Dose	9 (8.1)	25 (8.0)	36 (7.7)
Disease Progression	3 (2.7)	9 (2.9)	15 (3.2)
Sepsis	1 (0.9)	3 (1.0)	3 (0.6)
Death	0 (0.0)	2 (0.6)	3 (0.6)
Lung Neoplasm Malignant	1 (0.9)	2 (0.6)	3 (0.6)

Death Category Primary Cause of Death	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Cerebral Haemorrhage	0 (0.0)	1 (0.3)	1 (0.2)
Cerebral Infarction	0 (0.0)	1 (0.3)	1 (0.2)
Lung Adenocarcinoma	1 (0.9)	1 (0.3)	1 (0.2)
Malignant Neoplasm Progression	0 (0.0)	1 (0.3)	1 (0.2)
Metastases To Central Nervous System	0 (0.0)	1 (0.3)	1 (0.2)
Non-Small Cell Lung Cancer Metastatic	1 (0.9)	1 (0.3)	1 (0.2)
Pneumonia	1 (0.9)	1 (0.3)	2 (0.4)
Respiratory Failure	0 (0.0)	1 (0.3)	1 (0.2)
Septic Shock	1 (0.9)	1 (0.3)	1 (0.2)
COVID-19	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory Tract Infection	0 (0.0)	0 (0.0)	1 (0.2)

Source: Applicant Table. Module 2.7.4/Table 16. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

Table 41 TEAEs with Fatal Outcome (Safety Analysis Sets)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Patients with any TEAE with Fatal Outcome	5 (4.5)	15 (4.8)	20 (4.3)
Death	0 (0.0)	3 (1.0)	4 (0.9)
Pneumonia	1 (0.9)	3 (1.0)	4 (0.9)
Sepsis	1 (0.9)	3 (1.0)	3 (0.6)
Septic shock	1 (0.9)	2 (0.6)	2 (0.4)
COVID-19	1 (0.9)	1 (0.3)	2 (0.4)
Cerebral haemorrhage	0 (0.0)	1 (0.3)	1 (0.2)
Cerebral infarction	0 (0.0)	1 (0.3)	1 (0.2)
Respiratory failure	1 (0.9)	1 (0.3)	2 (0.4)
Respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.2)
Thrombosis	0 (0.0)	0 (0.0)	1 (0.2)

Source: Applicant Table. Module 2.7.4/Table 17. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

Table 42 Drug-related TEAEs with Fatal Outcome (Safety Analysis Sets)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Patients with any Drug-Related TEAE with Fatal Outcome	0 (0.0)	5 (1.6)	5 (1.1)
Death	0 (0.0)	3 (1.0)	3 (0.6)
Pneumonia	0 (0.0)	2 (0.6)	2 (0.4)

Source: Applicant Table. Module 2.7.4/Table 18. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

The Applicant's Position:

The primary causes of death were typical of a patient population with locally advanced or metastatic NSCLC. TEAEs with fatal outcome were infrequent in all safety analysis sets, and there was no solid evidence of causality with sunvozertinib.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information shown below in the safety populations of interest.

Table 43: Summary of On-study Death (Safety Analysis Sets) – Applicant Table

Death Category Primary Cause of Death	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
All Deaths	36 (29.8)	33 (36.3)	40 (36.0)
Deaths from First Dose until 28 Days after Last Dose	8 (6.6)	7 (7.7)	9 (8.1)
Disease progression	4 (3.3)	4 (4.4)	3 (2.7)
Lung neoplasm malignant	1 (0.8)	1 (1.1)	1 (0.9)
Respiratory tract infection	1 (0.8)	1 (1.1)	0 (0.0)
COVID-19	1 (0.8)	1 (1.1)	0 (0.0)
Pneumonia	1 (0.8)	0 (0.0)	1 (0.9)
Lung adenocarcinoma	0 (0.0)	0 (0.0)	1 (0.9)
Non-small cell lung cancer metastatic	0 (0.0)	0 (0.0)	1 (0.9)
Sepsis	0 (0.0)	0 (0.0)	1 (0.9)
Septic shock	0 (0.0)	0 (0.0)	1 (0.9)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.5 and Module 5.3.5.2/WU-KONG1B CSR/Table 38.
Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.

Table 44: TEAEs with Fatal Outcome (Safety Analysis Sets) – Applicant Table

Preferred Term	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
Patients with any TEAE with Fatal Outcome	3 (2.5)	2 (2.2)	5 (4.5)
COVID-19	1 (0.8)	1 (1.1)	1 (0.9)
Respiratory tract infection	1 (0.8) *	1 (1.1)	0 (0.0)
Thrombosis	1 (0.8) *	1 (1.1)	0 (0.0)
Pneumonia	1 (0.8)	0 (0.0)	1 (0.9)
Sepsis	0 (0.0)	0 (0.0)	1 (0.9)
Septic shock	0 (0.0)	0 (0.0)	1 (0.9)
Respiratory failure	0 (0.0)	0 (0.0)	1 (0.9)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.6.1 and Module 5.3.5.2/WU-KONG1B CSR/Table 39. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.
* TEAE of respiratory tract infection and thrombosis occurred in one patient, reported as with fatal outcome.

Table 45: Drug -related TEAEs with Fatal Outcome (Safety Analysis Sets) – Applicant Table

Preferred Term	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
Patients with any Drug-Related TEAE with Fatal Outcome	0 (0.0)	0 (0.0)	0 (0.0)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.6.2 and Module 5.3.5.2/WU-KONG1B CSR/Table 14.3.1.6.2. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.

FDA Table 46: Summary of Study Deaths in WU-KONG1B

Death Category Primary Cause of Death	Primary 200 mg (N=91) n (%)	Primary 300 mg (N = 111) n (%)
All Deaths	40 (44)	53 (48)
Disease progression	20 (22)	22 (20)
Lung neoplasm malignant	8 (9)	10 (9)
Death	1 (1.1)	4 (3.6)
Respiratory failure	1 (1.1)	4 (3.6)
Sepsis	0	2 (1.8)
Malignant neoplasm progression	3 (3.3)	1 (0.9)
Cachexia	0	1 (0.9)
Hanging	0	1 (0.9)
Lung adenocarcinoma	0	1 (0.9)
Metastases to meninges	0	1 (0.9)
Neoplasm malignant	0	1 (0.9)
Non-small cell lung cancer metastatic	0	1 (0.9)
Pneumonia	1 (1.1)	1 (0.9)
Asphyxia	1 (1.1)	0
COVID-10	1 (1.1)	0
Condition aggravated	1 (1.1)	0
General physical health deterioration	1 (1.1)	0
Metastatic neoplasm	1 (1.1)	0
Multiple organ dysfunction syndrome	1 (1.1)	0

Source: 120 day safety update with DCO December 2, 2024.
Variables used: USUBJID, APOP, USUBJID, APOP, DTHFL, DTHDT, TRTSDT, TRTEDT, DTHCAUS.
Note: Custom grouped terms are designated by '(GT)'.

Pneumonia (GT) includes: Pneumonia, Covid-19, respiratory tract infection
Sepsis (GT) includes sepsis and septic shock

FDA Assessment:

FDA does not consider attribution when assessing treatment emergent adverse events, particularly in single arm trials. FDA reviewed all fatal adverse events that occurred in patients enrolled in WU-KONG1B who received either 200 mg or 300 mg of sunvozertinib that occurred within 30 days of the last dose of study therapy by the data cutoff date of December 2, 2024, and were at least potentially related to study therapy. FDA excluded events of death clearly due to disease progression from the overall incidence of fatal adverse reactions.

Fatal adverse reactions occurred in 4.5% and 2.2% of patients in the 300 mg and 200 mg cohorts, respectively.

FDA Table 47: Fatal adverse events in the safety population of WU-KONG1B (with FDA assessment of causality)

Patient ID (sunvozertinib dose)	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality
(b) (6) 200 mg	A 72-year-old female with NSCLC was randomized to sunvozertinib 200 mg QD. On Day 6, the patient was hospitalized due to Grade 3 COVID-19, respiratory failure with dyspnea, cough and fever. On Day 8, sunvozertinib was interrupted. The patient was treated with anti-viral therapy, antibiotics, and corticosteroids, and the event worsened to Grade 4. The patient died on Day 19. The primary cause of death was reported as due to **COVID-19.**	COVID-19 infection was confirmed by PCR test. FDA considers this death unlikely to be related to sunvozertinib; however, the contribution of study drug to the fatal event of **COVID-19** cannot be ruled out.
(b) (6) 200 mg	56-year-old female patient with NSCLC was randomized to sunvozertinib 200 mg QD. On Day 62, sunvozertinib treatment was interrupted due to a serious adverse event (SAE) of Grade 4 decreased oxygen saturation. On Day 63, SAEs of respiratory tract infection and thrombosis were reported, and sunvozertinib treatment was permanently discontinued. The patient died at home on Day 63. The primary cause of death was reported as **respiratory tract infection.**	Patient was hospitalized on Day 8 for dyspnea and decreased oxygen saturation and treated with dexamethasone. The AE resolved and the patient was discharged on Day 16. The narrative is most consistent with a fatal adverse event of **thrombosis**, and the contribution of sunvozertinib cannot be ruled out.
(b) (6) (300 mg)	73-year-old male with NSCLC was randomized to sunvozertinib 300 mg QD. On Day 211, patient experienced Grade 2 bacterial pneumonia. The chest CT showed pulmonary inflammation during scheduled tumor assessment, and bronchoscopy and sputum culture identified staphylococcus aureus. On Day 218, sunvozertinib treatment was	FDA considers this death unlikely to be related to sunvozertinib; however, the contribution of the study drug to the fatal adverse event of **septic shock** cannot be ruled out.

Patient ID (sunvozertinib dose)	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality
	interrupted due to bacterial pneumonia. On Day 219, this AE worsened to Grade 3 and the patient was hospitalized. The patient was treated with broad-spectrum antibiotics. The patient's health status deteriorated and the patient died on Day 237. The primary cause of death was reported as **septic shock**.	
(b) (6) (300 mg)	89-year-old female patient with NSCLC was randomized to sunvozertinib 300 mg QD. On Day 3, patient experienced Grade 2 diarrhea and was hospitalized on Day 6 for Grade 3 diarrhea and hematemesis. Patient received hydration and electrolytes, and sunvozertinib therapy was interrupted from Days 7 to 21. This AE resolved on Day 11. Sunvozertinib was dose reduced to 200 mg QD starting on Day 22. On Day 64, sunvozertinib treatment was discontinued due to decreased platelet count and decreased hemoglobin. On Day 66, patient was hospitalized due to severe dyspnea with signs of respiratory failure. The chest X-ray showed diffuse haziness in the right middle and lower lung fields when compared to the X-ray on Day 62 which was clear. Patient was treated with antibiotics and died. The primary cause of death was reported as **pneumonia**.	FDA considers this death unlikely to be related to sunvozertinib; however, the contribution of the study drug to the fatal adverse event of **pneumonia** cannot be ruled out.
(b) (6) (300 mg)	64-year-old female patient with NSCLC was randomized to sunvozertinib 300 mg QD. On Day 100, sunvozertinib treatment was interrupted and discontinued on Day 107 due to pneumonitis. On Day 111, the patient experienced fever, septic shock, and oxygen desaturation. Blood culture showed Enterobacter hormaechei. On Day 112, the second set of blood cultures showed Enterobacter cloacae. On Day 114 (16 days from the last dose of sunvozertinib treatment), the patient passed away, and the primary cause of death was reported as **sepsis**.	FDA considers this death unlikely to be related to sunvozertinib; however, the contribution of study therapy to the fatal adverse event of **sepsis** cannot be ruled out.
(b) (6) 300 mg	66-year-old female with NSCLC was randomized to sunvozertinib 300 mg QD. On Day 358, treatment was interrupted due to renal failure. On Day 363, the patient experienced a Grade 2 SAE of ischemic stroke and was admitted to the hospital. Sunvozertinib was discontinued. On Day 370, (13 days after the last dose of sunvozertinib), the patient died and the cause of death was reported as **ischemic infarction.**	The tumor assessment on Day 336 was stable disease. The patient had a history of hypertension and dyslipidemia. FDA considers this death unlikely to be related to sunvozertinib; however, the contribution of the study therapy to the fatal adverse event of **ischemic infarction** cannot be ruled out.

Patient ID (sunvozertinib dose)	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality
(b) (6) (300 mg)	64-year-old male with NSCLC was randomized to sunvozertinib 300 mg QD. On Day 32, patient experienced Grade 4 suspected drug-induced liver injury and was hospitalized. Sunvozertinib treatment was discontinued. Laboratory tests revealed AST 283 UI/L (Grade 3), ALT 1082 UI/L (Grade 4), alkaline phosphatase 579 IU/L, and total bilirubin 8.43 mg/dL. Hepatitis viral serologies were negative. An abdominal ultrasound showed abundant left pleural effusion with passive atelectasis of the left lower lobe. On Day 34, hepatic biopsy revealed acute necroinflammatory and cholestatic hepatitis of mild intensity, acute hepatitis with mixed pattern secondary to hepatotoxicity. On Day 54, the ALT/AST returned to normal and alkaline phosphatase and total bilirubin were 249 IU/L and 11 mg/dL, respectively. On Day 49, patient experienced Grade 3 COVID-19, which was confirmed by a positive PCR test. Sputum sample revealed polymicrobial flora and MRSA. On Day 60, chest X ray showed bilateral pulmonary infiltrates. On Day 65, patient decided to pursue supportive care only. On Day 69, the patient died, and the primary cause of death was reported as **COVID-19**.	FDA considers this death unlikely to be related to sunvozertinib; however, the contribution of study therapy to the fatal adverse event of COVID-19 cannot be ruled out.

8.2.6.2 Serious Adverse Events

The Applicant's Position:

Data:

[*Source:* Module 2.7.4/Section 2.5]

TESAEs reported in ≥ 2% of patients, including fatal events by PT, are summarized in Table . In the pooled 300 mg safety analysis set, TESAEs were reported in 36.0% of patients. Among them, 21.5% had TESAEs of causality with sunvozertinib that could not be excluded by investigator's judgement. The most common TESAEs that occurred in at least 2% of patients were pneumonia, followed by diarrhea, COVID-19, and ILD.

Table 48 Common (≥ 2%) TESAEs (Safety Analysis Sets)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Patients with Any Treatment-Emergent SAE	41 (36.9)	112 (36.0)	172 (36.8)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Pneumonia	6 (5.4)	15 (4.8)	26 (5.6)
Diarrhoea	9 (8.1)	12 (3.9)	12 (2.6)
COVID-19	3 (2.7)	8 (2.6)	9 (1.9)
Interstitial lung disease	1 (0.9)	7 (2.3)	8 (1.7)

Source: Applicant Table. Module 2.7.4/Table 20. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

The Applicant's Position

TESAEs occurred in 36% of patients in the pooled 300 mg analysis set. The majority of individual TESAEs occurred in less than 2% in frequency, and types of TESAEs were consistent across the analysis sets. The most frequent TESAE was pneumonia, which is considered possibly related to the underlying disease. Another common TESAE of diarrhea is considered related to wild-type EGFR inhibition, and clinically manageable.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following table below for the safety populations of interest.

Table 49: Common TESAEs (Safety Analysis Sets) – Applicant Table

Preferred Term	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
Patients with Any Treatment-Emergent SAE	51 (42.1)	37 (40.7)	41 (36.9)
Pneumonia	8 (6.6)	6 (6.6)	6 (5.4)
Dyspnoea	5 (4.1)	4 (4.4)	1 (0.9)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.7.1 and Module 5.3.5.2/WU-KONG1B CSR/Table 40. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021. Common TESAEs were listed based on the incidence (≥2%) in the pooled 200 mg safety analysis set.

FDA also reviewed the Applicant's 120-day safety update with a data cutoff date of December 2, 2024. Treatment emergent serious adverse events (SAEs) occurred in 41% and 39% for the 200 mg and 300 mg sunvozertinib cohorts, respectively. Grade 3 to 4 SAEs occurred in 32% of patients treated with either the 200 mg or 300 mg sunvozertinib cohorts. The table is provided below.

FDA Table 50: All Serious Treatment-Emergent Adverse Events, WU-KONG1B – 120-Day Safety Update

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any SAE	37 (41)	29 (32)	43 (39)	35 (32)
Gastrointestinal disorders				
Diarrhea (GT)	0	0	10 (9)	10 (9)
Abdominal pain (GT)	0	0	2 (1.8)	1 (0.9)
Intestinal infarction	0	0	1 (0.9)	1 (0.9)
Proctitis	0	0	1 (0.9)	1 (0.9)
Small intestinal obstruction	0	0	1 (0.9)	1 (0.9)
Vomiting (GT)	0	0	1 (0.9)	1 (0.9)
Pancreatitis (GT)	2 (2.2)	2 (2.2)	0	0
Hemorrhoids	1 (1.1)	1 (1.1)	0	0
Large intestinal obstruction	1 (1.1)	1 (1.1)	0	0
Nausea	1 (1.1)	1 (1.1)	0	0
Stomatitis (GT)	1 (1.1)	1 (1.1)	0	0
Gastric polyps	1 (1.1)	0	0	0
Infections and infestations				
Pneumonia (GT)	8 (8.9)	6 (6.6)	9 (8.1)	6 (5.4)
Sepsis (GT)	1 (1.1)	1 (1.1)	4 (3.6)	2 (1.8)
COVID-19	1 (1.1)	0	3 (2.7)	2 (1.8)
Device related infection	2 (2.2)	2 (2.2)	1 (0.9)	1 (0.9)
Cellulitis	0	0	1 (0.9)	1 (0.9)
Gastroenteritis	0	0	1 (0.9)	1 (0.9)
Large intestine infection	0	0	1 (0.9)	0
Pulmonary tuberculosis	0	0	1 (0.9)	0
Hepatitis B reactivation	1 (1.1)	1 (1.1)	0	0
Infectious pleural effusion	1 (1.1)	1 (1.1)	0	0
Urinary tract infection (GT)	1 (1.1)	1 (1.1)	0	0
Respiratory tract infection	1 (1.1)	0	0	0
Respiratory, thoracic and mediastinal disorders				
Pneumonitis (GT)	0	0	3 (2.7)	3 (2.7)
Dyspnea (GT)	4 (4.4)	4 (4.4)	1 (0.9)	1 (0.9)
Pleural effusion	1 (1.1)	1 (1.1)	1 (0.9)	0
Respiratory failure	1 (1.1)	0	1 (0.9)	0
Hypoxia	0	0	1 (0.9)	0
Hemothorax	1 (1.1)	1 (1.1)	0	0

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Cough (GT)	1 (1.1)	0	0	0
Metabolism and nutrition disorders				
Decreased appetite	1 (1.1)	0	2 (1.8)	2 (1.8)
Dehydration	0	0	1 (0.9)	1 (0.9)
Hypercalcaemia	0	0	1 (0.9)	1 (0.9)
Hypoglycaemia	0	0	1 (0.9)	1 (0.9)
Hyponatraemia	0	0	1 (0.9)	1 (0.9)
Nervous system disorders				
Neuropathy peripheral (GT)	1 (1.1)	0	1 (0.9)	1 (0.9)
Ischemic stroke	1 (1.1)	1 (1.1)	1 (0.9)	0
Aphasia	0	0	1 (0.9)	1 (0.9)
Intracranial aneurysm	0	0	1 (0.9)	0
Dizziness (GT)	1 (1.1)	1 (1.1)	0	0
Vascular disorders				
Hemorrhage (GT)	1 (1.1)	0	6 (5)	6 (5)
Hypotension (GT)	0	0	2 (1.8)	2 (1.8)
Deep vein thrombosis	0	0	1 (0.9)	1 (0.9)
Venous thrombosis limb	0	0	1 (0.9)	0
Blue toe syndrome	1 (1.1)	0	0	0
Thrombosis	1 (1.1)	0	0	0
Cardiac disorders				
Pericardial effusion	0	0	2 (1.8)	2 (1.8)
Stress cardiomyopathy	0	0	1 (0.9)	1 (0.9)
Investigations				
Amylase increased	0	0	1 (0.9)	1 (0.9)
Blood creatine phosphokinase increased	0	0	1 (0.9)	1 (0.9)
Blood creatinine increased	0	0	1 (0.9)	1 (0.9)
Ejection fraction decreased	0	0	1 (0.9)	1 (0.9)
Lipase increased	0	0	1 (0.9)	1 (0.9)
Lymphocyte count decreased	1 (1.1)	1 (1.1)	0	0
Neutrophil count decreased	1 (1.1)	1 (1.1)	0	0
White blood cell count decreased	1 (1.1)	1 (1.1)	0	0
Renal and urinary disorders				
Acute kidney injury (GT)	1 (1.1)	1 (1.1)	2 (1.8)	2 (1.8)
Blood and lymphatic system disorders				
Anemia	2 (2.2)	2 (2.2)	1 (0.9)	1 (0.9)

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Disseminated intravascular coagulation	0	0	1 (0.9)	1 (0.9)
General disorders and administration site conditions				
General physical health deterioration	0	0	1 (0.9)	1 (0.9)
Pain	0	0	1 (0.9)	0
Hepatobiliary disorders				
Hepatic function abnormal	1 (1.1)	1 (1.1)	1 (0.9)	0
Suspected drug-induced liver injury	0	0	1 (0.9)	1 (0.9)
Injury, poisoning and procedural complications				
Hyphema	0	0	1 (0.9)	1 (0.9)
Femoral neck fracture	1 (1.1)	1 (1.1)	0	0
Lumbar vertebral fracture	1 (1.1)	1 (1.1)	0	0
Road traffic accident	1 (1.1)	1 (1.1)	0	0
Spinal compression fracture	1 (1.1)	1 (1.1)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Malignant neoplasm progression	0	0	1 (0.9)	1 (0.9)
Hepatic cancer	0	0	1 (0.9)	0
Reproductive system and breast disorders				
Uterine polyp	1 (1.1)	1 (1.1)	0	0
Skin and subcutaneous tissue disorders				
Rash (GT)	2 (2.2)	2 (2.2)	1 (0.9)	1 (0.9)
Skin toxicity	1 (1.1)	1 (1.1)	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain (GT)	1 (1.1)	1 (1.1)	0	0

Source: NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adae-120d.xpt, NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adsl-120d.xpt.

Note: Custom grouped terms are designated by '(GT)'.
Acute kidney injury (GT) includes: Acute kidney injury and renal failure.
Diarrhea (GT) includes: Colitis, and Diarrhea.
Hemorrhage (GT) includes: Gastric hemorrhage, Gastritis hemorrhagic, Hematuria, Hemoptysis, Intraventricular hemorrhage, Upper gastrointestinal hemorrhage, and Vaginal hemorrhage.
Hypotension (GT) includes: Hypotension, and Orthostatic hypotension.
Musculoskeletal pain (GT) includes: Back pain, and Pain in extremity.
Neuropathy peripheral (GT) includes: Peripheral sensory neuropathy, and Polyneuropathy.
Pancreatitis (GT) includes: Pancreatitis and Acute pancreatitis
Pneumonia (GT) includes: Pneumonia, Pneumonia bacterial, and COVID-19 pneumonia
Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.
Sepsis (GT) includes: Sepsis, Septic shock, and Enterobacter sepsis.
Urinary tract infection (GT) includes: Escherichia urinary tract infection.

Serious adverse reactions in ≥2 % of patients who received sunvozertinib 200 mg QD were pneumonia (9%); dyspnea (4.4%); and pancreatitis, device related infection, and rash (2.2% each).

Serious adverse reactions in ≥2 % of patients who received sunvozertinib 300 mg QD were diarrhea (9%), pneumonia (8%), sepsis (3.6%), pneumonitis (2.7%), and COVID-19 (2.7%).

Hemorrhage occurred in 5% and 1.1% for patients who received 300 mg and 200 mg sunvozertinib, respectively. FDA evaluated each individual preferred term for the group term and identified the incidence of each individual preferred term was one patient (0.9%) each for vaginal hemorrhage, upper gastrointestinal hemorrhage, intraventricular hemorrhage, hemorrhagic gastritis and gastric hemorrhage for sunvozertinib 300 mg and one patient (1.1%) for hemoptysis for sunvozertinib 200 mg.

Grade ≥3 SAEs in ≥2% of patients were diarrhea (9% and 0% for the 300 mg and 200 mg cohorts, respectively), pneumonia (5% and 7% for the 300 mg and 200 mg cohorts, respectively), pneumonitis (2.7% and 0% for the 300 mg and 200 mg cohorts, respectively), and dyspnea (0.9% and 4.4% for the 300 mg and 200 mg cohorts, respectively).

8.2.6.3 Dropouts and/or Discontinuations Due to Adverse Effects

Data and the Applicant's Position:

[*Source:* Module 2.7.4/ Section 2.6]

TEAEs leading to treatment discontinuation reported in at least 2 patients were summarized by PT and presented in Table 51. Across the 3 safety analysis sets, ILD/pneumonitis and pneumonia were the most common TEAEs leading to treatment discontinuation. The primary cause of death for 2 patients in the overall safety population could not be collected, and thus the Applicant took a cautious way to report as grade 5 AEs leading to treatment discontinuation.

Table 51 Common (≥ 2 Patients) TEAEs Leading to Treatment Discontinuation (Safety Analysis Sets)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Patients with any TEAE Leading to Drug Discontinuation	14 (12.6)	38 (12.2)	52 (11.1)
Interstitial lung disease	2 (1.8)	9 (2.9)	10 (2.1)
Pneumonia	3 (2.7)	5 (1.6)	7 (1.5)
Pneumonitis	2 (1.8)	5 (1.6)	5 (1.1)
Septic shock	2 (1.8)	2 (0.6)	2 (0.4)
Death	0 (0.0)	1 (0.3)	2 (0.4)
Rash papular	1 (0.9)	1 (0.3)	2 (0.4)
Vomiting	1 (0.9)	1 (0.3)	2 (0.4)

Source: Applicant Table. Module 2.7.4/Table 24. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

The Applicant's Position:

TEAEs leading to treatment discontinuation occurred in approximately 11% - 12% of patients. Per the study protocol, all confirmed ILD cases should stop treatment, and constitute the most common reason for treatment discontinuation.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information below in the safety populations of interest.

Table 52: Common (≥ 2 Patients) TEAEs Leading to Treatment Discontinuation (Safety Analysis Sets) – Applicant Table

Preferred Term	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
Patients with any TEAE Leading to Treatment Discontinuation	11 (9.1)	7 (7.7)	14 (12.6)
Pneumonia	2 (1.7)	1 (1.1)	3 (2.7)
Interstitial lung disease	1 (0.8)	0 (0.0)	2 (1.8)
Pneumonitis	0 (0.0)	0 (0.0)	2 (1.8)
Septic shock	0 (0.0)	0 (0.0)	2 (1.8)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.8.3 and Module 5.3.5.2/WU-KONG1B CSR/Table 36. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.

The FDA's Assessment:

FDA also evaluated TEAEs leading to treatment discontinuation from the Applicant's 120-day safety update with a data cutoff date of December 2, 2024. The data are presented in the table below.

FDA Table 53: TEAEs leading to Drug Discontinuation, WU-KONG1B – 120-Day Safety Update

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any TEAE	7 (8)	5 (5)	15 (14)	9 (8)
Respiratory, thoracic and mediastinal disorders				
Pneumonitis (GT)	0	0	4 (3.6)	3 (2.7)
Infections and infestations				
Pneumonia (GT)	2 (2.2)	2 (2.2)	3 (2.7)	2 (1.8)
Septic shock	0	0	2 (1.8)	1 (0.9)
COVID-19	0	0	1 (0.9)	0
Skin and subcutaneous tissue disorders				
Rash (GT)	2 (2.2)	2 (2.2)	1 (0.9)	1 (0.9)

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Gastrointestinal disorders				
Vomiting (GT)	1 (1.1))	0	1 (0.9)	0
Diarrhea (GT)	1 (1.1)	1 (1.1)	0	0
Pancreatitis acute	1 (1.1)	1 (1.1)	0	0
Vascular disorders				
Hemorrhage (GT)	0	0	1 (0.9)	1 (0.9)
Ischemic stroke	0	0	1 (0.9)	0
Thrombosis	1 (1.1)	0	0	0
Neoplasms benign, malignant and unspecified				
Malignant neoplasm progression	0	0	1 (0.9)	1 (0.9)
Nervous system disorders				
Neuropathy peripheral (GT)	1 (1.1)	1 (1.1)	0	0

Source: NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adae-120d.xpt, NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adsl-120d.xpt.
Note: Custom grouped terms are designated by '(GT)'.
Hemorrhage (GT) includes: Intraventricular hemorrhage.
Neuropathy peripheral (GT) includes: Peripheral sensory neuropathy.
Pneumonia (GT) includes: Pneumonia, respiratory tract infection
Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.
Rash (GT) includes: Rash papular, skin toxicity

Permanent discontinuation of the study drug for all grade TEAEs occurred in 14% and 8% for the 300 mg and 200 mg cohorts, respectively. Grade 3 to 4 permanent discontinuation occurred in 8% and 5% for the 300 mg and 200 mg cohorts, respectively. Adverse reactions leading to treatment discontinuation in ≥ 2% of patients were pneumonitis (3.6% and 0% for the 300 mg and 200 mg cohorts, respectively), pneumonia (2.7% and 2.2% for the 300 mg and 200 mg cohorts, respectively), and rash (0.9% and 2.2% for the 300 mg and 200 mg cohorts, respectively).

8.2.6.4 Dose Interruptions, and/or Reductions Due to Adverse Effects

Drug Interruption due to TEAEs

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 2.8]

TEAEs leading to dose interruption were reported in 54.3%, 59.5% and 51.0% of patients in the pooled 300 mg, primary and overall safety analysis sets, respectively. TEAEs leading to drug interruption reported in ≥ 2% of patients by safety analysis sets are summarized in Table 54. Across

three safety analysis sets, diarrhea was the most common TEAE leading to drug interruption, followed by blood CPK increased. Other TEAEs reported in less frequency included COVID-19, pneumonia, vomiting, and decreased appetite.

TEAEs leading to drug interruption were generally expected with an EGFR inhibitor in patient population of advanced NSCLC.

Table 54 Common (≥ 2%) TEAEs Leading to Drug Interruption (Safety Analysis Sets)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Patients with any TEAE Leading to Drug Interruption	66 (59.5)	169 (54.3)	238 (51.0)
Diarrhea	16 (14.4)	34 (10.9)	37 (7.9)
Blood creatine phosphokinase increased	10 (9.0)	31 (10.0)	36 (7.7)
COVID-19	3 (2.7)	16 (5.1)	22 (4.7)
Pneumonia	2 (1.8)	11 (3.5)	15 (3.2)
Vomiting	6 (5.4)	11 (3.5)	19 (4.1)
Decreased appetite	3 (2.7)	10 (3.2)	13 (2.8)
Nausea	5 (4.5)	10 (3.2)	11 (2.4)
Rash	4 (3.6)	7 (2.3)	12 (2.6)
Suspected COVID-19	0 (0.0)	7 (2.3)	7 (1.5)
Anemia	1 (0.9)	6 (1.9)	11 (2.4)
Lipase increased	0 (0.0)	6 (1.9)	12 (2.6)
Fatigue	3 (2.7)	5 (1.6)	7 (1.5)
Blood creatinine increased	4 (3.6)	4 (1.3)	6 (1.3)
Neutrophil count decreased	3 (2.7)	4 (1.3)	6 (1.3)

Source: Applicant Table. Module 2.7.4/Table 28. Data cut-off: Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

Dose Reduction due to TEAEs

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 2.7]

TEAEs leading to dose reduction reported in ≥ 2% of patients by PT and safety analysis set are summarized in Table 56. TEAEs leading to dose reduction were reported in 33.8%, 42.3% and 30.2% of patients in the pooled 300 mg, primary and overall safety analysis set, respectively. Across the safety analysis sets, diarrhea and blood CPK increased were the two most common TEAEs leading to dose reduction. Other TEAEs reported in less frequency were paronychia and lipase increased.

TEAEs leading to dose reduction were generally expected with an EGFR inhibitor in patient population of advanced NSCLC.

Table 55 Common (≥ 2%) TEAEs Leading to Dose Reduction (Safety Analysis Sets)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Patients with Any TEAE Leading to Dose Reduction	47 (42.3)	105 (33.8)	141 (30.2)
Blood creatine phosphokinase increased	8 (7.2)	24 (7.7)	31 (6.6)
Diarrhoea	12 (10.8)	22 (7.1)	28 (6.0)
Paronychia	1 (0.9)	8 (2.6)	10 (2.1)
Lipase increased	3 (2.7)	3 (1.0)	3 (0.6)

Source: Applicant Table. Module 2.7.4/Table 26. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information below in the safety populations of interest.

Table 56: Common TEAEs Leading to Drug Interruption (Safety Analysis Sets) – Applicant Table

Preferred Term	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
Patients with any TEAE Leading to Drug Interruption	58 (47.9)	44 (48.4)	66 (59.5)
Vomiting	8 (6.6)	8 (8.8)	6 (5.4)
Blood creatine phosphokinase increased	5 (4.1)	4 (4.4)	10 (9.0)
COVID-19	5 (4.1)	4 (4.4)	3 (2.7)
Lipase increased	5 (4.1)	3 (3.3)	0 (0.0)
Rash	4 (3.3)	4 (4.4)	4 (3.6)
Dyspnoea	4 (3.3)	2 (2.2)	1 (0.9)
Amylase increased	3 (2.5)	3 (3.3)	1 (0.9)
Diarrhoea	3 (2.5)	2 (2.2)	16 (14.4)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.10.1 and Module 5.3.5.2/WU-KONG1B CSR/Table 32. Data cut-off: Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021. Common TEAEs leading to drug interruption were listed based on the incidence (≥2%) in the pooled 200 mg safety analysis set.

Table 57: Common TEAEs Leading to Dose Reduction (Safety Analysis Sets) – Applicant Table

Preferred Term	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
Patients with Any TEAE Leading to Dose Reduction	24 (19.8)	21 (23.1)	47 (42.3)

Blood creatine phosphokinase increased	4 (3.3)	4 (4.4)	8 (7.2)
Diarrhoea	3 (2.5)	3 (3.3)	12 (10.8)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.9.1 and Module 5.3.5.2/WU-KONG1B CSR/Table 34. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021. Common TEAEs leading to dose reduction were listed based on the incidence (≥2%) in the pooled 200 mg safety analysis set.

The FDA's Assessment:

FDA also evaluated TEAEs leading to treatment interruption and dose reductions from the Applicant's 120-day safety update with a data cutoff date of December 2, 2024. The data are presented in the following two tables below.

FDA Table 58: TEAEs leading to Dose Interruption, WU-KONG1B – 120-Day Safety Update

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any TEAE	44 (48)	30(33)	68 (61)	49 (44)
Diarrhea (GT)	2 (2.2)	0	17 (15)	8 (7)
Blood creatine phosphokinase increased	4 (4.4)	2 (2.2)	10 (9)	9 (8)
Rash (GT)	7 (8)	5 (5)	7 (6)	3 (2.7)
Vomiting (GT)	8 (9)	0	6 (5)	1 (0.9)
Nausea	1 (1.1)	0	6 (5)	0
Pneumonia (GT)	7 (8)	1 (1.1)	6 (5)	3 (2.7)
Fatigue (GT)	1 (1.1)	0	5 (4.5)	4 (3.6)
Neutrophil count decreased	2 (2.2)	2 (2.2)	4 (3.6)	3 (2.7)
Blood creatinine increased	1 (1.1)	0	4 (3.6)	0
Acute kidney injury (GT)	1 (1.1)	1 (1.1)	3 (2.7)	1 (0.9)
Hemorrhage (GT)	0	0	3 (2.7)	3 (2.7)
Decreased appetite	0	0	3 (2.7)	2 (1.8)
Ejection fraction decreased	2 (2.2)	1 (1.1)	2 (1.8)	1 (0.9)
Paronychia	2 (2.2)	0	2 (1.8)	0
Aspartate aminotransferase increased	1 (1.1)	1 (1.1)	2 (1.8)	1 (0.9)
Abdominal pain (GT)	1 (1.1)	1 (1.1)	2 (1.8)	1 (0.9)
White blood cell count decreased	1 (1.1)	1 (1.1)	2 (1.8)	1 (0.9)
Urinary tract infection (GT)	1 (1.1)	1 (1.1)	2 (1.8)	0
Lung diffusion test decreased	0	0	2 (1.8)	1 (0.9)
Arrhythmia (GT)	0	0	2 (1.8)	0
Amylase increased	3 (3.3)	3 (3.3)	1 (0.9)	1 (0.9)
Device related infection	2 (2.2)	2 (2.2)	1 (0.9)	1 (0.9)

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Dyspnea (GT)	2 (2.2)	2 (2.2)	1 (0.9)	1 (0.9)
Anemia	2 (2.2)	2 (2.2)	1 (0.9)	0
Blood alkaline phosphatase increased	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Hypokalemia	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Lymphocyte count decreased	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Hepatic function abnormal	1 (1.1)	1 (1.1)	1 (0.9)	0
Platelet count decreased	1 (1.1)	1 (1.1)	1 (0.9)	0
Abdominal discomfort	0	0	1 (0.9)	1 (0.9)
Cellulitis	0	0	1 (0.9)	1 (0.9)
Deep vein thrombosis	0	0	1 (0.9)	1 (0.9)
Dehydration	0	0	1 (0.9)	1 (0.9)
Gastroenteritis	0	0	1 (0.9)	1 (0.9)
General physical health deterioration	0	0	1 (0.9)	1 (0.9)
Humerus fracture	0	0	1 (0.9)	1 (0.9)
Hypercalcemia	0	0	1 (0.9)	1 (0.9)
Hyperlipasemia	0	0	1 (0.9)	1 (0.9)
Hypermagnesemia	0	0	1 (0.9)	1 (0.9)
Hyphema	0	0	1 (0.9)	1 (0.9)
Hypocalcemia	0	0	1 (0.9)	1 (0.9)
Hypoglycemia	0	0	1 (0.9)	1 (0.9)
Hypotension (GT)	0	0	1 (0.9)	1 (0.9)
Leukopenia	0	0	1 (0.9)	1 (0.9)
Muscular weakness	0	0	1 (0.9)	1 (0.9)
Neutropenia	0	0	1 (0.9)	1 (0.9)
Pericardial effusion	0	0	1 (0.9)	1 (0.9)
Proctitis	0	0	1 (0.9)	1 (0.9)
Pneumonitis (GT)	0	0	1 (0.9)	1 (0.9)
Sepsis	0	0	1 (0.9)	1 (0.9)
Small intestinal obstruction	0	0	1 (0.9)	1 (0.9)
Suspected drug-induced liver injury	0	0	1 (0.9)	1 (0.9)
Blood creatine phosphokinase MB increased	0	0	1 (0.9)	0
Generalised tonic-clonic seizure	0	0	1 (0.9)	0
Hypomagnesaemia	0	0	1 (0.9)	0
Hypoxia	0	0	1 (0.9)	0
Influenza	0	0	1 (0.9)	0
Influenza like illness	0	0	1 (0.9)	0
Intestinal obstruction	0	0	1 (0.9)	0
Myocardial injury	0	0	1 (0.9)	0

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Musculoskeletal pain (GT)	0	0	1 (0.9)	0
Pulmonary tuberculosis	0	0	1 (0.9)	0
Pyrexia (GT)	0	0	1 (0.9)	0
Skin infection	0	0	1 (0.9)	0
Skin laceration	0	0	1 (0.9)	0
Syncope	0	0	1 (0.9)	0
Venous thrombosis limb	0	0	1 (0.9)	0
Visual acuity reduced	0	0	1 (0.9)	0
Weight decreased	0	0	1 (0.9)	0
Lipase increased	3 (3.3)	1 (1.1)	0	0
Pancreatitis	2 (2.2)	1 (1.1)	0	0
Alanine aminotransferase increased	1 (1.1)	1 (1.1)	0	0
Enterobacter sepsis	1 (1.1)	1 (1.1)	0	0
Gamma-glutamyltransferase increased	1 (1.1)	1 (1.1)	0	0
Hepatitis	1 (1.1)	1 (1.1)	0	0
Hyponatremia	1 (1.1)	1 (1.1)	0	0
Infectious pleural effusion	1 (1.1)	1 (1.1)	0	0
Ischemic stroke	1 (1.1)	1 (1.1)	0	0
Large intestinal obstruction	1 (1.1)	1 (1.1)	0	0
Malaise	1 (1.1)	1 (1.1)	0	0
Meningitis	1 (1.1)	1 (1.1)	0	0
Oxygen saturation decreased	1 (1.1)	1 (1.1)	0	0
Pleural effusion	1 (1.1)	1 (1.1)	0	0
Road traffic accident	1 (1.1)	1 (1.1)	0	0
Uterine polyp	1 (1.1)	1 (1.1)	0	0
Constipation	1 (1.1)	0	0	0
Dizziness (GT)	1 (1.1)	0	0	0
Headache (GT)	1 (1.1)	0	0	0
Oedema (GT)	1 (1.1)	0	0	0
Prothrombin time prolonged	1 (1.1)	0	0	0
SARS-CoV-2 test positive	1 (1.1)	0	0	0
Stomatitis (GT)	1 (1.1)	0	0	0
Tinnitus	1 (1.1)	0	0	0

Source: NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adae-120d.xpt, NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adsl-120d.xpt.
Note: Custom grouped terms are designated by '(GT)'.
Acute kidney injury (GT) includes: Acute kidney injury, and Renal failure.
Arrhythmia (GT) includes: Electrocardiogram PR prolongation, and Electrocardiogram QT prolonged.
Diarrhoea (GT) includes: Colitis, and Diarrhoea.

Fatigue (GT) includes: Asthenia, and Fatigue.
Hemorrhage (GT) includes: Gastritis hemorrhagic, Gingival bleeding, Hemorrhage, and Upper gastrointestinal hemorrhage.
Musculoskeletal pain (GT) includes: Myalgia.
Pneumonia (GT) includes: Lower respiratory tract infection, Pneumonia, and Pneumonia bacterial, COVID-19 pneumonia.
Rash (GT) includes: Dermatitis, Dermatitis acneiform, Eczema, Rash, and Rash maculo-papular.
Stomatitis (GT) includes: Mucosal inflammation.
Urinary tract infection (GT) includes: Escherichia urinary tract infection, and Urinary tract infection.

Dosage interruptions due to adverse reactions occurred in 61% and 48% in the 300 mg and 200 mg cohorts, respectively. Adverse reactions requiring dosage interruption in ≥5% of patients in the 300 mg cohort were diarrhea (15%), increased blook creatine phosphokinase (9%), rash (6%), vomiting (5%), nausea (5%) and in the 200 mg cohort were vomiting (9%), pneumonia (8%) and rash (5%).

FDA Table 59: TEAEs leading to Dose Reduction, WU-KONG1B – 120-Day Safety Update

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any TEAE	21 (23)	12 (13)	48 (43)	36 (32)
Diarrhea (GT)	3 (3.3)	0	12 (11)	10 (9)
Blood creatine phosphokinase increased	4 (4.4)	3 (3.3)	8 (7)	6 (5)
Rash (GT)	4 (4.4)	1 (1.1)	5 (4.5)	4 (3.6)
Fatigue (GT)	0	0	4 (3.6)	1 (0.9)
Hemorrhage (GT)	0	0	3 (2.7)	3 (2.7)
Lipase increased	0	0	3 (2.7)	3 (2.7)
Stomatitis (GT)	2 (2.2)	2 (2.2)	2 (1.8)	2 (1.8)
Anaemia	2 (2.2)	1 (1.1)	2 (1.8)	2 (1.8)
Acute kidney injury (GT)	0	0	2 (1.8)	1 (0.9)
Weight decreased	0	0	2 (1.8)	1 (0.9)
Alanine aminotransferase increased	0	0	2 (1.8)	0
Blood creatinine increased	2 (2.2)	1 (1.1)	1 (0.9)	0
Nausea	1 (1.1)	1 (1.1)	1 (0.9)	0
Hypokalaemia	0	0	1 (0.9)	1 (0.9)
Neurotoxicity	0	0	1 (0.9)	1 (0.9)
Neutropenia	0	0	1 (0.9)	1 (0.9)
Paronychia	0	0	1 (0.9)	1 (0.9)
Pruritus	0	0	1 (0.9)	1 (0.9)
Pneumonia (GT)	0	0	1 (0.9)	1 (0.9)
Acne	0	0	1 (0.9)	0
Aspartate aminotransferase increased	0	0	1 (0.9)	0

	200 mg N = 91 n (%)		300 mg N=111 n (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Blood creatine phosphokinase MB increased	0	0	1 (0.9)	0
Hypomagnesaemia	0	0	1 (0.9)	0
Myoglobin blood increased	0	0	1 (0.9)	0
Visual impairment	0	0	1 (0.9)	0
Vomiting (GT)	0	0	1 (0.9)	0
Hepatitis B reactivation	1 (1.1)	1 (1.1)	0	0
Lymphocyte count decreased	1 (1.1)	1 (1.1)	0	0
Platelet count decreased	1 (1.1)	1 (1.1)	0	0
Decreased appetite	1 (1.1)	0	0	0

Source: NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adae-120d.xpt, NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adsl-120d.xpt.
Note: Custom grouped terms are designated by '(GT)'.
Acute kidney injury (GT) includes: Renal failure.
Fatigue (GT) includes: Asthenia, and Fatigue.
Haemorrhage (GT) includes: Gastric haemorrhage, Haematuria, and Vaginal haemorrhage.
Rash (GT) includes: Dermatitis acneiform, Drug eruption, Eczema, and Rash.
Stomatitis (GT) includes: Mucosal inflammation, and Stomatitis.

Dose reductions due to adverse reactions occurred in 43% and 23% for the 300 mg and 200 mg cohorts, respectively. Adverse reactions requiring dose reduction in ≥3% of patients in the 300 mg cohort were diarrhea (11%), rash (4.5%), and fatigue (3.6%); and in the 200 mg cohort were rash (4.4%) and diarrhea (3.3%).

8.2.6.5 Significant Adverse Events

Data and the Applicant's Position:

[*Source*: Module 2.7.4/Section 2.3]

For the purpose of this section, severe TEAEs (grade 3 or higher) are considered to be significant. Common grade 3 or higher TEAEs (≥ 2% of patients) are summarized in Table 61. The most common TEAEs of grade 3 or higher included blood CPK increased, diarrhea, anemia, and pneumonia, which are expected for an EGFR TKI in NSCLC, and clinically manageable.

Table 60: Common (≥ 2%) TEAEs of Grade ≥ 3 (Safety Analysis Sets)

Preferred Term	Primary (N = 111) n (%)	Pooled 300 mg (N = 311) n (%)	Overall (N = 467) n (%)
Patients with Any TEAE of Grade ≥ 3	76 (68.5)	199 (64.0)	289 (61.9)
Blood creatine phosphokinase increased	17 (15.3)	53 (17.0)	62 (13.3)
Diarrhoea	22 (19.8)	41 (13.2)	46 (9.9)
Anaemia	10 (9.0)	32 (10.3)	48 (10.3)
Pneumonia	5 (4.5)	17 (5.5)	28 (6.0)

Hypokalaemia	5 (4.5)	11 (3.5)	15 (3.2)
Lipase increased	4 (3.6)	11 (3.5)	15 (3.2)
Asthenia	6 (5.4)	10 (3.2)	12 (2.6)
Lymphocyte count decreased	3 (2.7)	10 (3.2)	15 (3.2)
Decreased appetite	4 (3.6)	9 (2.9)	12 (2.6)
Amylase increased	3 (2.7)	8 (2.6)	12 (2.6)
Fatigue	4 (3.6)	8 (2.6)	10 (2.1)
Sepsis	3 (2.7)	7 (2.3)	7 (1.5)
COVID-19	3 (2.7)	6 (1.9)	7 (1.5)
Weight decreased	1 (0.9)	6 (1.9)	10 (2.1)
Neutrophil count decreased	3 (2.7)	5 (1.6)	9 (1.9)
Rash	4 (3.6)	5 (1.6)	10 (2.1)
Alanine aminotransferase increased	3 (2.7)	4 (1.3)	7 (1.5)
Aspartate aminotransferase increased	3 (2.7)	4 (1.3)	7 (1.5)
Septic shock	3 (2.7)	4 (1.3)	4 (0.9)
Dyspnoea	2 (1.8)	3 (1.0)	12 (2.6)

Source: Applicant Table. Module 2.7.4/Table 14. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information below in the safety populations of interest.

Table 61: Common TEAEs of Grade ≥ 3 (Safety Analysis Sets) – Applicant Table

Preferred Term	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
Patients with Any TEAE of Grade ≥ 3	72 (59.5)	56 (61.5)	76 (68.5)
Anemia	13 (10.7)	11 (12.1)	10 (9.0)
Dyspnea	8 (6.6)	6 (6.6)	2 (1.8)
Pneumonia	7 (5.8)	6 (6.6)	5 (4.5)
Blood creatine phosphokinase increased	6 (5.0)	5 (5.5)	17 (15.3)
Lymphocyte count decreased	5 (4.1)	5 (5.5)	3 (2.7)
Rash	4 (3.3)	4 (4.4)	4 (3.6)
Amylase increased	4 (3.3)	4 (4.4)	3 (2.7)
Lipase increased	4 (3.3)	2 (2.2)	4 (3.6)
Hypokalaemia	3 (2.5)	3 (3.3)	5 (4.5)
Neutrophil count decreased	3 (2.5)	3 (3.3)	3 (2.7)
Weight decreased	3 (2.5)	3 (3.3)	1 (0.9)
Diarrhea	3 (2.5)	2 (2.2)	22 (19.8)

Hyponatraemia	3 (2.5)	2 (2.2)	2 (1.8)
Nausea	3 (2.5)	2 (2.2)	2 (1.8)

Source: Applicant Table. Module 5.3.5.3/ISS/Section 4/Table 3.2.3.1 and Module 5.3.5.2/WU-KONG1B CSR/Table 30. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021. Common TEAEs of Grade ≥3 were listed based on the incidence (≥2%) in the pooled 200 mg safety analysis set.

FDA Table 62: Grade 3 to 4 TEAEs in ≥ 2 % of patients in WU-KONG1B - 120-Day Safety Update

	200 mg N=91 n (%) Grade 3-4	300 mg N=111 n (%) Grade 3-4
Any TEAE	**54 (59)**	**74 (67)**
Gastrointestinal disorders		
Diarrhea (GT)	2 (2.2)	23 (21)
Nausea	2 (2.2)	2 (1.8)
Stomatitis (GT)	2 (2.2)	2 (1.8)
General disorders and administration site conditions		
Fatigue (GT)	1 (1.1)	11 (10)
Skin and subcutaneous tissue disorders		
Rash (GT)	8 (9)	8 (7)
Infections and infestations		
Pneumonia (GT)	8 (9)	6 (5)
Renal and urinary disorders		
Acute kidney injury (GT)	1 (1.1)	4 (3.6)
Respiratory, thoracic and mediastinal disorders		
Dyspnea (GT)	6 (7)	3 (2.7)
Pneumonitis (GT)	0	4 (3.6)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain (GT)	2 (2.2)	0

Source: NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adae-120d.xpt, NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adsl-120d.xpt.

Note: Custom grouped terms are designated by '(GT)'.
Abdominal pain (GT) includes: Abdominal pain, Abdominal pain upper, Epigastric discomfort, and Gastrointestinal pain.
Acute kidney injury (GT) includes: Acute kidney injury, Azotaemia, Creatinine renal clearance decreased, Renal failure, and Renal impairment.
Diarrhea (GT) includes: Colitis, and Diarrhea.
Fatigue (GT) includes: Asthenia, and Fatigue.
Musculoskeletal pain (GT) includes: Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, and Spinal pain.
Pneumonia (GT) includes: Lower respiratory tract infection, Pneumonia, Pneumonia bacterial, and COVID-19 pneumonia.
Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.
Rash (GT) includes: Dermatitis, Dermatitis acneiform, Dermatitis bullous, Drug eruption, Eczema, Nodular rash, Rash, Rash

erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Skin exfoliation, and Skin toxicity.
Stomatitis (GT) includes: Aphthous ulcer, Cheilitis, Gingival ulceration, Mouth ulceration, Mucosal inflammation, and Stomatitis.

FDA Assessment:

For the safety population in the WU-KONG1B clinical trial, Grade 3 to 4 TEAEs occurred in 67% and 59% in the 300 mg and 200 mg cohorts, respectively. The most common (≥10% of patients) Grade 3 to 4 TEAEs were diarrhea (21% and 2.2% in the 300 mg and 200 mg cohorts, respectively) and fatigue (10% and 1.1% in the 300 mg and 200 mg cohorts, respectively). This was also consistent in the pooled safety population for diarrhea with 14% and 2.5% Grade 3 to 4 adverse events occurring in the 300 mg and 200 mg dose levels, respectively.

8.2.6.6 Treatment Emergent Adverse Events and Adverse Drug Reactions

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 2.2 and Section 2.10]

In pooled 300 mg safety analysis set, the most common (≥ 20%) TEAEs by PT were diarrhea (76.8%), blood CPK increased (49.2%), anemia (48.6%), rash (47.9%), paronychia (38.9%), decreased appetite (34.7%), nausea (33.4%), vomiting (33.1%), blood creatinine increased (32.8%), weight decreased (27.3%), and lipase increased (21.2%).

Safety data were reviewed by the applicant's medical and patient safety experts following the definition of ADRs from the ICH E6 guideline. AEs with similar medical concepts were grouped for analysis.

ADRs are limited to those events for which there is some basis for believing that there is a causal relationship between the occurrence of an AE and the use of a drug. Decisions on whether it is reasonable to believe that there is a causal relationship are a matter of clinical judgment and are based on factors including but not limited to:

- The frequency, severity, and seriousness of events. TEAEs reported in ≥ 10% of patients were considered to have met the ADR threshold for screening
- The timing of the event relative to the time of drug exposure
- The extent of dose response
- The extent to which the AE is consistent with the pharmacology of the drug
- The investigator assessment of causality
- Disease background

Table 63 presents the ADRs for sunvozertinib (N = 311).

Table 63: Incidence of Adverse Drug Reactions (Pooled 300 mg Safety Analysis Set) – Applicant Table

Adverse Drug Reaction	N = 311	
	All Grades* (%)	Grade 3 or higher# (%)
Gastrointestinal disorders		
Diarrhoea [a]	76.8	13.8
Stomatitis [b]	39.9	2.3
Nausea	33.4	1.3
Vomiting [c]	33.4	1.3
Weight decreased	27.3	1.9
Abdominal pain [d]	15.4	1.0
Constipation	13.2	0.3
Skin and subcutaneous tissue disorders		
Rash [e]	70.7	3.9
Paronychia [f]	40.8	1.9
Dry skin [g]	20.9	0.3
Pruritus	14.8	0.3
Investigations		
Blood creatine phosphokinase increased	49.2	17.0
Blood creatinine increased	32.8	0.3
Lipase increased	21.2	3.5
Amylase increased	19.9	2.6
Aspartate aminotransferase increased	19.6	1.3
Alanine aminotransferase increased	15.1	1.3
White blood cell count decreased	14.8	1.0
Neutrophil count decreased	11.9	1.6
Lymphocyte count decreased	10.3	3.2
Metabolism and nutrition disorders		
Decreased appetite	34.7	2.9
Hypokalaemia	19.9	3.5
Hypoalbuminaemia	16.7	0.0
Hyponatraemia	15.4	1.3
Blood and lymphatic system disorders		
Anaemia	48.6	10.3
General disorders and administration site conditions		
Fatigue	15.8	2.6
Asthenia	14.8	3.2
Nervous system disorders		
Headache	12.5	0.0

Adverse Drug Reaction	N = 311	
	All Grades* (%)	Grade 3 or higher# (%)
Renal and urinary disorders		
Proteinuria [h]	12.5	0.0
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease [i]	5.5	3.5
Eye disorders		
Keratitis [j]	1.0	0.3

Source: Applicant Table. Module 2.7.4/Table 30.
* Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5).
#: No fatal adverse reaction
[a] Diarrhoea includes Colitis, Diarrhoea.
[b] Stomatitis includes Angular cheilitis, Aphthous ulcer, Cheilitis, Mouth ulceration, Mucosal inflammation, Oral mucosal eruption, Oral pain, Stomatitis.
[c] Vomiting includes Retching, Vomiting.
[d] Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain upper, Flank pain, Gastrointestinal pain.
[e] Rash includes Acne, Dermatitis, Dermatitis acneiform, Dermatitis atopic, Dermatitis contact, Drug eruption, Eczema, Eczema asteatotic, Erythema, Folliculitis, Palmar-plantar erythrodysaesthesia syndrome, Papule, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Skin exfoliation.
[f] Paronychia includes Nail disorder, Nail infection, Nail toxicity, Onychoclasis, Onycholysis, Paronychia.
[g] Dry skin includes Dry skin, Skin fissures, Xeroderma, Xerosis.
[h] Proteinuria includes Albuminuria, Proteinuria.
[i] Interstitial lung disease includes Interstitial lung disease, Pneumonitis.
[j] Keratitis includes Injury corneal, Keratitis, Ulcerative keratitis.

Serious ADRs occurred in 15.1% of patients, and serious ADRs in ≥ 2% of patients were diarrhea and ILD/pneumonitis.

Permanent discontinuation of sunvozertinib treatment due to an ADR occurred in 6.4% of patients. ADRs leading to permanent discontinuation of sunvozertinib in ≥ 2% of patients was ILD/pneumonitis.

ADRs leading to dose reduction occurred in 28.9% of patients. ADRs leading to dose reduction in ≥ 5% of patients were blood CPK increased and diarrhea.

ADRs leading to dose interruption occurred in 38.9% of patients. ADRs leading to dose interruption in ≥ 5% of patients were diarrhea and blood CPK increased.

Overall, the ADRs are clinically manageable and can be monitored during the clinical use of the drug, and are considered consistent with wild-type EGFR inhibition by sunvozertinib.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information below in the safety populations of interest.

Table 64: Incidence of Adverse Reactions (Pooled 200 mg Safety Analysis Set) – Applicant Table

Adverse Reaction	N = 121	
	All Grades[1] (%)	Grade[1] 3 or 4 (%)
Gastrointestinal disorders		
Diarrhea	72.7	2.5
Stomatitis [a]	37.2	1.7
Nausea	32.2	2.5
Vomiting	32.2	0.8
Constipation	28.1	0.0
Weight decreased	19.8	2.5
Abdominal pain	16.5	1.7
Abdominal distension	12.4	0.0
Skin and subcutaneous tissue disorders		
Rash [b]	61.2	7.4
Paronychia	32.2	0.0
Pruritus	23.1	0.8
Dry skin	21.5	0.0
Metabolism and nutrition disorders		
Decreased appetite	43.8	1.7
General disorders and administration site conditions		
Fatigue [c]	36.4	3.3
Edema [d]	12.4	0.0
Infections and infestations		
Urinary tract infection [e]	20.7	0.8
Nervous system disorders		
Neuropathy peripheral [f]	14.0	0.0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	10.7	6.6
Interstitial lung disease [g]	1.7	0.0
Cardiac disorders		
Arrhythmia [h]	10.7	1.7
Eye disorders		
Dry eye	6.6	0.0
Blurred vision	5.8	0.0

Source: Applicant Table. 0001\m5\datasets\iss\analysis\adam\datasets\ADAE, ADSL.

[1] Adverse reactions graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0).

Grouped terms:

[a] Stomatitis includes aphthous ulcer, cheilitis, mouth ulceration, mucosal inflammation, and stomatitis.

[b] Rash includes dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, nodular rash, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.
[c] Fatigue includes asthenia and fatigue.
[d] Edema includes lip edema, edema, edema peripheral, and swelling.
[e] Urinary tract infection includes cystitis, escherichia urinary tract infection, urinary tract infection, and urinary tract infection pseudomonal.
[f] Neuropathy peripheral includes hypoaesthesia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, and peripheral sensory neuropathy.
[g] Interstitial lung disease includes interstitial lung disease and pneumonitis.

[h] Arrhythmia includes atrioventricular block first degree, electrocardiogram QT prolonged, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, and supraventricular tachycardia.

The FDA's Assessment:

FDA evaluated TEAEs for the pooled safety populations of patients treated at 200 mg QD and 300 mg QD. The results are presented in the table below.

FDA Table 65: Treatment Emergent Adverse Events for the Pooled Safety Populations – 120-Day Safety Update

Adverse Reaction	200 mg cohort N=91		300 mg cohort N=111	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhea (GT)	73	2.2	87	21
Stomatitis (GT)	40	2.2	45	1.8
Vomiting (GT)	35	0	44	0.9
Nausea	32	2.2	43	1.8
Constipation	27	0	16	0.9
Weight decreased	26	3.3	26	0.9
Abdominal pain (GT)	19	1.1	28	0.9
Abdominal distension	16	0	14	0
Skin and subcutaneous tissue disorders				
Rash (GT)	60	8	62	7
Paronychia (GT)	30	0	40	0.9
Pruritus	26	1.1	23	0.9
Dry skin (GT)	21	0	26	0
Metabolism and nutrition disorders				
Decreased appetite	52	0	42	3.6
General disorders and administration site conditions				

Adverse Reaction	200 mg cohort N=91		300 mg cohort N=111	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Fatigue (GT)	41	1.1	48	10
Edema (GT)	11	0	10	0
Malaise	11	1.1	3.6	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain (GT)	26	2.2	27	0
Infections and infestations				
Urinary tract infection (GT)	24	1.1	19	0
Pneumonia (GT)	25	13	35	7
Eye disorders				
Ocular toxicity (GT)	18	0	19	0
Nervous system disorders				
Peripheral neuropathy (GT)	14	0	16	0.9
Cardiac disorders				
Arrhythmia (GT)	12	1.1	14	0

Source: NDA219839/0001/m5/datasets/iss/analysis/adam/datasets/adae.xpt,
NDA219839/0001/m5/datasets/iss/analysis/adam/datasets/adsl.xpt.
Note: Custom grouped terms are designated by '(GT)'.
Abdominal pain (GT) includes: Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort, and Gastrointestinal pain.
Acute kidney injury (GT) includes: Acute kidney injury, Azotemia, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal failure, and Renal impairment.
Arrhythmia (GT) includes: Arrhythmia, Atrial fibrillation, Atrioventricular block first degree, Bundle branch block left, Bundle branch block right, Defect conduction intraventricular, Electrocardiogram PR prolongation, Electrocardiogram QRS complex prolonged, Electrocardiogram QT prolonged, Sinus bradycardia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Ventricular arrhythmia, and Ventricular extrasystoles.
Cough (GT) includes: Cough, and Productive cough.
Diarrhea (GT) includes: Colitis, Diarrhea, Enteritis, and Frequent bowel movements.
Dizziness (GT) includes: Dizziness, and Vertigo.
Dyspnea (GT) includes: Dyspnea, and Dyspnea exertional.
Fatigue (GT) includes: Asthenia, and Fatigue.
Hemorrhage (GT) includes: Cerebral hemorrhage, Conjunctival hemorrhage, Ear hemorrhage, Epistaxis, Gastric hemorrhage, Gastritis hemorrhagic, Gastrointestinal hemorrhage, Gingival bleeding, Hematuria, Hemoptysis, Hemorrhage, Hemorrhage intracranial, Hemorrhage subcutaneous, Hemorrhoidal hemorrhage, Intraventricular hemorrhage, Lower gastrointestinal hemorrhage, Rectal hemorrhage, Retinal hemorrhage, Upper gastrointestinal hemorrhage, and Vaginal hemorrhage.
Hypertension (GT) includes: Blood pressure increased, and Hypertension.
Hypotension (GT) includes: Blood pressure decreased, Hypotension, and Orthostatic hypotension.
Musculoskeletal pain (GT) includes: Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, and Pain in extremity.

Neuropathy peripheral (GT) includes: Hypoesthesia, Neuralgia, Neuropathy peripheral, Paresthesia, Peripheral motor neuropathy, Peripheral sensory neuropathy, and Polyneuropathy.
Edema (GT) includes: Face oedema, Generalised oedema, Lip oedema, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema, and Swelling.
Pneumonia (GT) includes: Atypical pneumonia, Lower respiratory tract infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial, and Pneumonia cytomegaloviral.
Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.
Rash (GT) includes: Dermatitis, Dermatitis acneiform, Dermatitis bullous, Drug eruption, Eczema, Eczema asteatotic, Nodular rash, Palmar-plantar erythrodysaesthesia syndrome, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, and Skin exfoliation.
Stomatitis (GT) includes: Aphthous ulcer, Cheilitis, Gingival ulceration, Mouth ulceration, Mucosal inflammation, Stomatitis, and Tongue ulceration.
Urinary tract infection (GT) includes: Cystitis, Escherichia urinary tract infection, Urinary tract infection, and Urinary tract infection pseudomonal.
Vomiting (GT) includes: Hematemesis, Retching, and Vomiting.

In the 200 mg cohort, the most common (≥20%) adverse reactions were: diarrhea (73%), rash (60%), decreased appetite (52%), stomatitis (40%), fatigue (41%), vomiting (35%), nausea (32%), paronychia (30%), , constipation (27%), musculoskeletal pain (26%), pruritus (26%), decreased weight (26%), pneumonia (25%), urinary tract infection (24%), dry skin (21%), and abdominal pain (19%).

In the 300 mg cohort, the most common (≥ 20%) adverse reactions were: diarrhea (87%), rash (60%), fatigue (48%), stomatitis (45%), vomiting (44%), nausea (43%), decreased appetite (42%), paronychia (40%), pneumonia (35%), abdominal pain (28%), musculoskeletal pain (27%), decreased weight (26%), dry skin (26%), and pruritus (23%).

Among the 121 patients who received sunvozertinib 200 mg QD in the pooled safety population, the most common (≥ 20%) adverse reactions were diarrhea (73%), rash (63%), decreased appetite (44%), stomatitis (38%), fatigue (36%), nausea (32%), paronychia (32%), vomiting (32%), constipation (28%), musculoskeletal pain (26%), pruritus (23%), dry skin (21%), urinary tract infection (21%), abdominal pain (20%) and decreased weight (20%).

Among the 311 patients who received sunvozertinib 300 mg QD in the pooled safety population, the most common (≥20%) adverse reactions were diarrhea (77%), rash (68%), stomatitis (40%), paronychia (39%), decreased appetite (35%), vomiting (34%), nausea (33%), fatigue (30%), and musculoskeletal pain (24%).

8.2.6.7 Laboratory Findings

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 3]

Hematology

Grade shift of hemoglobin decreased, white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased were observed across three safety analysis sets. The majority of the shifts or related TEAEs were of grade 1 or 2 in severity, and very few cases reported

hematology related SAE or required dose modification. The hematology changes generally did not lead to treatment discontinuation.

Clinical Chemistry

In an integrated assessment of liver function-related parameters and related TEAEs, less than 1% of patients had post-baseline transaminases (AST or ALT) ≥ 3 × ULN, and concurrent with bilirubin ≥ 2 × ULN. No case of Hy's law was reported. The safety risk of hepatic injury associated with sunvozertinib was considered low (Table 36 and Table 37).

The analysis of renal chemistry and related TEAEs suggested the safety risk of renal abnormalities associated with sunvozertinib was also considered low.

Grade shift of laboratory CPK increased and TEAEs of blood CPK increased were frequently reported after sunvozertinib treatment, while most of the events were grade 1 or 2 in severity, asymptomatic, and manageable in the clinic. The clinical impact of blood CPK increased was considered manageable.

Coagulation

The majority of patients experienced no shift from baseline in grade or a shift of ≤ 2 grade in coagulation parameters during the study.

The hepatic, renal, hematological, and other laboratory abnormality related safety risks with sunvozertinib treatment were considered low.

Table 66: Laboratory Abnormalities Associated with Liver Function (Safety Analysis Sets)

	Primary (N = 111) n/N1 (%)	Pooled 300 mg (N = 311) n/N1 (%)	Overall (N = 467) n/N1 (%)
Patients with ALT or AST ≥ 3 × ULN	7/111 (6.3)	23/310 (7.4)	35/465 (7.5)
Patients with Bilirubin ≥ 2 × ULN	2/111 (1.8)	4/310 (1.3)	4/465 (0.9)
Patients with (ALT or AST ≥ 3 × ULN) and Bilirubin ≥ 2 × ULN	1/111 (0.9)	3/310 (1.0)	3/465 (0.6)
Patients with (ALT or AST ≥ 3 × ULN) and Bilirubin ≥ 2 × ULN and ALP < 2 × ULN	0/111 (0.0)	2/310 (0.6)	2/465 (0.4)

Source: Applicant Table. Module 2.7.4/Table 33. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.
ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ULN: Upper Limit of Normal Range. The percentage was calculated based on the number of patients with at least one non-missing measurement as the denominator (N1).

56Table 67: Selected Laboratory Abnormalities Worsening from Baseline in ≥ 20% of Patients (Pooled 300 mg Safety Analysis Set)

Laboratory Abnormality	N=311	
	All Grades (%)	Grade 3 or Grade 4 (%)
Clinical Chemistry		
Increased CPK	75.3	18.5
Increased creatinine	63.2	0.6

Laboratory Abnormality	N=311	
	All Grades (%)	Grade 3 or Grade 4 (%)
Increased lipase	45.7	16.1
Decreased sodium	42.1	2.3
Increased amylase	39.6	9.1
Decreased albumin	39.4	0.0
Decreased potassium	35.9	6.1
Increased aspartate aminotransferase	35.2	1.6
Increased alanine aminotransferase	28.7	1.9
Increased alkaline phosphatase	22.9	0.6
Increased magnesium	20.1	2.3
Hematology		
Decreased hemoglobin	64.5	9.7
Decreased lymphocytes	53.9	15.5
Decreased leukocytes	30.0	1.6
Decreased neutrophils	24.8	3.2

Source: Applicant Table. Module 2.7.4/Table 39. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.
The denominator used to calculate the incidence (%) varied from 275 to 310 based on the number of patients with a baseline and at least one post-treatment value.

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information below, in the safety populations of interest.

Table 68: Laboratory Abnormalities Associated with Liver Function (Safety Analysis Sets) – Applicant Table

	Pooled 200 mg (N = 121) n/N1 (%)	Primary 200 mg (N = 91) n/N1 (%)	Primary 300 mg (N = 111) n/N1 (%)
Patients with ALT or AST ≥3×ULN	9/120 (7.5)	5/90 (5.6)	7/111 (6.3)
Patients with Bilirubin ≥2×ULN	0/120 (0.0)	0/90 (0.0)	2/111 (1.8)
Patients with (ALT or AST ≥3×ULN) and Bilirubin ≥2×ULN	0/120 (0.0)	0/90 (0.0)	1/111 (0.9)
Patients with (ALT or AST ≥3×ULN) and Bilirubin ≥2×ULN and ALP <2×ULN	0/120 (0.0)	0/90 (0.0)	0/111 (0.0)

Source: Applicant Table. Module 2.7.4/Table 35 and Module 5.3.5.2/WU-KONG1B CSR/Table 44. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.

ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ULN: Upper Limit of Normal Range. The percentage was calculated based on the number of patients with at least one non-missing measurement as the denominator (N1).

Table 69: Selected Laboratory Abnormalities Worsening from Baseline in ≥ 20% of Patients (Pooled 200 mg Safety Analysis Set) – Applicant Table

Laboratory Abnormality	N=121[1]	
	All Grades[2] (%)	Grade 3 or Grade 4 (%)
Hematology		
Hemoglobin decreased	60.0	10.0
Lymphocyte count decreased	58.3	17.5
Neutrophils decreased	38.3	4.2
Leukocytes decreased	35.0	3.3
Clinical Chemistry		
CPK increased	54.9	5.9
Creatinine increased	51.3	0.0
Lipase increased	44.5	15.1
Aspartate aminotransferase increased	44.2	3.3
Amylase increased	36.4	9.3
Sodium decreased	35.3	2.5
Alanine aminotransferase increased	30.0	3.3
Albumin decreased	30.0	0.0
Potassium decreased	27.7	3.4
Urinalysis		
Protein increased	36.0	0.0

Source: Applicant Table. 0001\m5\datasets\iss\analysis\adam\datasets\ADLB, ADSL. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29JUL2024, DZ2019E0002 27SEP2021.

[1] The denominator used to calculate the incidence (%) varied from 89 to 120 based on the number of patients with a baseline and at least one post-treatment value. [2] NCI CTCAE v5.0.

FDA Table 70: Selected Laboratory Abnormalities Worsening from Baseline in ⩾ 20% of Patients in WU-KONG1B – 120-Day Safety Update

Laboratory Abnormality	200 mg cohort N=91		300 mg cohort N=111	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Creatinine increased	62	0	67	0

Laboratory Abnormality	200 mg cohort N=91		300 mg cohort N=111	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Creatine kinase increased	57	8	81	16
Lipase increased	47	13	56	16
Aspartate aminotransferase increased	44	4.4	41	0.9
Amylase increased	37	9	46	9
Sodium decreased	33	3.4	47	2.7
Decreased albumin	32	0	38	0
Decreased potassium	29	3.4	38	4.5
Alanine aminotransferase increased	28	4.4	30	2.7
Magnesium increased	23	4.4	17	0.9
Alkaline phosphatase increased	21	2.2	28	0.9
Hematology				
Hemoglobin decreased	61	12	68	8
Lymphocytes decreased	54	20	59	18
Neutrophils decreased	41	4.4	27	5
Urinalysis				
Urine protein increased	38	0	49	0

Source: 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: NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adlb-120d.xpt, NDA219839/0021/m5/datasets/dz2019e0001-partb/analysis/adam/datasets/adsl-120d.xpt.

In the 200 mg cohort, the most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were: decreased lymphocytes (20%), increased lipase (13%), decreased hemoglobin (12%), increased amylase (9%), increased creatine kinase (8%), decreased neutrophils (4.4%), increased aspartate aminotransferase (4.4%), increased alanine aminotransferase (4.4%), increased magnesium (4.4%), decreased potassium (3.4%), decreased sodium (3.4%), and increased alkaline phosphatase (2.2%).

In the 300 mg cohort, the most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (18%), increased lipase (16%), increased creatine kinase (16%), increased amylase (9%), decreased hemoglobin (8%), increase decreased neutrophils (5%), decreased potassium (4.5,), increased alanine aminotransferase (2.7%), and decreased sodium (2.7%).

Among the 121 patients who received sunvozertinib 200 mg QD in the pooled safety population, the most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes (18%), increased lipase (15%), decreased hemoglobin (10%), increased amylase (9%), increased creatine kinase (6%), decreased neutrophils (4.2%), decreased potassium (3.4%), increased aspartate aminotransferase (3.3%), increased alanine aminotransferase (3.3%), decreased sodium (2.5%), increased magnesium (2.5%), and increased alkaline phosphatase (2.5%).

Among the 311 patients who received sunvozertinib 300 mg QD in the pooled safety population, the most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were increased creatine kinase (19%), increased lipase (16%), decreased lymphocytes (15%), decreased hemoglobin (10%), increased amylase (9%), decreased potassium (6%), decreased neutrophils (3.2%), increased magnesium (2.3%), and decreased sodium (2.3%).

8.2.6.8 Vital Signs

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 4]

Approximately 25% of patients were reported to have AE of weight decreased, often with complicated reasons and factors (e.g. underlying disease, decreased appetite, and GI discomfort, etc.). No patient discontinued treatment due to AE of weight decreased. No clinically significant changes in blood pressure and pulse rate were noted.

The FDA's Assessment:

Clinically significant changes of vital signs were reported as TEAEs during the clinical trial. No relevant trends in vital sign examinations were reported with sunvozertinib therapy.

TEAEs of diarrhea (87% and 73% in the 300 mg and 200 mg cohorts, respectively) and vomiting (22% and 35% in the 300 mg and 200 mg cohorts, respectively), may have been contributing factors for the incidence of decreased weight (26% in both cohorts) with sunvozertinib.

No significant trends regarding the rates of TEAEs of hypertension (2.7% and 5% in the 300 mg and 200 mg cohorts, respectively), hypotension (4.5% and 3.3% in the 300 mg and 200 mg cohorts, respectively), and tachycardia (2.7% and 2.2% in the 300 mg and 200 mg cohorts, respectively), were observed in the WU-KONG1B clinical trial.

8.2.6.9 Electrocardiograms (ECGs)

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 4.6]

In WU-KONG studies, 12-lead ECGs were conducted to evaluate the effects of sunvozertinib on ECG parameters (QT, QTcF, PR, QRS and heart rate). There is no evidence showing that sunvozertinib affects ECG parameters, and as discussed in Section 8.2.6.10, the risk of QT prolongation is considered low.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.6.10 QT

Data and the Applicant's Position:

[*Source:* Module 2.7.4/Section 4.6]

The summary of QTcF interval prolongation (in absolute and change from baseline values) are presented in Table 71. In the pooled 300 mg safety analysis set, two patients (0.7%) were reported to have QTcF value > 500 msec, concurrent with increase from baseline > 60 msec. C-QTc analysis indicated a QTc effect exceeding 10 msec can be excluded under the clinically relevant plasma concentration of sunvozertinib. The overall risk of sunvozertinib causing QT prolongation is considered low.

Table 71: QTcF Prolongation Post Baseline (Safety Analysis Sets)

	Primary (N = 111) n (%)	**Pooled 300 mg (N = 311) n (%)**	**Overall (N = 467) n (%)**
QTcF (msec)			
N1	108	307	459
> 450	30 (27.8)	61 (19.9)	106 (23.1)
> 480	8 (7.4)	12 (3.9)	18 (3.9)
> 500	4 (3.7)	5 (1.6)	7 (1.5)
QTcF Change from Baseline (msec)			
N1	105	302	453
> 30	23 (21.9)	62 (20.5)	85 (18.8)
> 60	2 (1.9)	6 (2.0)	9 (2.0)
> 60 and QTcF > 500	2 (1.9)	2 (0.7)	4 (0.9)

Source: Applicant Table. Module 2.7.4/Table 40. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29 JUL2024, DZ2019E0002 27SEP2021, DZ2020E0001 03APR2023.
QTcF: Fridericia corrected QT (QTcF) interval. The denominator for percentage was number of patients with non-missing data (N1).

The FDA's Assessment:

On May 8, 2025, the Applicant responded to FDA's May 2, 2025, Information Request and provided the following information below in the safety populations of interest.

Table 72: QTcF Prolongation Post Baseline (Safety Analysis Sets) – Applicant Table

	Pooled 200 mg (N = 121) n (%)	Primary 200 mg (N = 91) n (%)	Primary 300 mg (N = 111) n (%)
QTcF (msec)			
N1	117	87	108
> 450	36 (30.8)	32 (36.8)	30 (27.8)
> 480	3 (2.6)	2 (2.3)	8 (7.4)
> 500	1 (0.9)	0 (0.0)	4 (3.7)
QTcF Change from Baseline (msec)			
N1	116	86	105
> 30	14 (12.1)	11 (12.8)	23 (21.9)
> 60	1 (0.9)	0 (0.0)	2 (1.9)
> 60 and QTcF > 500	1 (0.9)	0 (0.0)	2 (1.9)

Source: Applicant Table. Module 2.7.4/Table 41 and Module 5.3.5.2/WU-KONG1B CSR/Table 48. Data cut-off: DZ2019E0001 Part A 24APR2024, DZ2019E0001 Part B 29 JUL2024, DZ2019E0002 27SEP2021.

QTcF: Fridericia corrected QT (QTcF) interval. The denominator for percentage was number of patients with non-missing data (N1).

FDA Assessment:

Refer to the FDA Assessment under QT prolongation below.

Immunogenicity

Data and the Applicant's position

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.7 Analysis of Submission-Specific Safety Issues

[*Source:* Module 2.7.4/Section 2.9]

AESIs were identified based on assessment of nonclinical and clinical safety data, ADRs of approved EGFR TKIs, and taking into consideration of disease background. This section presents the assessment using AESI terms, events with similar medical concepts were grouped (Grouped Term, GT) for analysis. Similar trend of results was observed across the three safety analysis sets.

The results presented below are primarily focusing on the pooled 300 mg safety analysis set (N=311).

Diarrhea

Data and the Applicant's position

In the pooled 300 mg safety analysis set, diarrhea (GT) was reported in 76.8% of patients and as an SAE in 4.5% of patients. The majority of events reported were grade 1 or 2 in severity, with no grade 4 or 5 events being reported. The median time to the first onset of diarrhea was 8 days, and the majority of events were deemed recovered (82.7%) or recovering (4.8%) by DCO. The median time to resolution was 11 days. Note that the calculation included the intermittent and sporadic or occasional diarrhea, and therefore may overestimate the duration for recovery due to the inclusion of days without diarrhea.

Similar results were observed in primary and overall safety analysis sets. Among all 467 patients in the overall safety analysis set, one (0.3%) patient of 200 mg permanently discontinued sunvozertinib treatment due to diarrhea.

In summary, the majority of diarrhea events were grade 1 or 2 in severity and did not generally lead to discontinuation of sunvozertinib. The median onset time of diarrhea was 8 days after administration, which is considered a suitable timeframe to facilitate monitoring for prompt intervention. The majority of cases were manageable without dose reduction or discontinuation. These results suggested that diarrhea did not bring significant safety and tolerability burden in the advanced NSCLC patient population, and unlikely would prevent patients from continuing with sunvozertinib treatment.

The FDA's Assessment:

Among the 121 patients in the pooled safety population for the sunvozertinib 200 mg dose level, serious gastrointestinal adverse reactions occurred in 1.7% of patients including 0.8% Grade 3 nausea. Diarrhea occurred in 73%, including 2.5% Grade 3. Diarrhea leading to dosage interruption or dose reduction occurred in 5% of patients and required permanent discontinuation of sunvozertinib in 0.8% of patients.

Among the 311 patients in the pooled safety population for the sunvozertinib 300 mg dose level, serious gastrointestinal adverse reactions occurred in 5% of patients including 0.8% Grade 3 nausea. Diarrhea occurred in 77%, including 14% Grade 3. Diarrhea leading to dosage interruption or dose reduction occurred in 11% of patients and required permanent discontinuation of sunvozertinib in 0.3% of patients.

In the safety population in WU-KONG1B, FDA noted that a higher incidence of Grade 3 diarrhea occurred at the 300 mg dose (21%) compared to the 200 mg dose (2.2%) and that there was a higher incidence of dose interruptions or dose reductions in the 300 mg cohort (11%) compared to the 200 mg cohort (5%).

Based on the observed seriousness and severity of gastrointestinal adverse reactions, FDA has included this in the Warnings and Precautions section of the USPI (Section 5.2).

Nausea/Vomiting

Data and the Applicant's Position:

These two events were grouped for analysis given the medical similarity.

In the pooled 300 mg safety analysis set, 46.3% of patients reported nausea/vomiting (GT), with most events being grade 1 or 2 in severity. The frequencies of SAEs, dose interruptions and dose reductions were low, and one patient discontinued treatment because of vomiting. The median time to the first onset of these events was 17.5 days. Most (83.8%) events were deemed recovered by the DCO, and the median time to resolution was 9 days.

In summary, the majority of nausea and vomiting were grade 1 and 2 in severity and reversible, and generally did not lead to treatment discontinuation. The events of nausea/vomiting were considered likely to be of minimal clinical impact to patients continuing with sunvozertinib treatment.

The FDA's Assessment:

Among the 121 patients in the pooled safety population for the sunvozertinib 200 mg, nausea and vomiting occurred in 43% of patients, including 3.3% Grade 3 events. Nausea and vomiting leading to dosage interruption or dose reduction occurred in 7% of patients and permanent discontinuation of sunvozertinib in 0.8% of patients.

Among the 311 patients in the pooled safety population for the sunvozertinib 300 mg, nausea and vomiting occurred in 43% of patients, including 1.3% Grade 3 events. Nausea and vomiting leading to dosage interruption or dose reduction occurred in 6% of patients and permanent discontinuation of sunvozertinib in 0.3% of patients.

In the safety population in WU-KONG1B, FDA noted a higher incidence of vomiting (44% and 35% in the 300 mg and 200 mg cohorts, respectively) and nausea (43% and 32% in the 300 mg and 200 mg cohorts, respectively) in the 300 mg cohort. FDA included diarrhea, nausea and vomiting under gastrointestinal adverse reactions in the Warnings and Precautions section of the USPI (Section 5.2)

Stomatitis

Data and the Applicant's Position:

In pooled 300 mg safety analysis set, stomatitis (GT) was reported in 39.2% of patients. Most events were grade 1 or 2 in severity, with no grade 4 events, and no SAEs were reported. Stomatitis leading to dose interruption and reduction were reported in 1.0% and 1.6% of patients, respectively, and no patient permanently discontinued treatment due to this event. The median time to the first onset of stomatitis was 15 days. The majority of stomatitis events (84.5%) were deemed recovered by DCO, and the median time to resolution of events was 23 days.

In summary, the majority of events of stomatitis were grade 1 or 2 in severity and reversible. Stomatitis is considered to have minimal clinical impact to patients continuing with sunvozertinib treatment.

The FDA's Assessment:

In the safety population in WU-KONG1B, a higher incidence of stomatitis occurred in the 300 mg cohort with 45% of events in the 300 mg cohort and 40% in the 200 mg cohorts. Grade 3 or 4 stomatitis occurred in two patients in each cohort (1.8% Grade 3 or 4 events and 2.2% Grade 3 or 4 in patients in the 300 mg and 200 mg cohorts, respectively). Rates of stomatitis were also consistent in the pooled safety populations with 40% and 38% adverse events occurring in the 300 mg and 200 mg dose levels, respectively. Stomatitis has been included as an adverse reaction in Section 6 of the USPI.

Rash

Data and the Applicant's Position:

In the pooled 300 mg safety analysis set, rash (GT) was reported in 68.2% of patients, with 3.5% experienced grade 3 events, and no grade 4 events were reported. Two (0.6%) patients were reported as SAEs. The median time to the first onset of rash was 12 days. Dose interruption and dose reduction occurred in 3.5% and 2.6% of patients, respectively. Two (0.6%) patients permanently discontinued treatment due to this event. Most events were recovered (63.3%) or recovering (7.4%) by DCO, and the median time to resolution of rash was 57 days.

In summary, the majority of rash reported were grade 1 and 2 in severity, and most events were deemed recovered/recovering. Rash was not considered to bring significant safety and tolerability burden in the proposed patient population, and was unlikely to prevent patients from continuing with sunvozertinib treatment.

The FDA's Assessment:

FDA generally agrees with the Applicant with the exception that the rash group term included dermatitis, dermatitis acneiform, dermatitis bullous, drug eruption, eczema, nodular rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, and skin exfoliation when conducting the analysis for sunvozertinib.

Among the 121 patients in the pooled safety population for the 200 mg dose level, dermatologic adverse reactions occurred in 68% of patients including 9% acneiform dermatitis. Grade 3 dermatologic reactions were rash (7%), acneiform dermatitis (0.8%), and pruritus (0.8%).

Among the 311 patients in the pooled safety population for the 300 mg dose level, dermatologic adverse reactions occurred in 72% of patients including 11% acneiform dermatitis. Grade 3 dermatologic adverse reactions were rash (3.9%), urticaria (0.6%) and pruritus (0.3%).

Based on the observed seriousness and severity of dermatologic adverse reactions, especially for acneiform dermatitis, FDA has included this in the Warnings and Precautions section of the USPI (Section 5.3).

Paronychia

Data and the Applicant's Position:

In the pooled 300 mg safety analysis set, paronychia (PT) occurred in 38.9% of patients, and 1.9% experienced grade 3 event, with no grade 4 or SAEs reported. Paronychia leading to dose interruption and dose reduction were reported in 1.6% and 2.6% of patients, respectively, and no patient permanently discontinued treatment due to this event. The median time to the first onset of paronychia was 61 days. More than half of the events were recovered (54.2%) by DCO, with 9.0% of events recovering. The median time to resolution of paronychia was 56.5 days.

In summary, paronychia is considered to have minimal clinical impact to a patients' continuing treatment with sunvozertinib.

The FDA's Assessment:

In the primary safety population in WU-KONG1B, paronychia including nail infection occurred in 40% and 29% in the 300 mg and 200 mg cohorts, respectively. The incidence of paronychia was higher in the 300 mg dose level compared to the 200 mg dose level. This was also consistent in the pooled safety population with 39% and 34% adverse events occurring in the 300 mg and 200 mg dose levels, respectively. Paronychia has been included as an adverse reaction in Section 6 of the USPI.

ILD/Pneumonitis

Data and the Applicant's Position:

In the pooled 300 mg safety analysis set, ILD/pneumonitis was reported in 5.5% of patients, and 3.5% of patients experienced ≥ grade 3 events. No fatal ILD/pneumonitis was reported. Twelve (3.9%) patients developed SAEs, including 7 cases of ILD and 5 cases of pneumonitis. As per the study protocol, patients with ILD should permanently discontinued treatment, regardless of severity. All patients with ILD and the majority of patients with pneumonitis permanently discontinued treatment. The median time to the first onset of ILD/pneumonitis was 67 days. 29.4% of events were deemed recovered and 29.4% were recovering by DCO. The median duration to recovery was 65 days.

The incidence of ILD/pneumonitis should be considered in the context of underlying disease and previous anti-cancer therapies received by patients. NSCLC and its treatment are factors pre-disposing patients to the occurrence of ILD. The incidence of ILD with EGFR TKIs were within the range from 1.3% to 5.3%. Due to the absence of comparator or placebo arm of the open-label studies, it is not possible to establish sunvozertinib's contribution to the reported incidence of ILD, however, the frequency is in line with epidemiology data in NSCLC patients (Ohmori T, et al., 2021).

In summary, the occurrence of sunvozertinib-related ILD was in low incidence. However, given its severity, continuous effort has been put in pharmacovigilance, surveillance and ongoing review of the trend of ILD occurrence. With extensive experience of handling EGFR TKI related ILD in the clinic, this safety risk is considered manageable.

The proposed label wording for prescribers and patients is similar to that of currently approved EGFR TKIs and the approaches taken in sunvozertinib clinical studies. Special Warnings and Precautions in the prescribing information will help ensure prescribers and patients aware of the potential risk of ILD so that appropriate monitoring and dose modification measures can be implemented.

The FDA's Assessment:

In in the WU-KONG1B clinical trial, ILD/pneumonitis was reported in 4.5% and 3.6% Grade 3 or 4 in the 300 mg and 0% in the 200 mg cohort. ILD/pneumonitis led to dose interruption or reduction in one patient (0.9%) and permanent discontinuation in 3.6% of patients.

Among the 311 patients in the pooled safety population for the 300 mg dose level, ILD/pneumonitis was observed in 5% and 3.5% Grade 3 or 4. ILD/pneumonitis led to dose interruption in two patients (0.6%) and permanent discontinuation in 4.5% of patients.

Among the 121 patients in the pooled safety population for the 200 mg dose level, ILD/pneumonitis was observed in 1.7%; there were no Grade $\geq$3 events of ILD/pneumonitis. Given the seriousness and severity of ILD/pneumonitis with sunvozertinib, FDA has included this as a Warnings and Precautions section in the USPI (Section 5.1) for sunvozertinib.

QT prolongation

Data and the Applicant's Position:

Considering the potential risk and prior experience with EGFR TKIs, QT prolongation was included in this analysis with the PT of Electrocardiogram QT prolonged.

In the pooled 300 mg safety analysis set, QT prolongation was reported in 5.8% of patients, with grade 3 events being reported in 3 (1.0%) patients. No grade 4 or higher event was reported, and one (0.3%) patient reported an SAE. QT prolongation led to dose interruption and dose reduction in 1.3% and 0.3% of patients, respectively. No patient permanently discontinued treatment due to this event. The median time to the first onset of QT prolongation was 18.5 days. The majority of events were recovered (84.8%) or recovering (6.1%), and the median time to resolution was 23 days.

C-QTc analysis showed no clinically relevant effects on the QTc interval at the to-be-market dosage of sunvozertinib.

In summary, the risk of QT prolongation with sunvozertinib treatment at the intended marketing dosage is considered low, with no evidence showing that this is associated with an increased risk of cardiac arrhythmia or Torsades de Pointes (TdP). Most events were manageable, and unlikely to prevent patients from continuing with sunvozertinib treatment.

The FDA's Assessment:

FDA evaluated arrhythmia as a potential safety signal for sunvozertinib. FDA used the following preferred terms for the arrhythmia grouped term: atrial fibrillation, atrioventricular block first

degree, bundle branch block right, defect conduction intraventricular, electrocardiogram PR prolongation, electrocardiogram QT prolonged, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, and ventricular extrasystoles to evaluate arrhythmia, including QT prolongation.

For the safety population in WU-KONG1B, arrhythmia occurred in 14% and 12% in the 300 mg and 200 mg cohorts. This was also consistent in the pooled safety population for arrhythmia with 16% and 11% adverse events occurring in the 300 mg and 200 mg dose levels, respectively. Arrhythmia has been included as an adverse reaction in Section 6 of the USPI.

Blood CPK increased

Data and the Applicant's Position:

In the pooled 300 mg safety analysis set, blood CPK increased (GT) was reported in 49.2% of patients, including 12.5% and 4.5% of patients with grade 3 or grade 4 events, respectively. Most events were asymptomatic and identified by laboratory examinations. SAEs were reported in 0.6% of patients. Dose interruption and reduction due to this event occurred in 10.0% and 8.0% of patients, respectively, and one (0.3%) patient permanently discontinued treatment due to this event. No rhabdomyolysis was reported. The median time to the first onset of blood CPK increased was 36 days. Most events were recovered (80.6%) or recovering (6.1%) by DCO. The median time to resolution was 29 days.

In summary, blood CPK increased was reported frequently following sunvozertinib treatment at the to-be-marketed dosage, while the majority of events were grade 1 or 2, asymptomatic, could be managed through dose modification or supportive treatment, and generally did not lead to treatment discontinuation. Blood CPK increased is not considered bringing significant safety and tolerability burden in the proposed population, and unlikely to prevent patients from continuing with sunvozertinib treatment.

The FDA's Assessment:

FDA evaluated increased creatine phosphokinase or creatine kinase that worsened from baseline in patients who received sunvozertinib in WU-KONG1B. For the safety population in the WU-KONG1B clinical trial, increased CPK occurred in 81% and 57% in the 300 mg and 200 mg cohorts, respectively and Grade 3 to 4 events occurred in 16% and 8% in the 300 mg and 200 mg cohorts, respectively. This was also consistent in the pooled safety population for increased CPK with 75% and 55% laboratory abnormalities occurring in the 300 mg and 200 mg dose levels, respectively and Grade 3 to 4 events occurring in 19% and 6% in the 300 mg and 200 mg cohorts, respectively.

Keratitis

Data and the Applicant's Position:

The keratitis was listed in "Warnings and Precautions" of drug label of other approved EGFR TKIs. Corneal epithelial atrophy was also noted in nonclinical toxicity studies of sunvozertinib. During

the ADR analysis, keratitis was grouped with corneal epithelium defect, corneal edema, injury corneal, keratitis, and ulcerative keratitis for analysis. In the 300 mg pooled safety analysis set, 3 (1.0%) patients reported keratitis (GT) related events, including one grade 1 injury corneal, one grade 1 keratitis, and one grade 3 ulcerative keratitis.

Given that the event of keratitis may impact patients' quality of life, the applicant has proactively included this information in the Warnings and Precautions of the prescribing information for prescribers and patients.

The FDA's Assessment:

Ophthalmologic examinations including visual acuity, pupils, intraocular pressure, external examination, slit-lamp, and fundoscopic examination (pupil dilation is not required) and others if clinically indicated were required at screening; and study discontinuation. In the WU-KONG1B clinical trial, ocular toxicity occurred in 19% and 18% in the 300 mg and 200 mg cohorts, respectively. Ocular toxicity led to dose interruption or dose reduction in one patient (0.9%) in each cohort.

Keratitis occurred in a total of four patients (1% and 0.8% in the 300 mg and 200 mg pooled safety population, respectively). Given the seriousness of ocular toxicity, especially keratitis, FDA has included a Warnings and Precautions section (Section 5.4) of the USPI for sunvozertinib.

8.2.8 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data and the Applicant's Position:

[*Source*: Module 2.7.4/Section 2.11**]**

The PRO-CTCAE and FACT-Item GP5 were added to WU-KONG1 study since protocol Version 6.0. The results were exploratory, descriptive, and supplementary to the reported TEAE results in (b) (4)

Approximately 60% of patients provided pre- and post-treatment PRO-CTCAE data. Numerically, a lower percentage of patients at 300 mg reported worsening of fatigue from baseline, compared to that of 200 mg, consistent with the lower percentage of patients with TEAEs of fatigue at 300 mg than that of 200 mg. For other parameters, the percentage of patients reported worsening of symptoms from baseline were either comparable between the two dose cohorts, or numerically lower in 200 mg.

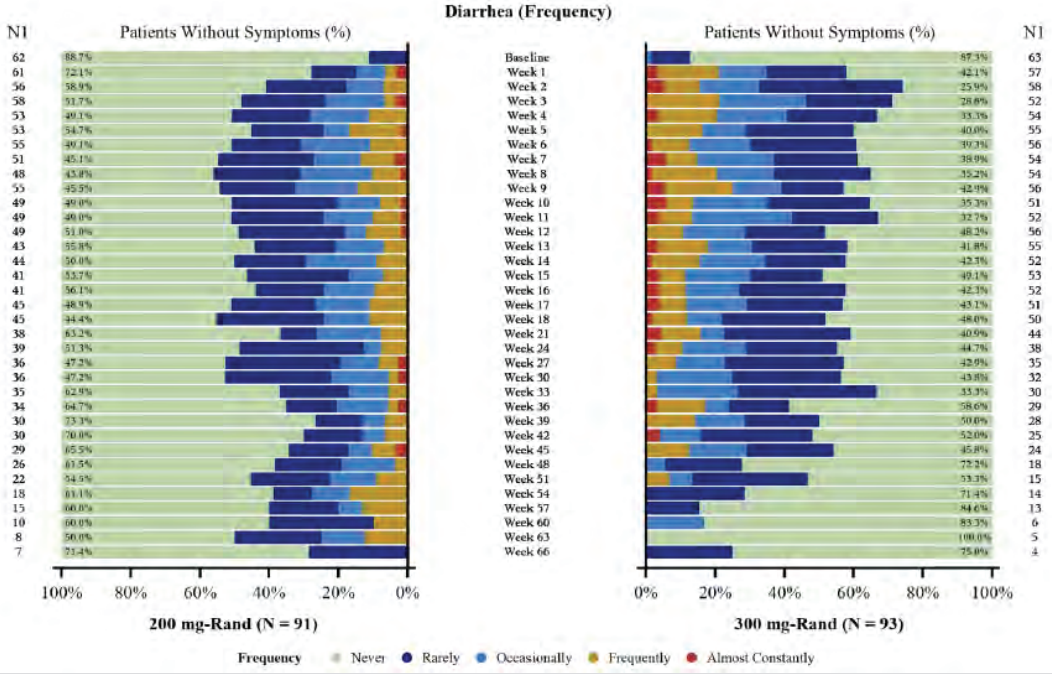
For FACT-Item GP5, a relatively higher number of patients at 300 mg had symptoms before treatment, compared to that of 200 mg. After sunvozertinib treatment, the overall percentage of patients with worsening of symptoms were lower at 300 mg than that of 200 mg, while the percentage of patients reported worsening to score 3 or 4 was slightly higher at 300 mg than that of 200 mg.

The FDA's Assessment:

The Applicant collected PRO-CTCAE symptoms weekly for the first 18 weeks, then every three weeks for symptoms (abdominal pain, acne, bloating, blurred vision, constipation, cracking at the corners of the mouth, decreased appetite, diarrhea, fatigue, itching, mouth/throat sores, nail discoloration, nail loss, nail ridging, nausea, nosebleed, rash, skin dryness, and vomiting). In general, the data quality was reasonable to allow for descriptive interpretation of tolerability results. The observed frequency/severity/presence of the assessed symptoms was similar or better in the 200 mg arm. For brevity, longitudinal graphical displays of selected symptoms diarrhea, rash and stomatitis are presented below.

Below is the stacked barchart showing the proportion of patients who had diarrhea (frequency) at each assessment timepoint at 200 mg and 300 mg.

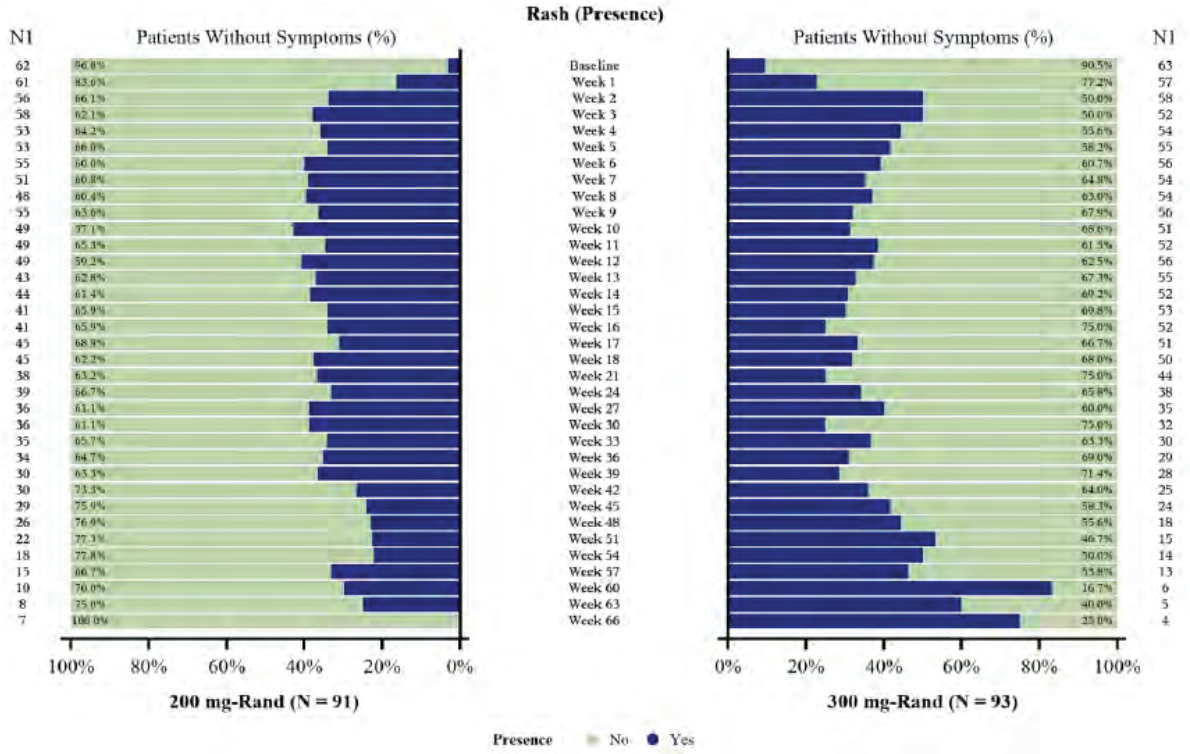
Figure 14.3.6.1.2.2
Butterfly Chart of PRO-CTCAE Data by Visit
Randomized Patients in Safety Analysis Set



Source: Applicant CSR, Figure 14.3.6.1.2.2

Below is the stacked barchart showing the proportion of patients who had rash (presence) at each assessment timepoint at 200 mg and 300 mg.

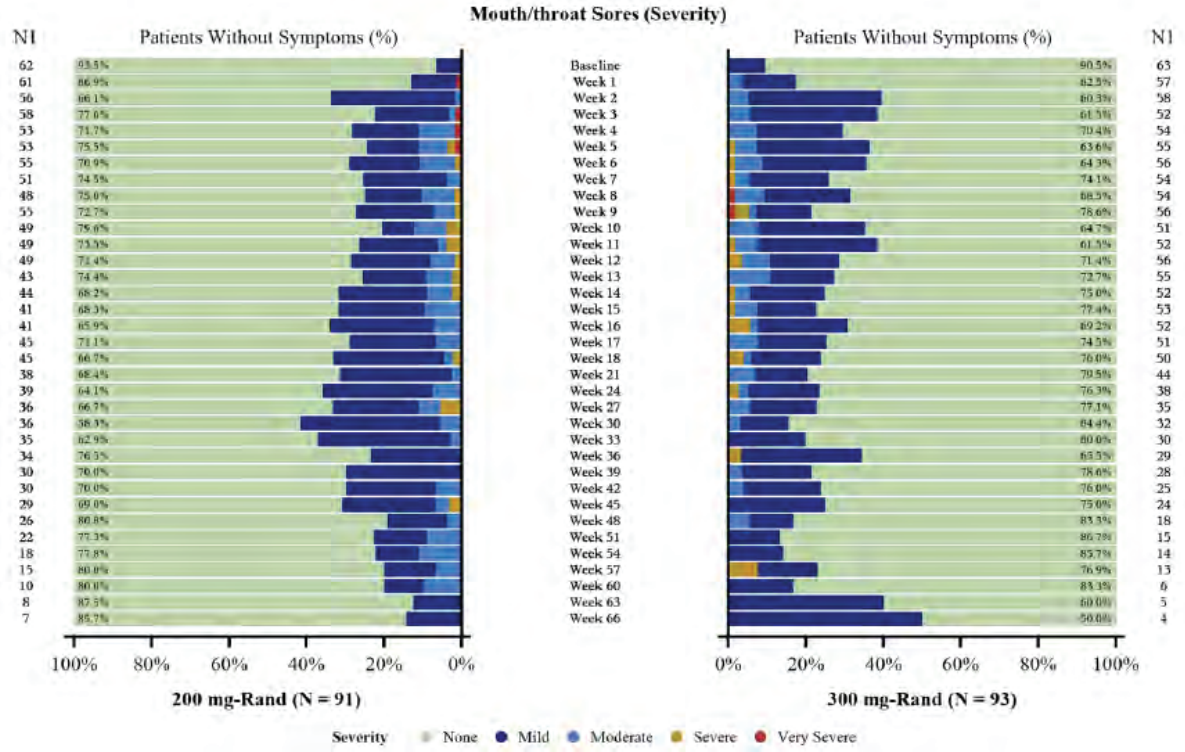
Figure 14.3.6.1.2.2
Butterfly Chart of PRO-CTCAE Data by Visit
Randomized Patients in Safety Analysis Set



Source: Applicant CSR, Figure 14.3.6.1.2.2

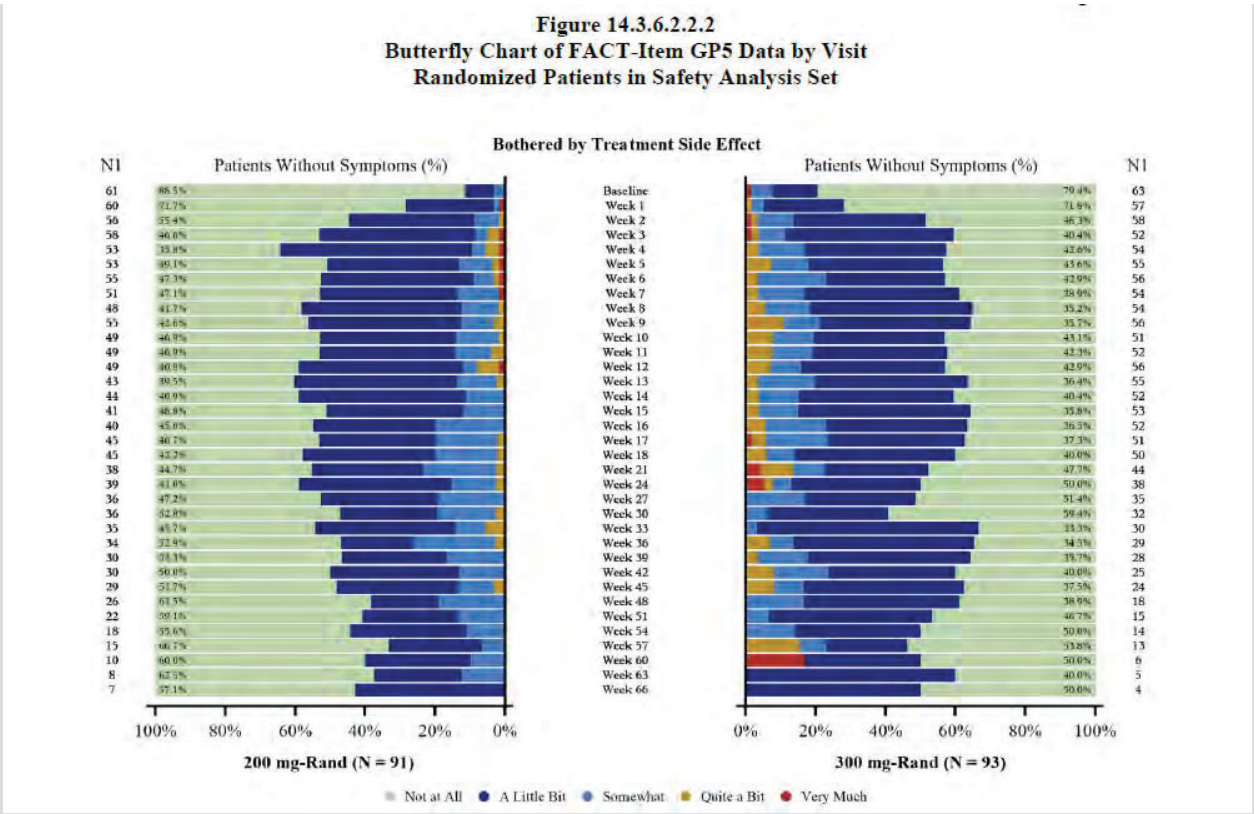
Below is the stacked barchart showing the proportion of patients who had mouth sores (severity) at each assessment timepoint at 200 mg and 300 mg.

Figure 14.3.6.1.2.2
Butterfly Chart of PRO-CTCAE Data by Visit
Randomized Patients in Safety Analysis Set



Source: Applicant CSR, Figure 14.3.6.1.2.2

The Applicant collected FACT-GP5 weekly for the first 18 weeks, then every three weeks. Below is the stacked barchart showing the proportion of patients who had side effect bother at each timepoint at 200 mg and 300 mg.



Source: Applicant CSR, Figure 14.3.6.2.2.2

There was a similar or higher proportion of patients who had any bother and severe bother in the 300 mg cohort at most timepoints, however more patients in the 300 mg cohort had side effect bother at baseline.

Overall, the PRO tolerability data supports the clinician reported safety data and the relative tolerability of the 200 mg dose.

8.2.9 Safety Analyses by Demographic Subgroups

The Applicant's Position:

Data:

[*Source*: Module 2.7.4/Section 5]

For the pooled 300 mg (N=311) and primary safety analysis sets (N=111), safety profiles among subgroups defined by intrinsic factors of age (<65 vs ≥ 65 to < 75 vs ≥ 75), sex (male vs female), race (non-Asian vs. Asian), and ECOG performance status (0, ≥1) were analyzed. The analysis was based on AE category and the most common (≥ 20%) TEAEs.

Age:

The overall tolerability profile was generally consistent for patients aged < 65 years and those ≥ 65 years, with the possible exception of a lower frequency of diarrhea, as well as higher frequency of blood CPK increased and paronychia in younger patients than that of older patients.

Sex:

The overall safety profiles were comparable between male and female patients, with the possible exception of higher incidence of nausea/vomiting, and lower incidence of decreased appetite and weight decreased in female than male patients.

Race:

The overall safety profiles were comparable between non-Asian and Asian patients, with the possible exception of higher incidence of vomiting as well as lower incidence of blood CPK increased, rash, anemia and weight decreased in non-Asian patients than that of Asian patients.

ECOG performance status:

The overall safety profiles were generally comparable between patients with ECOG performance score 0 and ≥ 1, with the possible exception of higher incidence of anemia and vomiting, as well as lower incidence of blood CPK increased and creatinine increased in patients with ECOG performance score ≥ 1 than those with score of 0.

Renal function:

Per the study protocol, patients with serum creatinine ≥ 1.5 × ULN and creatinine clearance ≤ 50 mL/min were excluded. Subgroup analysis was not performed for patients with different renal function. No apparently clinically meaningful difference in sunvozertinib PK was noted between patients with mild or moderate renal impairment (CLcr 30 to 89 mL/min) and patients with normal renal function based on the population PK analysis.

Hepatic function:

The clinical studies included in the integrated safety analysis excluded patients with ALT and AST ≤ 2.5 × ULN if no liver involvement or ≤ 5 × ULN with liver involvement, or patients with total bilirubin ≤ 1.5 × ULN if no liver metastases or ≤ 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases., and thus no subgroup analysis was conducted to evaluate the effect of hepatic function.

No apparently clinically meaningful difference in sunvozertinib PK was noted between patients with mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin >1 to 1.5 × ULN with any AST) and patients with normal hepatic function based on the population PK analysis.

A dedicated hepatic impairment study (WU-KONG27) revealed that no clinically meaningful difference was noticed between participants with moderate hepatic impairment and normal hepatic function per Child-Pugh and NCI-ODWG criteria. The effect of severe hepatic impairment on sunvozertinib PK is unknown.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.10 Specific Safety Studies/Clinical Trials

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.11 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

Data and the Applicant's Position:

As of July 29, 2024, no case of pregnancy was reported in any of the safety population and no lactating women were exposed to the study drug.

There is no clinical data regarding the potential effect of sunvozertinib on pregnancy or development of the embryo or fetus. There is no experience with the drug having been administered to pregnant or lactating women.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

Data and the Applicant's Position:

Sunvozertinib has not been evaluated in patients < 18 years old.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data and the Applicant's Position:

[*Source*: Module 2.7.4/Section 5.5]

Overdose

Per the study protocol, overdose of sunvozertinib was defined as any dose above the planned dose level.

The highest dose of sunvozertinib explored in clinical studies was 400 mg QD, which was also the MTD. In the overall safety analysis set, a total of 9 patients were exposed to sunvozertinib at dose level of 400 mg QD or above, no AEs associated with overdose were reported.

Drug Abuse

Based on its pharmacological properties, intended use and mode of action, sunvozertinib is unlikely to have a potential for drug abuse and no clinical findings indicated that sunvozertinib induced drug abuse.

Withdrawal and Rebound

There were reports about disease flare upon withdrawal of EGFR TKIs, such as erlotinib and gefitinib, etc., which has resulted in recommendations to minimize washout period or continue EGFR TKI treatment as long as possible beyond progression.

The pharmacokinetic half-life of sunvozertinib was ~50 hours, and thus it is postulated that there could be a low risk of development of disease flare within a short washout period.

The FDA's Assessment:

Sunvozertinib is unlikely to be abused, has no known potential for dependence, withdrawal, or rebound events.

8.2.12 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data and the Applicant's Position:

[*Source*: Module 2.7.4/Section 6]

Sunvozertinib was granted conditionally approval by China National Medical Products Administration (NMPA) on August 22, 2023. As of August 21, 2024, sunvozertinib was provided to approximately (b) (4) patient-year.

The available data have been analyzed to provide a critical analysis of the benefit-risk profile of sunvozertinib in the context of new information that emerged during the relevant reporting period (August 22, 2023 to August 21, 2024).

During the reporting period, no new safety concern was identified. The benefits and risks (safety experience) with sunvozertinib treatment have been assessed in both clinical studies and post-marketing experience. The overall assessment indicated a positive benefit-risk profile of sunvozertinib. The applicant considers that benefit-risk profile for sunvozertinib in the current approved indication remains favorable.

The FDA's Assessment:

Sunvozertinib 300 mg QD was granted conditional approval in China. The Applicant has identified ILD/pneumonitis as an identified risk with sunvozertinib. Other potential risks also include diarrhea, increased CPK, and keratitis.

Expectations on Safety in the Postmarket Setting

The Applicant's Position

Sunvozertinib has a safety profile that is similar to that of the already approved EGFR TKIs, which offers a convenient route of use, and improvement of certain safety concerns when compared to immunotherapies or chemotherapies. The TEAEs are tolerable and clinically manageable. The efficacy and safety results demonstrated that sunvozertinib has a favorable benefit-risk profile for patients with prior platinum treated NSCLC with EGFR exon20ins.

(b) (4)

The risks associated with sunvozertinib treatment discussed in this document have been characterized and are proposed in the drug label. Routine pharmacovigilance will be conducted to monitor and continue to update the safety profile of sunvozertinib.

The FDA's Assessment:

(b) (4)

Refer to the Section 8.2.13 Integrated Assessment of Safety on FDA's assessment regarding a recommended dose of sunvozertinib 200 mg QD.

The safety profile of sunvozertinib 200 mg QD in the postmarket setting is expected to be similar to that observed in the clinical trials reviewed in this application.

8.2.13 Integrated Assessment of Safety

Data and the Applicant's Position

[*Source*: Module 2.7.4]

Safety data presented in this NDA package were derived from clinical studies of sunvozertinib monotherapy in patients with NSCLC, including WU-KONG1, WU-KONG2 and WU-KONG6.

Based on the safety data from 311 and 111 patients included in the pooled 300 mg and primary safety analysis sets (all patients were dosed at 300 mg QD, (b) (4)), and supportive information from a total of 467 patients (across 50 mg to 400 mg QD) in the overall safety analysis set, the applicant considers that the safety profile of sunvozertinib has been well characterized.

The safety profile of sunvozertinib is expected for an EGFR TKI in advanced NSCLC patient population. The most frequently reported TEAEs were those anticipated with wild-type EGFR inhibition. The proposed USPI provides the guidance to physicians regarding identification and management of safety related risks associated with sunvozertinib treatment, which are consistent with those approved EGFR TKIs, and are familiar to healthcare providers in the clinic who treat NSCLC.

The FDA's Assessment:

FDA generally agrees with the Applicant that the overall safety profile of sunvozertinib can be appropriately managed by prescribing oncologists, with routine medical standards of practice (e.g., patient monitoring, dose delay, reduction, interruption, dose discontinuation, and/or supportive care. and that labeling is sufficient to address the safety concerns associated with the use of sunvozertinib.

FDA identified interstitial lung disease (ILD)/pneumonitis, gastrointestinal adverse reactions, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity for inclusion in Section 5 of the proposed USPI. FDA considers the agreed-upon product labelling adequate to address safety concerns associated with the use of sunvozertinib.

SUMMARY AND CONCLUSIONS

8.3 Statistical Issues

The FDA's Assessment:

The efficacy evaluation of this application focused on data and results from WU-KONG1B, an open-label, randomized dose extension study evaluating patients with NSCLC with EGFR exon20 insertion mutations at two doses. The primary endpoint is confirmed ORR assessed by IRC per RECIST v1.1, supported by the key secondary endpoint of DoR. Though patients were randomized to different doses, efficacy analyses were conducted within the individual dose cohorts in a manner consistent with a single-arm trial, therefore there was no control for multiplicity in any of the hypothesis tests included in this report. As such, the p-values reported by the Applicant should be interpreted with caution.

The Applicant also provided results from WU-KONG1A, a multinational phase 1 study, WU-KONG2, a China-only phase 1 study, and WU-KONG 6, a China-only phase 2 study. FDA reviewed the results reported by the Applicant as supportive to the application.

While the Applicant used 97.5% CIs for confirmed ORR, FDA considered results of ORR with a 95% CI. The confirmed ORR with 95% CI based on the exact Clopper Pearson method for the 200 mg cohort is 46% (95% CI: 35, 57) and that for the 300 mg-All cohort is 46% (95% CI: 36, 56). Median estimates of DoR per Kaplan-Meier methods were not met in either cohort at the initial data cut-off, and were 11.1 (8.2, NE) months and 9.8 (8.3, 13.9) months at the time of 120-day safety update. Durability of response was observed, with 72% of responders in the 200 mg cohort and 65% of responders in the 300 mg cohort experiencing response of at least 6 months. PFS by IRC was evaluated using this same safety data cutoff only among patients concurrently randomized to 200 mg and 300 mg doses, and the medians were 8.4 (95% CI: 6.8, 13.9) months and 7.7 (95% CI: 6.0, 9.8) months, respectively.

In summary, the primary efficacy data of confirmed ORR and DoR from the WU-KONG1B study demonstrate clinical meaningful durable anti-tumor activity of sunvozertinib in patients with previously treated, locally advanced or metastatic NSCLC harboring EGFR exon20

insertion mutations. A similar benefit in terms of efficacy (i.e., ORR) was observed for the two doses.

8.4 Conclusions and Recommendations

The FDA's Assessment:

WU-KONG1B is a multiregional, open-label, dose randomization clinical trial in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations with disease progression on or after platinum-based chemotherapy. Patients with measurable disease at baseline were randomized (1:1) to receive either sunvozertinib 200 mg QD (N=85) or 300 mg QD (N=89). An additional 18 patients were not randomized and received sunvozertinib 300 mg QD (N=107 total patients received sunvozertinib 300 mg QD). All patients had received prior platinum-based chemotherapy, 42% had received prior anti-PD-(L)1 therapy, and 14% had received prior amivantamab. The primary efficacy outcome measure was ORR as assessed by BIRC according to RECIST v1.1. In the sunvozertinib 200 mg QD cohort (n=85), ORR was 46% (95% CI: 35, 57) and the median duration of response (DOR) was 11.1 months (95% CI: 8.2, NE). For the sunvozertinib 300 mg QD cohort (n=107), the ORR was 46% (95% CI: 36, 56) and the median DOR was 9.8 months (95% CI: 8,14). In an exploratory subgroup analysis of patients who received prior amivantamab and platinum-based chemotherapy, the ORR was 25% (95% CI: 5, 57) in the 12 patients who received sunvozertinib 200 mg and 36% (95% CI: 13, 65) in the 14 patients who received sunvozertinib 300 mg.

Sunvozertinib has a manageable safety profile when assessed in the context of a life-threatening disease. The primary safety population consisted of the 91 patients in the 200 mg QD cohort and the 111 patients in the sunvozertinib 300 mg QD cohort in WU-KONG1B who received at least one dose of study therapy. Pooled safety data from patients with locally advanced or metastatic NSCLC who received at least one dose of study therapy, which included the patients in the primary safety population, were supportive and consisted of 121 patients who received sunvozertinib 200 mg QD in WU-KONG1 and WU-KONG2, and 311 patients who received sunvozertinib 300 mg QD in WU-KONG1, WU-KONG2, and WU-KONG6.

In the primary safety population from the WU-KONG1B dose-randomization trial (n=91 at 200 mg and n=111 at 300 mg), a higher rate of adverse reactions was observed at the 300 mg dose compared to the 200 mg dose. Compared to the 200 mg QD dosage, the 300 mg QD dosage had more events of Grade ≥3 diarrhea (2.2% vs 21%) and elevated CPK levels (5% vs 15%). Compared to the 200 mg dose, the 300 mg dose also had higher rates of adverse reactions leading to dose interruptions (48% vs 59%), dose reductions (23% vs 42%), and permanent discontinuation of sunvozertinib (8% vs 13%). In the pooled safety populations (n=121 at 200 mg and n=311 at 300 mg), ILD/pneumonitis occurred in 1.7% with 0% Grade ≥3 events for the 200 mg group and 5.5% with 1.3% Grade 3 and 2.3% Grade 4 events for the 300 mg group.

Sunvozertinib has an acceptable safety profile for the intended population of patients with a life-threatening disease and few alternative treatments, including no other option for orally administered therapy. The serious adverse reactions include ILD/pneumonitis, gastrointestinal adverse reactions, dermatologic adverse reactions, and ocular toxicity.

The benefit-risk profile in the indicated population is considered favorable based on the observed response rate and durable responses in a patient population with a life-threatening disease and an unmet medical need. This application represents a new treatment option for an indication with unmet medical need. The Applicant used advice from the FDA Oncology Center of Excellence's Project Optimus to conduct a dose randomization study, which led to a lower dose being approved. Due to comparable efficacy results and reduced toxicity observed with the 200 mg dose compared to the 300 mg dose, the FDA review team recommends a treatment dose of sunvozertinib 200 mg orally daily.

Given the size of the efficacy population and the single-arm data of WU-KONG1B, we recommend accelerated approval of this application. Based on a favorable benefit-risk assessment, the FDA recommends accelerated approval for sunvozertinib 200 mg QD for the following indication:

"For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy."

The Applicant is conducting an ongoing multiregional, randomized clinical trial of sunvozertinib versus platinum-based chemotherapy to verify the clinical benefit of sunvozertinib in patients with locally advanced or metastatic NSCLC whose tumors harbor an EGFR exon 20 insertion mutation. The dual primary endpoints of the trial are PFS and OS.

8.4.1 Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication *(enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response)*:

   ZEGFROVY is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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

Flora Mulkey, Statistical Team Leader

X

Katie Chon, Primary Clinical Reviewer

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

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

10. Pediatrics

The Applicant's Position:

On February 14, 2024, the Applicant reached an agreement with FDA for the plan of full waiver of pediatric studies in all age subsets, as described in the Agreed Initial Pediatric Study Plan in Module 1.6.3.

The FDA's Assessment:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Sunvozertinib received a full waiver of pediatric studies for the treatment of NSCLC and advanced solid tumors that harbor an EGFR/HER2 mutation across all pediatric age groups. The agreed initial pediatric study plan (iPSP) was included in the original NDA submission per 505B(a)(3)(A)(ii)(II) of the FD&C Act.

11. Labeling Recommendations

The Applicant's Position:

This is an original application. Please see the proposed USPI in Module 1.14.1.3.

The FDA's Assessment:

Key Labeling Changes

The proposed labeling submitted by the Applicant required extensive revision by FDA. The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 CFR, labeling guidances and current labeling practices of the Office of Oncologic Diseases.

The following table below summarizes key changes.

FDA Table 73: Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI

(b) (4)

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The FDA review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of sunvozertinib for the indicated population. Recommendations for the safe and effective use of sunvozertinib are made in labeling and FDA-approved patient labeling. There are no additional risk management strategies required beyond the recommended labeling.

13. Postmarketing Requrements and Commitment

The FDA's Assessment:

The following postmarketing requirement will be included in the action letter:

Postmarketing Requirement 1:

Conduct a multicenter, randomized clinical trial intended to verify and describe the clinical benefit of sunvozertinib in patients with locally advanced, unresectable or metastatic non-small cell lung cancer whose tumors have EGFR exon 20 insertion mutations. The final analysis should include the final progression-free survival and overall survival results. This data may be obtained from the ongoing clinical trial, entitled, DZ2022E0005 (WU-KONG28), "A Phase 3, Open-Label, Randomized, Multi-Center Study of DZD9008 versus Platinum-Based Doublet Chemotherapy as First-Line Treatment for Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor Exon 20 Insertion Mutation."

Trial Completion:	01/2026
Final Report Submission:	07/2026

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

	The following were evaluated and considered as part of FDA's review:	Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes **X** No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes **X** No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes **X** No

The majority of patients in the primary efficacy and safety populations for sunvozertinib are Asian or White and non-Hispanic/non-Latino, and the racial and ethnic demographics are not representative of the racial and ethnic diversity 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 diversity at the time of this approval.

14. Division Director (DHOT) (NAME ONLY)

X

Tiffany Ricks

15. Division Director (OCP)

X

Atiqur Rahman

16. Division Director (OB)

X

Shenghui Tang

17. Division Director (Clinical)

X

Paz Vellanki, MD, PhD

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

Angelo de Claro, MD

19. Appendices

19.1 References

The Applicant's References:

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19.2 Financial Disclosure

The Applicant's Position:

As noted in Section 8.1.2, the Applicant has adequately assessed clinical investigators for any financial interest/arrangements as defined in 21 CFR Part 54 and no disclosable financial interests were found.

Covered Clinical Study (Name and/or Number): * DZ2019E0001 Part B (WU-KONG1B)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 937		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: Dizal (Jiangsu) Pharmaceutical Co., Ltd.		
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	Yes ☒	No ☐ (Request information from

potential bias provided:		Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: NA	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.

19.3 Nonclinical Pharmacology/Toxicology

Data

All data presented in Section 5 Nonclinical Pharmacology/Toxicology.

The Applicant's Position:

Not applicable.

The FDA's Assessment: Not Applicable

19.4 OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1 Population PK Analysis

19.4.1.1 Executive Summary

The FDA's Assessment:

- The population PK (PopPK) model adequately described the PK data of sunvozertinib (DZD9008) and its metabolite DZ0753 in both healthy volunteers and patients with a NSCLC. The PK of sunvozertinib was characterized by a two-compartment model with absorption characterized by 2 transit-compartments. DZ0753 disposition was also characterized by a two-compartment model.
- No clinically meaningful differences in sunvozertinib PK were observed based on correlations between individual predicted exposure and factors such as age, sex, race, smoking status, formulation, food status, PPI use, concomitant use of CYP3A4 inhibitors and inducers, renal function or hepatic function. As such, no dose adjustments are warranted based on these baseline covariates in NSCLC patients.
- Differences between healthy volunteers and patients, as well as body weight, were identified as significant covariates affecting the apparent clearance and central volume of distribution for both sunvozertinib and DZ0753. However, the impact of body weight on exposure was less than the overall variability observed in NSCLC patients. As such, no dose adjustment for sunvozertinib is necessary based on body weight in this patient population.

19.4.1.2 PPK Assessment Summary

The Applicant's Position:

[*Source*: Module 2.7.2/Section 2.4]

The sunvozertinib PK was adequately described by a two-compartment model with 2 transit-compartments to describe the oral absorption. The formation of DZ0753 was dependent on sunvozertinib metabolism with fraction of metabolism assumed to be 38.8%. A pre-systemic bio-transformation was implemented as a first-order conversion rate parameter describing mass transfer and metabolism of sunvozertinib to DZ0753 from the second transit compartment to the central compartment of the metabolite. The PK of metabolite DZ0753 was described by a two-compartment model. Patient status (Healthy or Patient) and body weight were identified as significant covariates on the CL/F and Vc/F of both sunvozertinib and DZ0753.

General Information			
Objectives of PPK Analysis		• To characterize the PK of sunvozertinib and its active metabolite, DZ0753 and to quantify sources of variability • Predict individual exposure of sunvozertinib and DZ0753 for E-R assessment	
Study Included		WU-KONG1A (only DZD9008), WU-KONG1B, WU-KONG2 (only DZD9008), WU-KONG6, WU-KONG7, and WU-KONG12	
Dose(s) Included		50 mg, 100 mg, 200 mg, 300 mg, 400 mg	
Population Included		Healthy and NSCLC patients	
Population Characteristics (Table 74 and Table 75)	General	Age median (range): 58 (19 – 96) years Weight median (range): 65.7 (30 – 118) kg Sex: Female: 310 (54.3%); Male: 261 (45.7%) Race: White: 158 (27.7%); Asian: 355 (62.2%); Black: 45 (7.9%); Other: 10 (1.8%); Missing: 2 (0.4%); American Indian/Alaskan naïve: 1 (0.2%)	
	Organ Impairment	Hepatic (NCI): Normal: 511 (89.5%); Mild: 60 (10.5%) Renal (CLcr): Normal: 287 (50.3%); Mild 193 (33.8%); Moderate 90 (15.8%); missing 1 (0.2%)	
	Pediatrics (if any)	Not included	
No. of Patients, PK Samples, and BLQ		16907 PK samples from 575 study participants 958 Pre-dose BLQs, 555 post-dose BLQs Population PK model evaluated 13743 PK samples from 571 study participants after exclusion and applying M6 method.	
Sampling Schedule	Rich Sampling	Check PopPK report (Module 5.3.3.5/PopPK Report) for details	
	In ITT Population	Check PopPK report (Module 5.3.3.5/PopPK Report) for details	
Covariates Evaluated	Static	age, body weight, BMI, BSA, race, sex, disease status (cancer patient vs. healthy volunteer), smoking status, and laboratory values (ALP, ALT, AST, bilirubin), hepatic impairment, CLcr, eGFR, renal impairment	
	Time-varying	formulation, fed state, cytochrome P450 (CYP)3A4 modulators (inducers and inhibitors), use of PPI/antacids	
Final Model		**Summary**	**Acceptability [FDA's comments]**
Software and Version		NONMEM (Version 7.5.1)	Acceptable

	R (Version 4.2.3) PsN (Version 5.3.1)	
Model Structure	The sunvozertinib PK was found to be adequately described by a two-compartment model with 2 transit-compartments to describe the oral absorption. The formation of DZ0753 was dependent on sunvozertinib metabolism with fraction of metabolism assumed to be 38.8%. A pre-systemic bio-transformation was implemented as a first-order conversion rate parameter describing mass transfer and metabolism of sunvozertinib to DZ0753 from the second transit compartment to the central compartment of the metabolite. The PK of metabolite DZ0753 was described by a two-compartment model.	Acceptable
Model Parameter Estimates	Table 76	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All typical PK parameters and residual error variances of the final model could be estimated with relative standard errors (RSE) of 10.9% or less, and covariate effects and (co)variances related to interindividual variability were estimated with RSE < 25%. Shrinkage of both interindividual and intraindividual random effects was low (16.8% or lower for IIV, 5-6% on RUV).	Acceptable
BLQ for Parameter Accuracy	M6 Method Used.	
GOF, VPC	Goodness of fit plots based on population and individual model predictions, residual-based diagnostics, evaluation of random effect distributions based on histograms, evaluation of correlation between random effects and covariates. The final model showed no meaningful bias in goodness-of-fit plots and residual-based diagnostics and was able to adequately describe central tendency and variability of the observed data as confirmed by VPC. Figure 12, Figure 13 and Figure 14	Acceptable
Significant Covariates and Clinical Relevance	Differences between healthy participants and patients as well as for differences in body weight were observed and quantified as effects on the CL/F and Vc/F of sunvozertinib and DZ0753. Based on the estimated effect of baseline body weight in the final population PK model, relative exposure predicted at the 5th and 95th percentile of the body weight distribution in the analysis population fell outside the 80-125% range of no clinically meaningful effect. Similarly, a linear model describing the correlation between individual predicted exposures and body weight in NSCLC patients suggested a relative exposure	Acceptable

	outside the 80-125% range at the 5th and 95th body weight percentile in NSCLC patients, however, the variability related to body weight was less than the overall variability in individual predicted exposures in NSCLC patients. Finally, individual relative exposures within body weight quartiles showed considerable overlap between body weight quartiles as the overall variability in exposure. Taken together, these findings warranted no dose adjustments for sunvozertinib based on body weight in NSCLC patients. Figure 15	
Analysis Based on Simulation (optional)	Not Applicable	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	(b) (4)	As the recommended dosage for this regulatory approval is 200 mg, the steady-state Cmax and AUC of sunvozertinib was updated accordingly: *The steady-state Cmax and AUC of sunvozertinib are 412 (45%) ng/mL and 8,060 (42%) h*ng/mL, respectively.*

Table 74: Summary of Continuous Baseline Characteristics and Laboratory Values in the Population PK Dataset, Stratified by Study

	WK1A (N=112)	WK1B (N=202)	WK2 (N=48)	WK6 (N=101)	WK7 (N=40)	WK12 (N=68)	Overall (N=571)
Body weight (Kg)							
Mean (SD)	67.3 (15.6)	65.1 (14.6)	64.3 (13.7)	64.1 (11.7)	75.4 (12.8)	76.3 (11.8)	67.3 (14.4)
Median [Min, Max]	65.0 [39.0, 115]	64.0 [33.0, 118]	64.0 [30.0, 103]	64.5 [38.0, 91.0]	75.8 [53.3, 104]	77.1 [53.0, 105]	65.7 [30.0, 118]
BMI (Kg/m^2)							
Mean (SD)	25.1 (4.51)	24.4 (4.45)	23.7 (3.73)	24.1 (3.42)	25.2 (2.62)	25.7 (2.86)	24.7 (3.99)
Median [Min, Max]	24.6 [15.8, 40.3]	24.0 [13.9, 39.4]	23.3 [15.3, 32.1]	24.0 [17.2, 32.5]	25.5 [20.5, 29.3]	26.2 [19.9, 29.9]	24.4 [13.9, 40.3]
BSA (m^2)							
Mean (SD)	1.72 (0.217)	1.69 (0.202)	1.71 (0.211)	1.69 (0.182)	1.89 (0.212)	1.89 (0.187)	1.74 (0.214)

	WK1A (N=112)	WK1B (N=202)	WK2 (N=48)	WK6 (N=101)	WK7 (N=40)	WK12 (N=68)	Overall (N=571)
Median [Min, Max]	1.73 [1.28, 2.27]	1.68 [1.22, 2.29]	1.70 [1.10, 2.24]	1.69 [1.26, 2.10]	1.88 [1.48, 2.36]	1.90 [1.55, 2.33]	1.73 [1.10, 2.36]
Age (years)							
Mean (SD)	61.1 (12.5)	62.9 (10.9)	55.5 (9.55)	57.3 (10.4)	36.6 (10.7)	36.7 (11.7)	56.0 (14.7)
Median [Min, Max]	61.5 [34.0, 96.0]	63.5 [35.0, 89.0]	55.0 [32.0, 82.0]	58.0 [29.0, 79.0]	37.0 [19.0, 56.0]	36.0 [19.0, 60.0]	58.0 [19.0, 96.0]
AST (U/L)							
Mean (SD)	27.2 (18.9)	25.5 (15.0)	25.3 (7.06)	24.8 (15.6)	16.2 (3.34)	17.4 (5.00)	24.1 (14.5)
Median [Min, Max]	24.0 [12.0, 147]	23.0 [10.0, 184]	24.0 [15.0, 49.0]	20.0 [8.90, 106]	16.0 [10.0, 27.0]	16.0 [10.0, 41.0]	21.0 [8.90, 184]
ALT (U/L)							
Mean (SD)	25.5 (29.3)	20.5 (13.4)	22.0 (14.9)	22.1 (18.1)	15.0 (6.57)	16.9 (7.65)	21.1 (18.0)
Median [Min, Max]	19.0 [3.00, 216]	17.0 [5.00, 86.0]	15.5 [7.00, 77.0]	17.0 [6.00, 118]	14.0 [4.00, 36.0]	15.0 [6.00, 44.0]	17.0 [3.00, 216]
ALP (U/L)							
Mean (SD)	117 (139)	109 (84.3)	114 (53.7)	111 (117)	58.6 (17.0)	56.0 (15.8)	101 (97.0)
Median [Min, Max]	83.0 [37.0, 1260]	88.0 [38.0, 988]	98.5 [52.0, 275]	86.0 [34.6, 1160]	57.5 [26.0, 104]	55.0 [26.0, 105]	81.0 [26.0, 1260]
Total bilirubin (μ mol/L)							
Mean (SD)	8.75 (3.37)	9.10 (4.40)	10.5 (3.62)	10.6 (4.78)	9.45 (3.69)	9.53 (3.95)	9.49 (4.17)
Median [Min, Max]	8.10 [3.42, 20.0]	8.20 [1.71, 24.8]	10.2 [4.60, 23.1]	10.3 [2.20, 28.6]	8.55 [3.42, 22.2]	8.55 [3.42, 24.0]	8.60 [1.71, 28.6]
CrCl (mL/min)							
Mean (SD)	84.8 (30.9)	81.5 (28.8)	99.3 (31.7)	95.7 (27.8)	108 (18.9)	113 (22.7)	91.7 (30.1)
Median [Min, Max]	83.3 [34.8, 198]	78.4 [34.0, 206]	90.9 [46.3, 209]	93.5 [40.9, 232]	110 [70.0, 156]	111 [62.7, 169]	90.1 [34.0, 232]
eGFR (mL/min/1.73 m^2)							
Mean (SD)	85.5 (20.4)	84.6 (18.3)	97.6 (14.6)	96.0 (14.2)	99.5 (17.5)	101 (16.6)	90.9 (18.7)
Median [Min, Max]	89.8 [35.7, 128]	86.7 [37.3, 127]	98.0 [63.5, 129]	96.8 [48.4, 136]	98.3 [59.9, 150]	101 [63.4, 145]	93.6 [35.7, 150]

Source: Applicant Table. Module 5.3.3.5/PopPK Report Table 15.
WK1A = WU-KONG1A; WK1B = WU-KONG1B; WK2 = WU-KONG2; WK6 = WU-KONG6; WK7 = WU-KONG7; WK12 = WU-KONG12

Table 7557: Summary of Categorical Covariates in Population PK Dataset

	WK1A (N=112)	WK1B (N=202)	WK2 (N=48)	WK6 (N=101)	WK7 (N=40)	WK12 (N=68)	Overall (N=571)
Sex							
Female	61 (54.5%)	124 (61.4%)	25 (52.1%)	58 (57.4%)	15 (37.5%)	27 (39.7%)	310 (54.3%)
Male	51 (45.5%)	78 (38.6%)	23 (47.9%)	43 (42.6%)	25 (62.5%)	41 (60.3%)	261 (45.7%)
Patient status							
NSCLC	112 (100%)	202 (100%)	48 (100%)	101 (100%)	0 (0%)	0 (0%)	463 (81.1%)
Healthy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	40 (100%)	68 (100%)	108 (18.9%)
Race							

	WK1A (N=112)	WK1B (N=202)	WK2 (N=48)	WK6 (N=101)	WK7 (N=40)	WK12 (N=68)	Overall (N=571)
Asian	80 (71.4%)	124 (61.4%)	48 (100%)	101 (100%)	2 (5.0%)	0 (0%)	355 (62.2%)
Black	1 (0.9%)	2 (1.0%)	0 (0%)	0 (0%)	16 (40.0%)	26 (38.2%)	45 (7.9%)
Missing	1 (0.9%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)
Other	2 (1.8%)	1 (0.5%)	0 (0%)	0 (0%)	2 (5.0%)	5 (7.4%)	10 (1.8%)
White	28 (25.0%)	74 (36.6%)	0 (0%)	0 (0%)	20 (50.0%)	36 (52.9%)	158 (27.7%)
American Indian/Alaskan native	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	1 (0.2%)
Ethnicity							
Hispanic or Latino	1 (0.9%)	13 (6.4%)	0 (0%)	0 (0%)	3 (7.5%)	11 (16.2%)	28 (4.9%)
Not Hispanic nor Latino	111 (99.1%)	189 (93.6%)	48 (100%)	101 (100%)	37 (92.5%)	57 (83.8%)	543 (95.1%)
CYP3A4 inhibitor status							
No CYP3A4 inhibitor used	47 (42.0%)	111 (55.0%)	36 (75.0%)	58 (57.4%)	39 (97.5%)	63 (92.6%)	354 (62.0%)
Weak CYP3A4 inhibitor used	59 (52.7%)	77 (38.1%)	11 (22.9%)	34 (33.7%)	1 (2.5%)	5 (7.4%)	187 (32.7%)
Moderate CYP3A4 inhibitor used	6 (5.4%)	14 (6.9%)	1 (2.1%)	9 (8.9%)	0 (0%)	0 (0%)	30 (5.3%)
CYP3A4 inducer status							
No CYP3A4 inducer used	87 (77.7%)	152 (75.2%)	39 (81.3%)	80 (79.2%)	40 (100%)	68 (100%)	466 (81.6%)
Weak CYP3A4 inducer used	25 (22.3%)	50 (24.8%)	9 (18.8%)	21 (20.8%)	0 (0%)	0 (0%)	105 (18.4%)
PPI/antiacid use							
No PPI used	73 (65.2%)	130 (64.4%)	36 (75.0%)	90 (89.1%)	40 (100%)	68 (100%)	437 (76.5%)
PPI used	39 (34.8%)	72 (35.6%)	12 (25.0%)	11 (10.9%)	0 (0%)	0 (0%)	134 (23.5%)
Smoking status							
Current	3 (2.7%)	4 (2.0%)	1 (2.1%)	2 (2.0%)	0 (0%)	0 (0%)	10 (1.8%)
Former	36 (32.1%)	62 (30.7%)	17 (35.4%)	31 (30.7%)	0 (0%)	0 (0%)	146 (25.6%)
Never	73 (65.2%)	136 (67.3%)	30 (62.5%)	68 (67.3%)	0 (0%)	0 (0%)	307 (53.8%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	40 (100%)	68 (100%)	108 (18.9%)
Renal impairment							
Mild	44 (39.3%)	75 (37.1%)	21 (43.8%)	34 (33.7%)	7 (17.5%)	12 (17.6%)	193 (33.8%)
Moderate	25 (22.3%)	55 (27.2%)	2 (4.2%)	8 (7.9%)	0 (0%)	0 (0%)	90 (15.8%)
Normal	43 (38.4%)	71 (35.1%)	25 (52.1%)	59 (58.4%)	33 (82.5%)	56 (82.4%)	287 (50.3%)
Missing	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)
Hepatic impairment							
Mild	18 (16.1%)	22 (10.9%)	1 (2.1%)	16 (15.8%)	1 (2.5%)	2 (2.9%)	60 (10.5%)
Normal	94 (83.9%)	180 (89.1%)	47 (97.9%)	85 (84.2%)	39 (97.5%)	66 (97.1%)	511 (89.5%)

	WK1A (N=112)	WK1B (N=202)	WK2 (N=48)	WK6 (N=101)	WK7 (N=40)	WK12 (N=68)	Overall (N=571)
Prior therapy							
Treated	81 (72.3%)	202 (100%)	48 (100%)	101 (100%)	0 (0%)	0 (0%)	432 (75.7%)
Treatment naïve	31 (27.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	31 (5.4%)
Healthy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	40 (100%)	68 (100%)	108 (18.9%)
Formulation							
Formulation A	24 (21.4%)	0 (0%)	30 (62.5%)	0 (0%)	0 (0%)	12 (17.6%)	66 (11.6%)
Formulation B	88 (78.6%)	202 (100%)	12 (25.0%)	101 (100%)	40 (100%)	56 (82.4%)	499 (87.4%)
Formulation A & Formulation B	0 (0%)	0 (0%)	6 (12.5%)	0 (0%)	0 (0%)	0 (0%)	6 (1.1%)
Food status							
Fasted	48 (42.9%)	0 (0%)	48 (100%)	0 (0%)	0 (0%)	36 (52.9%)	132 (23.1%)
Fasted & Fed	12 (10.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	32 (47.1%)	44 (7.7%)
Fed	52 (46.4%)	202 (100%)	0 (0%)	101 (100%)	40 (100%)	0 (0%)	395 (69.2%)

Source: Applicant Table. Module 5.3.3.5/PopPK Report Table 16.
WK1A = WU-KONG1A; WK1B = WU-KONG1B; WK2 = WU-KONG2; WK6 = WU-KONG6; WK7 = WU-KONG7; WK12 = WU-KONG12

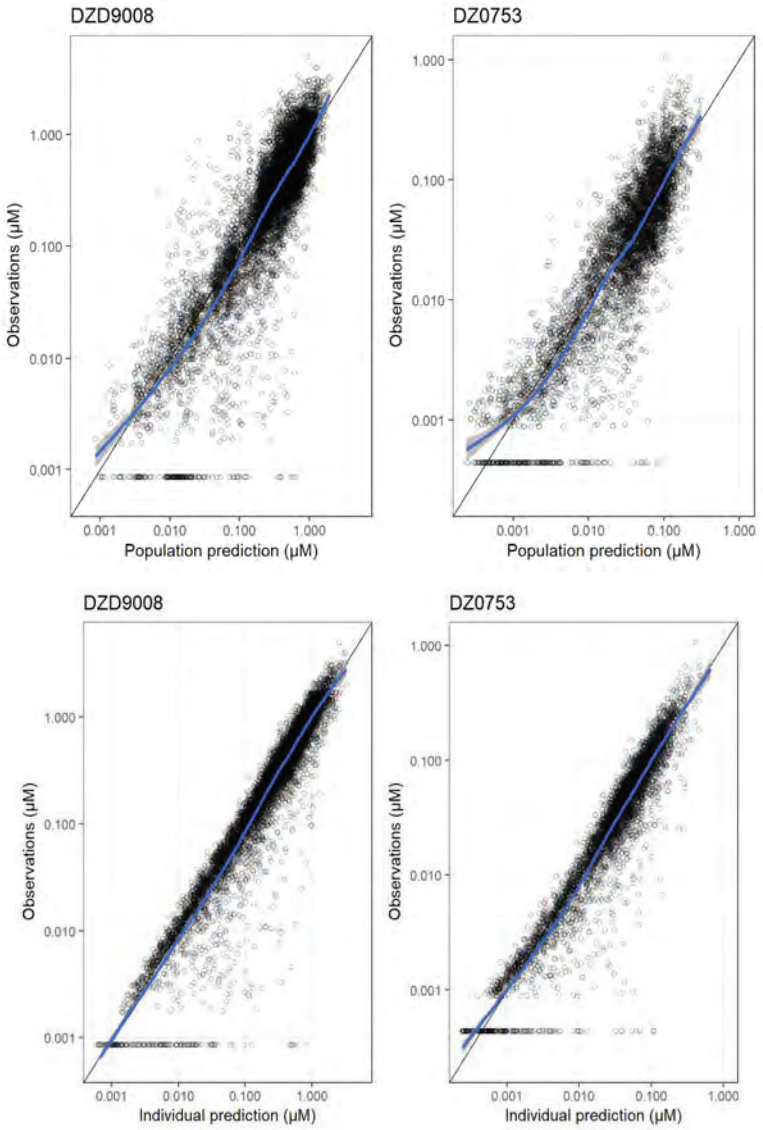
Table 765859: Parameter Estimates and SE from Final Population PK Model

Parameters	Estimates	%RSE	Bootstrap 95%CI	Shrinkage (%)
Population parameter				
DZD9008 CL/F (L/h)	22.1	2.66	[21.4, 23.1]	-
DZD9008 Vc/F (L)	954	3.76	[905, 1010]	-
Ka (h^{-1})	1.53	3.30	[1.43, 1.65]	-
DZD9008 Q/F (L/h)	15.0	10.9	[12.5, 18.8]	-
DZD9008 Vp/F (L)	569	5.86	[506, 650]	-
FM, fraction metabolized in absorption (%)	12.5	4.74	[10.9, 14.5]	-
DZ0753 CL/F (L/h)	91.4	3.18	[86.6, 96.9]	-
DZ0753 Vc/F (L)	1150	4.57	[981, 1340]	-
DZ0753 Q/F (L/h)	51.5	7.12	[44.1, 61.1]	-
DZ0753 Vp/F (L)	2960	6.57	[2460, 3510]	-
FM2, fraction metabolized (%)	38.8		fixed	-
Body weight on DZD9008 CL/F	0.731	10.6	[0.563, 0.858]	-
HV on DZD9008 CL/F	0.622	9.80	[0.522, 0.729]	-
Body weight DZ0753 on CL/F	1.62	8.13	[1.38, 1.84]	-
HV on DZ0753 CL/F	1.36	10.6	[1.15, 1.63]	-
Body weight on DZD9008 Vc/F	0.990	13.7	[0.741, 1.23]	-
HV on DZD9008 Vc/F	0.536	18.0	[0.359, 0.707]	-
Body weight on DZ0753 Vc/F	1.57	11.9	[1.16, 1.92]	-
HV on DZ0753 Vc/F	-0.298	22.1	[-0.41, -0.198]	-
Interindividual variability				

Parameters	Estimates	%RSE	Bootstrap 95%CI	Shrinkage (%)
CL/F DZD9008 variance	0.133	6.48	[0.119, 0.15]	3.93
CL/F DZD9008-Vc/F DZD9008 covariance	0.151	7.17	[0.133, 0.17]	-
Vc/F DZD9008 variance	0.324	6.98	[0.278, 0.369]	5.37
CL/F DZD9008 -CL/F DZ0753 covariance	0.145	8.23	[0.128, 0.167]	-
Vc/F DZD9008 -CL/F DZ0753 covariance	0.183	8.98	[0.154, 0.216]	-
CL/F DZ0753 variance	0.261	8.02	[0.22, 0.302]	9.07
CL/F DZD9008 -Vc/F DZ0753 covariance	0.112	13.9	[0.0841, 0.139]	-
Vc/F DZD9008 -Vc/F DZ0753 covariance	0.290	9.39	[0.239, 0.345]	-
CL/F DZ0753-Vc/F DZ0753 covariance	0.211	12.5	[0.164, 0.26]	-
Vc/F DZ0753 variance	0.379	11.3	[0.299, 0.472]	11.9
Ka variance	0.357	7.52	[0.31, 0.421]	16.8
Residual variability				
DZD9008 RUV variance	0.322	1.76	[0.31, 0.332]	5.66
DZ0753 RUV variance	0.375	1.88	[0.359, 0.389]	5.22

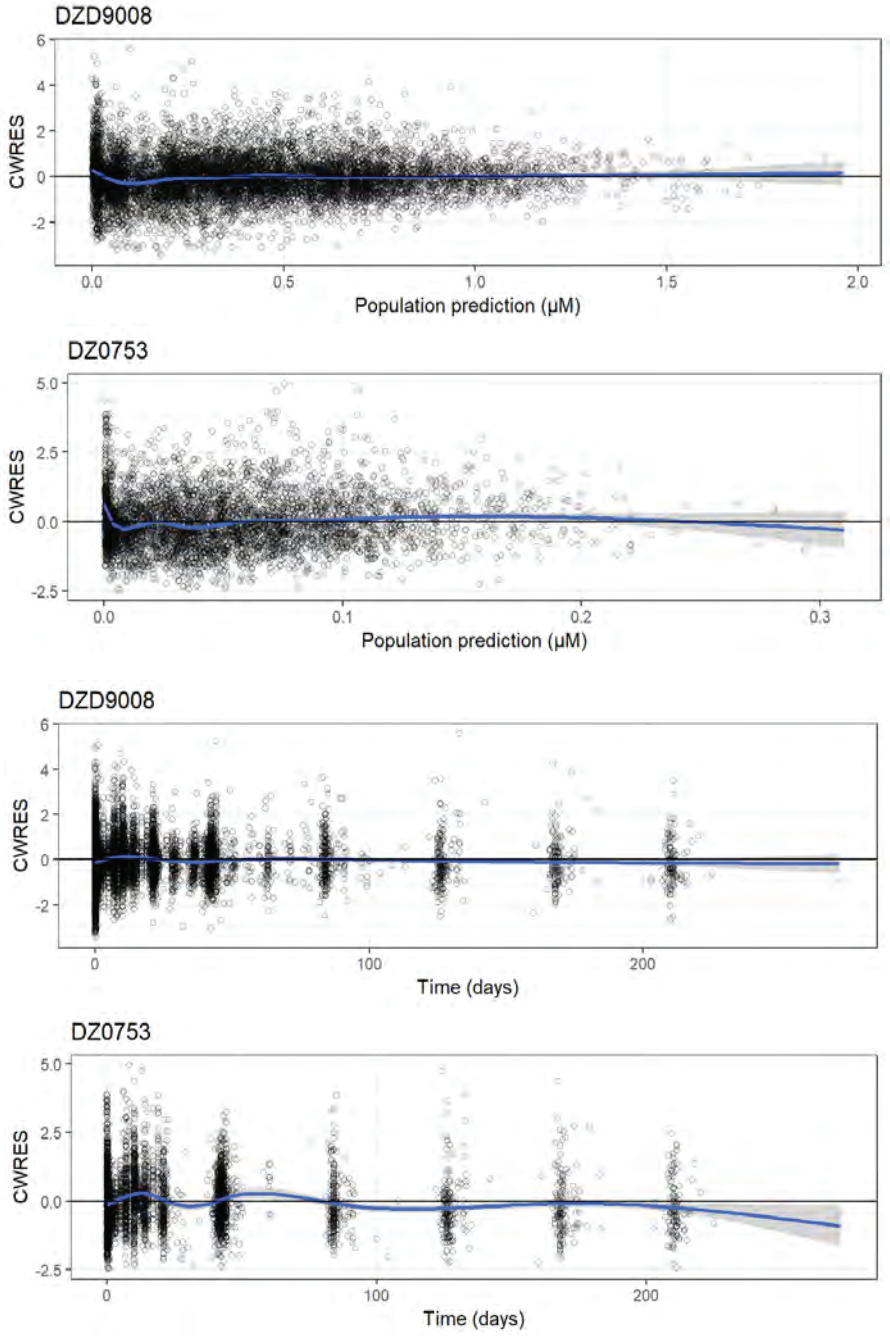
Source: Applicant Table. Module 5.3.3.5/PopPK Report/Table 10.
DZD9008 = sunvozertinib; CI = confidence interval; CL/F = apparent oral clearance; HV = healthy volunteer status; Ka = absorption rate constant; Q/F = intercompartmental clearance; RSE = relative standard error; RUV = residual unexplained variability; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution.

Figure 12 Observed Versus Population Predicted (Upper) and Observed Versus Individual Predicted (Lower) Concentrations for the Final Model



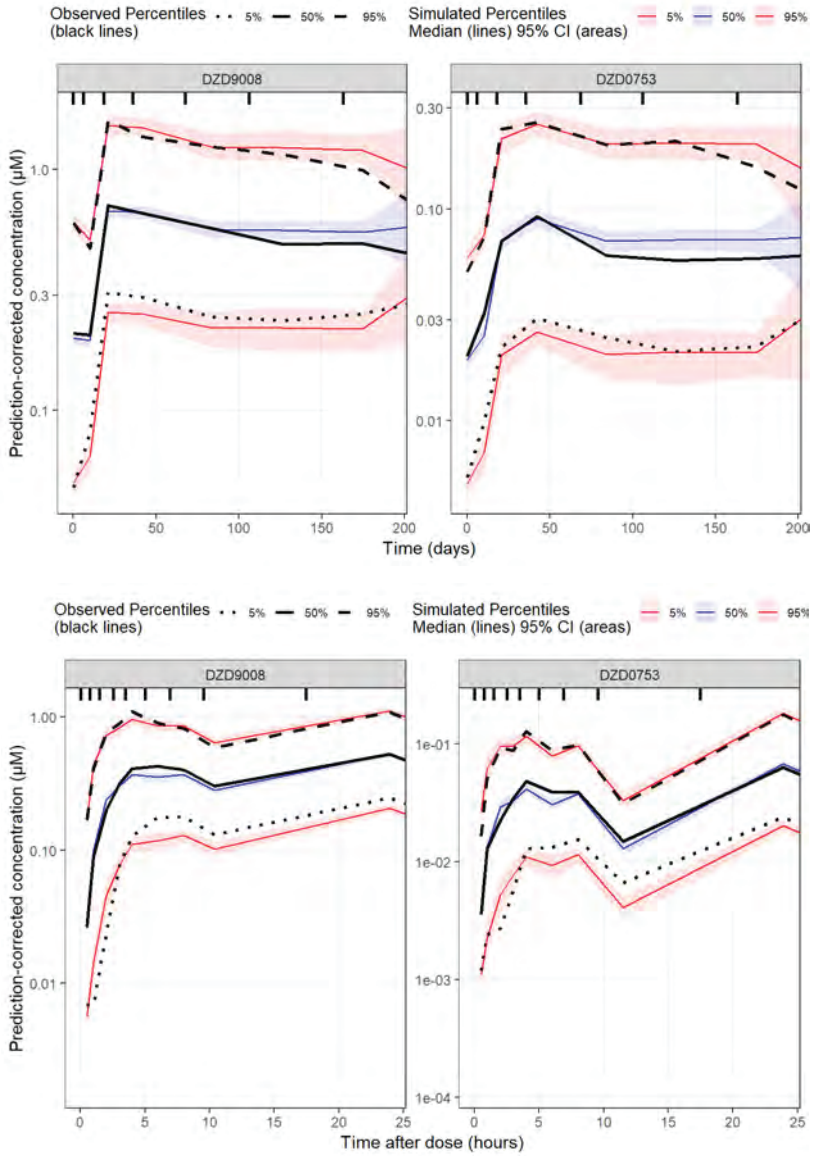
Source: Applicant Figure. Module 5.3.3.5/PopPK Report Figure 6-7.
Notes: Dots are individual data points, blue lines are smoothed gam line (with associated confidence interval). DZD9008 = sunvozertinib.

Figure 13: Goodness-of-fit Plots for the Final Population PK Model



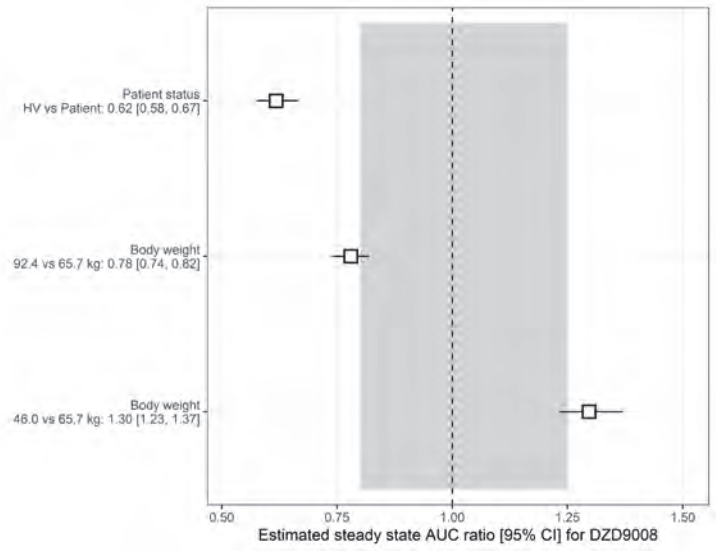
Source: Applicant Figure. Module 5.3.3.5/PopPK Report/Figure 40-41.
CWRES = conditional weighted residuals. DZD9008 = sunvozertinib.
Notes: Dots are individual data points, and blue lines are smoothed gam line (with associated confidence interval).

Figure 1414: Prediction-corrected VPC of Final Population PK Model against Time (Upper) and against Time after Dose (Lower)



Source: Applicant Figure. Module 5.3.3.5/PopPK Report/Figure 9-10.
CI=confidence interval; pcVPC = prediction = corrected visual predictive check. DZD9008 = sunvozertinib.
Notes: the black solid line is the observed median; and the black dashed lines are observed p5 and p95. The blue solid line is the simulated median; and the pink dashed lines are simulated p5 and p95. The blue area is the 95% CI of the simulated median, and the pink areas are the 95% CI of the simulated p5 and p95.

Figure 1515: Impact of Significant Covariates on Exposure



Source: Applicant Figure. Module 5.3.3.5/PopPK Report/Figure 11.
AUC=area under the curve; CI = confidence interval; HV = healthy volunteer. DZD9008 = sunvozertinib.
Notes: The dotted line represents the reference NSCLC patient with a body weight of 65.7 kg corresponding to the median body weight in the analysis population, the gray area represents the 80-125% range. Error bars represent 95% CI.

The FDA's Assessment:

PopPK Analysis

The PopPK analysis data set included 13964 PK samples for sunvozertinib and DZ0753 from 571 unique participants (108 healthy volunteers and 463 patients). The proportion of parent and metabolite below the lower limit of quantification (BLQ) samples was 2.10% and 7.30%, respectively. The M6 method was used to handle data below the limit of quantification postdose.

The final model provided a joint description of sunvozertinib and DZ0753 plasma concentrations. The sunvozertinib PK was found to be adequately described by a two-compartment model with 2 transit-compartments to describe the oral absorption. The model included a pathway to describe pre- systemic biotransformation of sunvozertinib to DZ0753 to account for Cmax of the metabolite occurring nearly simultaneously or earlier compared to Cmax of the parent, as observed in densely sampled PK data obtained in healthy volunteers. The pre-systemic biotransformation was implemented as a first-order conversion rate parameter describing mass transfer and metabolism of sunvozertinib to DZ0753 from the second transit compartment to the central compartment of the metabolite. The PK of metabolite DZ0753 was described by a two-compartment model. Patient status and body weight were retained in the final model covariates on apparent systemic clearance and apparent systemic central volume of both sunvozertinib and DZ0753. Interindividual variability was estimated on Ka, CL/F for both

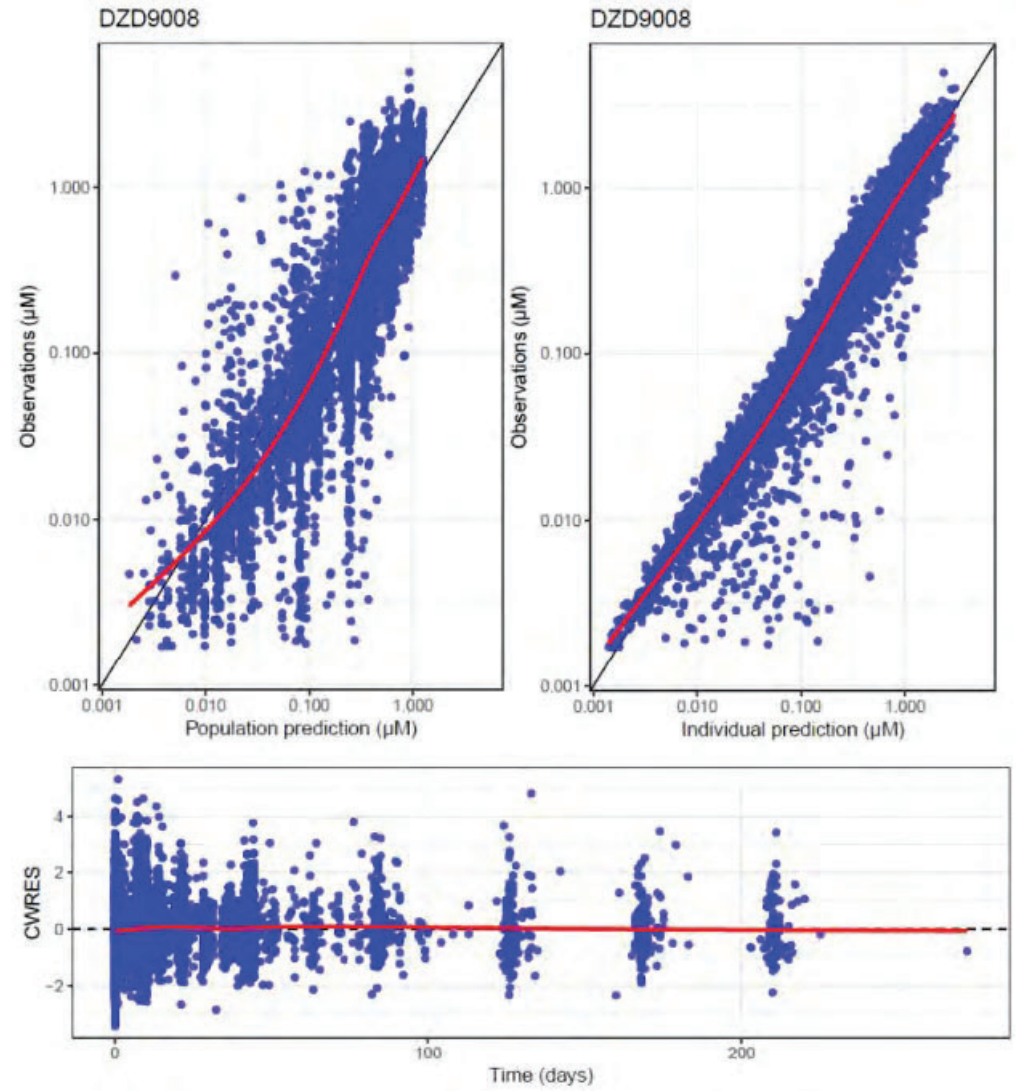
sunvozertinib and DZ0753, and Vc/F for both sunvozertinib and DZ0753 with a full covariance matrix on the clearance and volume terms. A proportional residual error variance was estimated for each of the analytes.

All typical PK parameters and residual error variances estimated by the reviewer remain consistent with the estimation provided by the applicant. With relative standard errors (RSE) of 10.9% or less, and covariate effects and (co) variances related to interindividual variability were estimated with %RSE < 25%. Shrinkage of both interindividual and intraindividual random effects was low (**Table 76**). The model showed no meaningful bias in goodness-of-fit plots and residual-based diagnostics (**FDA Figure 16**) and was able to adequately describe central tendency and variability of the observed data. Additionally, the final PopPK model adequately captured the observed data in participants with different health status **(FDA Figure 17**) as well as across different dose levels (**FDA Figure 18**) .

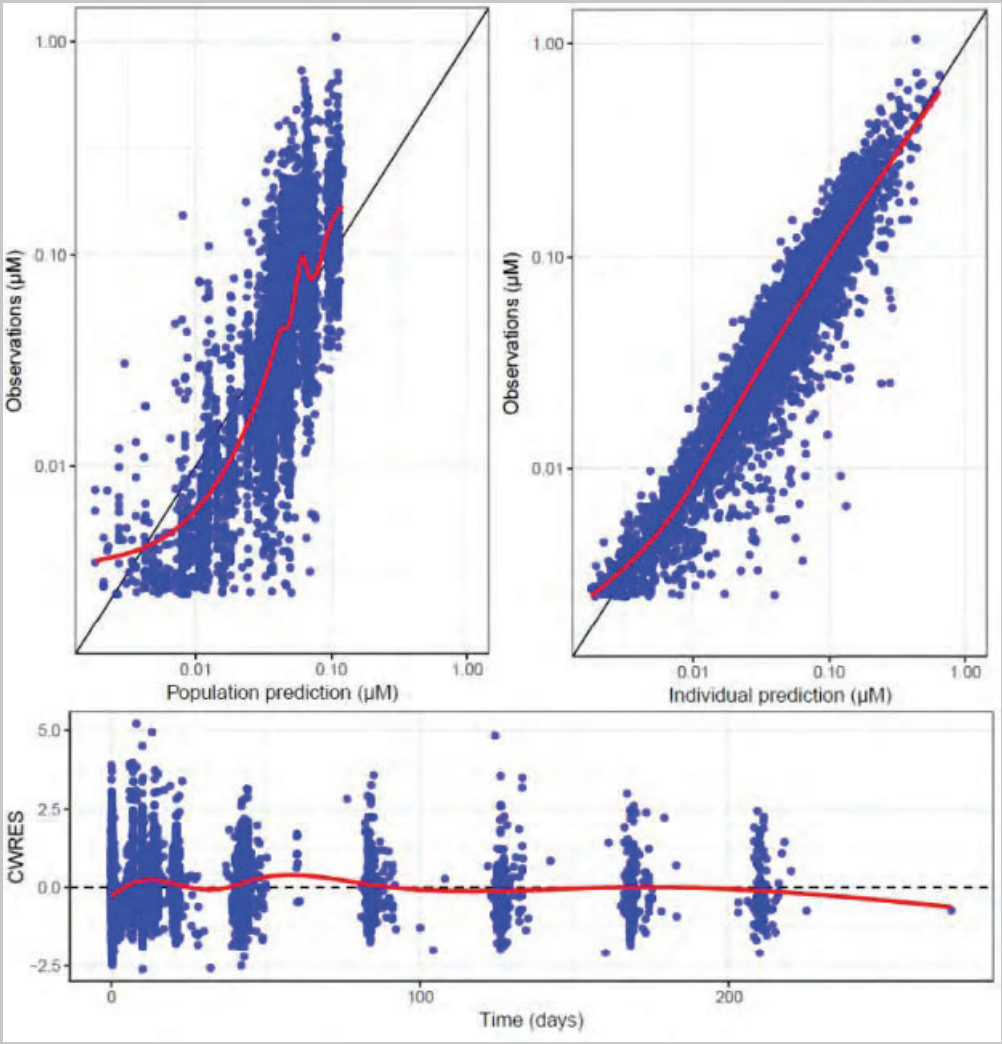
The effect of patient status covariate (HV vs Patient) and body weight included in the final population PK model was evaluated on AUC exposure of sunvozertinib. Healthy volunteers and participants with higher body weight were predicted with a lower exposure compared to patients and participants with lower body weight.

FDA Figure 16: Goodness-of-fit Plots for the Final Population PK Model

Sunvozertinib (DZD9008, Parent)

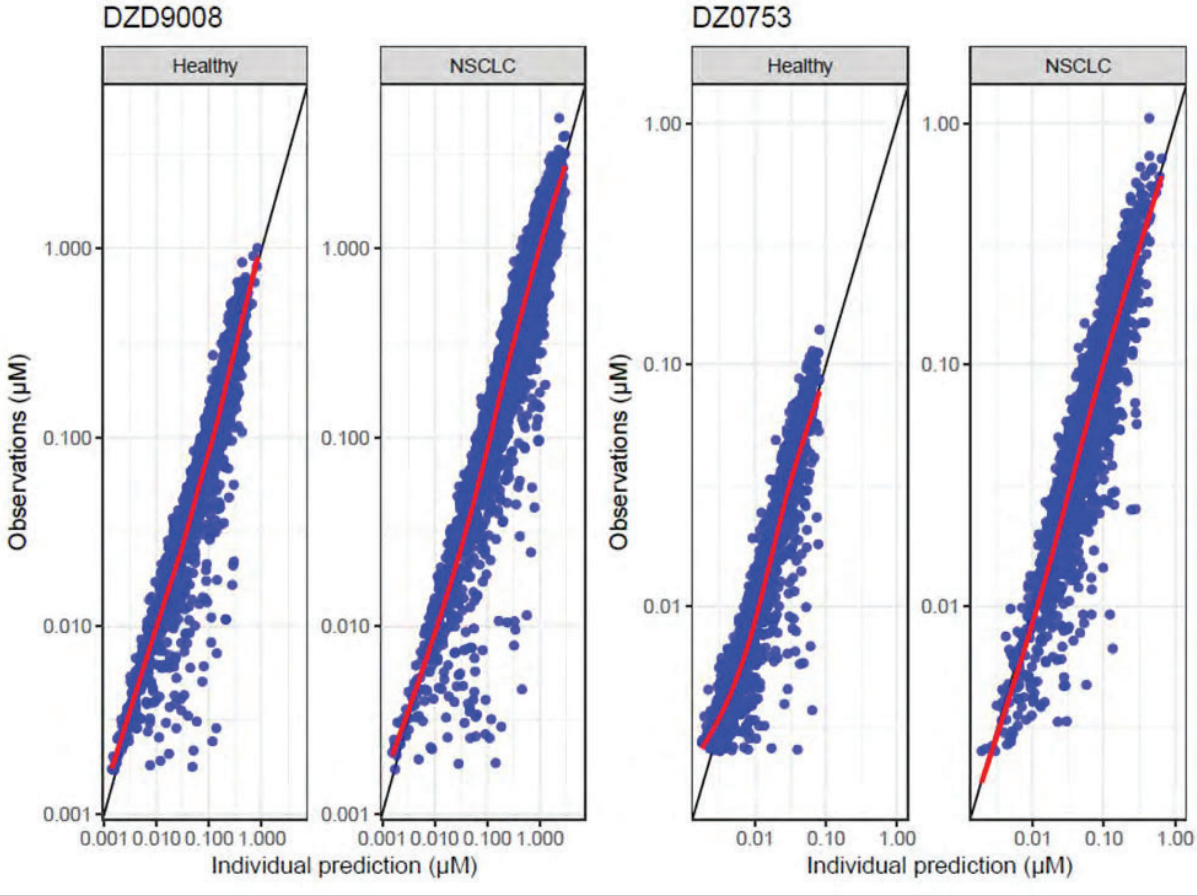


DZ0753 (Metabolite)



Source: Reviewer's Analysis

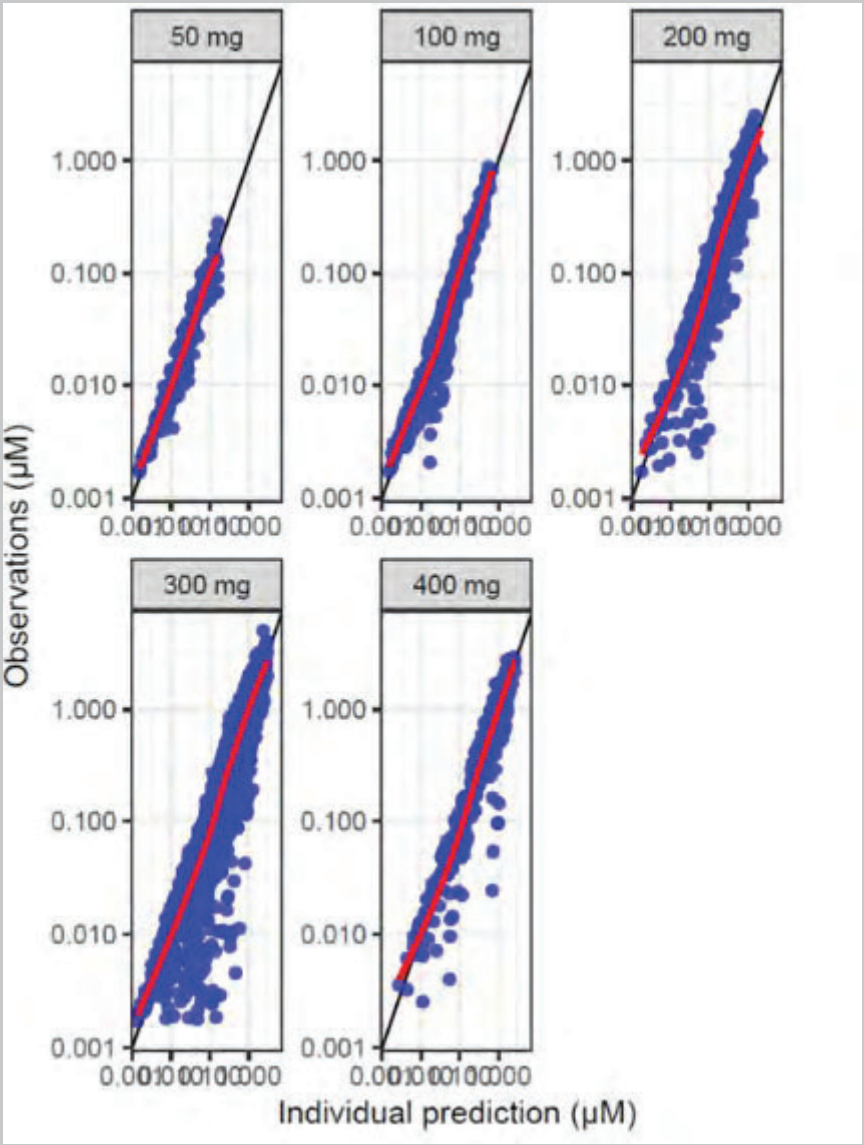
FDA Figure 17: Goodness-of-fit Plots for Healthy Volunteers versus Patients



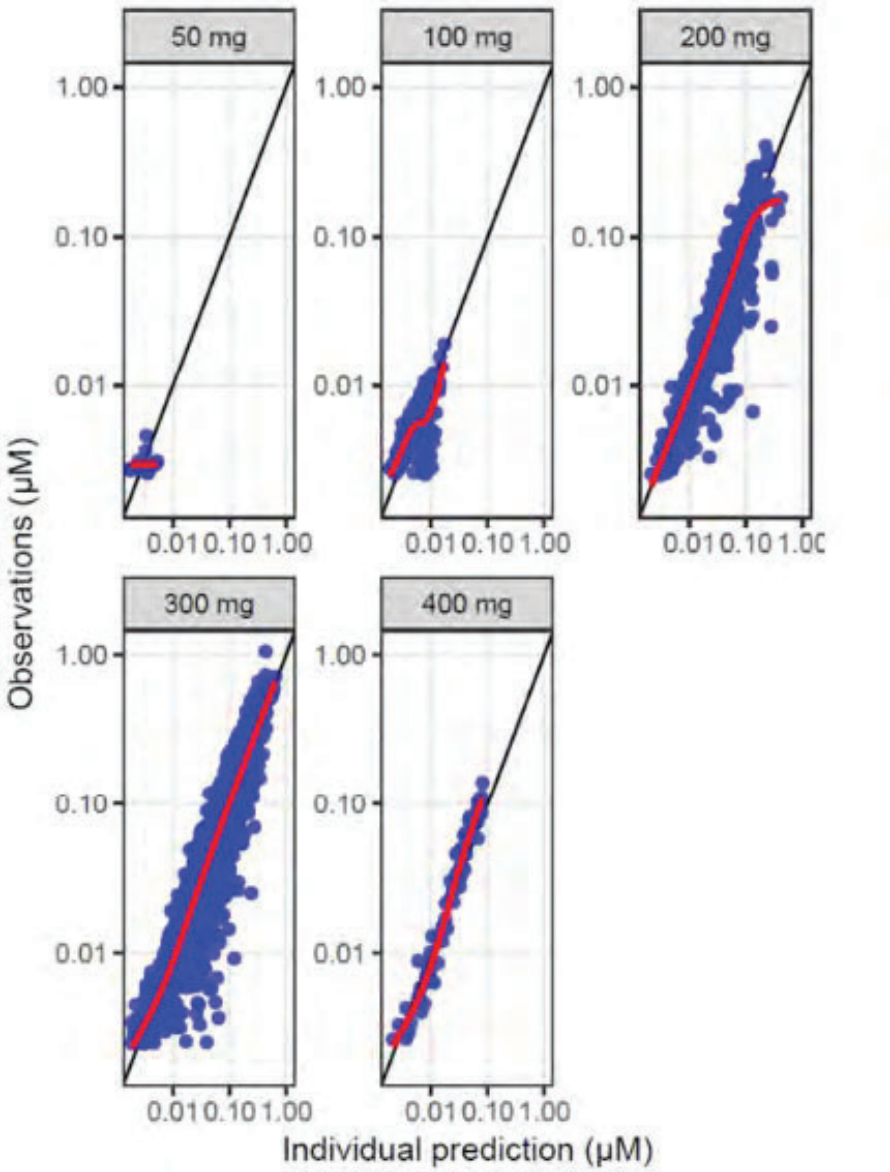
Source: Reviewer's Analysis

FDA Figure 18: Goodness-of-fit Plots Across Doses

Sunvozertinib (DZD9008, Parent)



DZ0753 (Metabolite)



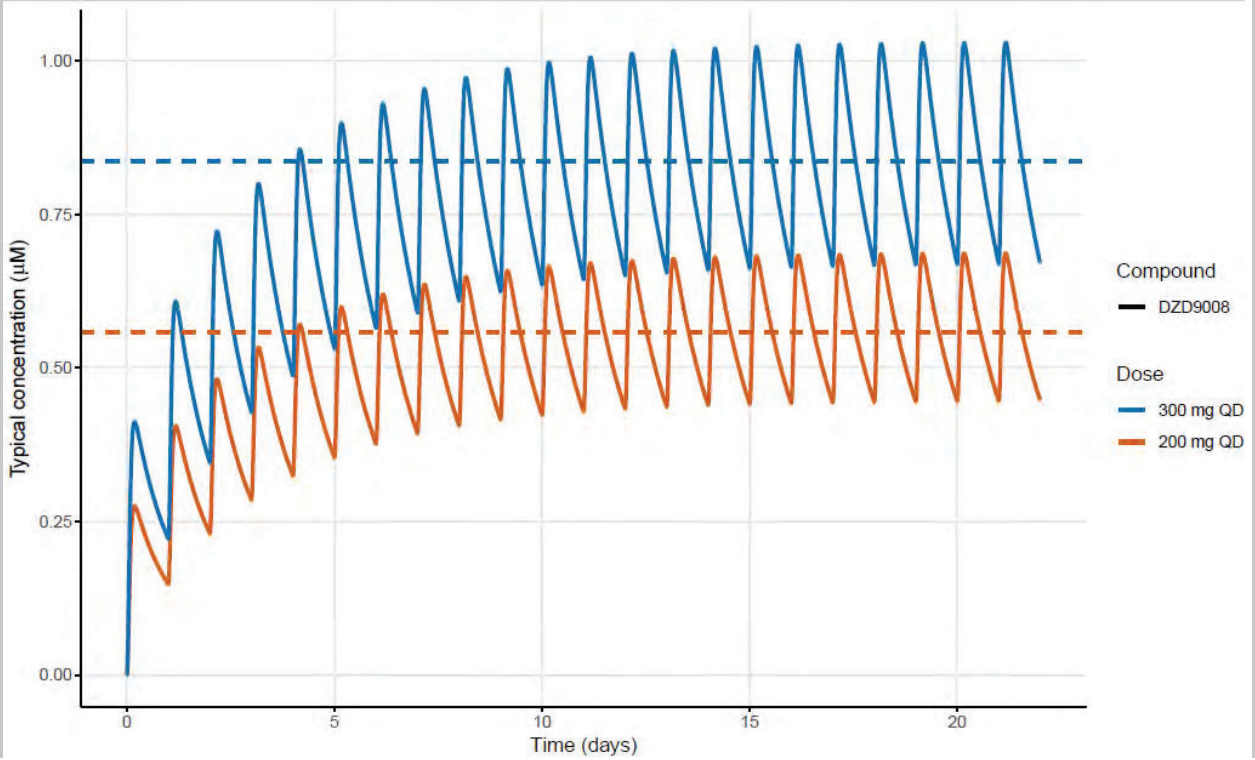
Source: Reviewer's Analysis

PopPK Model Based Simulation

Based on the final PopPK model, simulations were conducted to demonstrate the concentration-time profiles of sunvozertinib and DZ0753 after 200 mg and 300 mg QD in a typical NSCLC patient with body weight of 65.7 kg, predicted across the first 21-day treatment cycle (**FDA Figure 19).** Steady state appears to be achieved after 15 days of continuous dosing at both dose

levels, which is consistent with the mean elimination half-life of 44.5 to 57.3 hours, as estimated by individual clinical studies across dose levels.

FDA Figure 19: Typical Concentration-Time Profile for A 65.7 kg NSCLC Patient Following 200 mg and 300 mg QD



Note: The horizontal lines represent the average steady-steady concentrations at dosages of 200 mg and 300 mg, respectively.

Source: Reviewer's Analysis

PopPK Model based PPI DDI Investigation

In the original population PK analysis, the effect of PPI was evaluated based on a time varying covariate effect on the DZD9008 absorption rate constant (Ka). The covariate effect of PPI was not found to be significant (p=0.0290) and was therefore not included in the final joint population PK model of DZD9008 and DZ0753.

During the review cycle, questions were raised regarding whether a dedicated DDI with any acid

reducing agent (ARA) is required based on the in vitro observation that sunvozertinib displays pH dependent solubility with DDI potential with ARAs, despite that the in vitro study suggests a rapid dissolution and bioavailability is not limited by dissolution and , food effect on sunvozertinib exposure is limited. Therefore, additional PPI-related covariates were evaluated.

Comprehensive assessment of the impact of concomitant PPI use on the PK of sunvozertinib was conducted. Detailed information on subjects who used PPIs, including the total number of subjects, PK sampling details per individual (covering both pre- and post-PPI exposure periods), PPI dosage, frequency, and extent of co-medication use were summarized and the fraction of days with PPI use was derived and this was subsequently categorized to "No PPI used", "PPI taken on <=50% of days", and "PPI taken on >50% of days" in the model dataset (**FDA Table 76**). The patients have thereafter been grouped into:

• Group 1: No PPI taken, PPI taken on ≤50% of days, and PPI taken on > 50% of days.

• Group 2: No PPI taken, PPI taken in ≤ 50% of PK samples, and PPI taken in > 50% of PK samples.

Further population PK covariate analysis was conducted based on the above PPI concomitant usage categories. The concomitant usage of PPI on the PopPK parameters of Ka, CL/F, etc. was investigated based on the predefined PopPK modelling criteria described in the main model.

As a result, none of the covariates meaningfully explained unexplained variability as represented by the estimated variance associated with the random effect on the absorption rate constant (KA), i.e. no models resulted in at least 5% reduction in IIV. The finding of a lack of effect of PPI in the model-based evaluation was confirmed by visualization of individual estimated random effects and individual predicted exposures (AUC and Cmax) for patients with NSCLC participating in studies WUKONG1A, WU-KONG1B, WU-KONG2, and WU-KONG6 (**FDA Figure 20**)

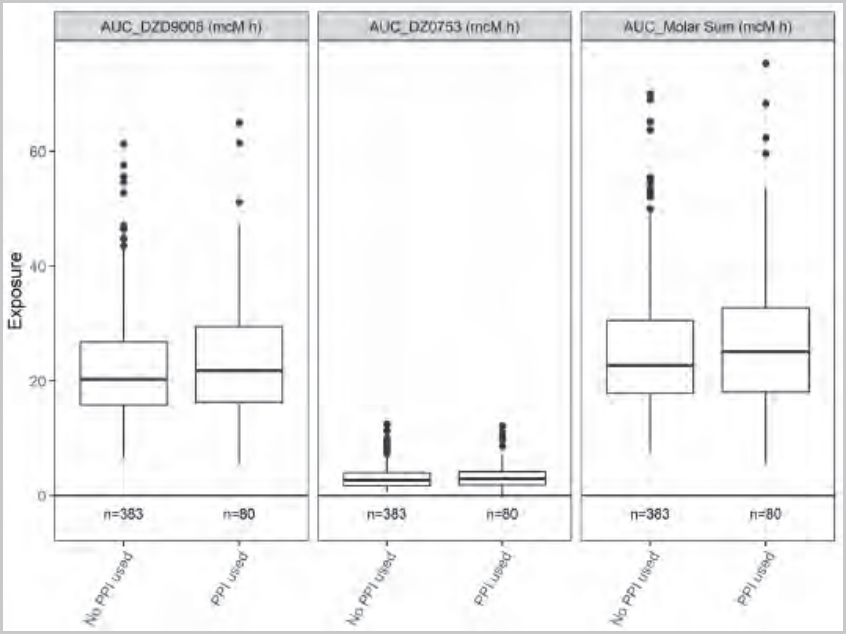
FDA Table 7660: Summary of PPI-related covariates and number of PK samples

	WU-KONG1A (N=112)	WU-KONG1B (N=202)	WU-KONG2 (N=48)	WU-KONG6 (N=101)	Overall (N=463)
PK samples					
Mean (SD)	23.3 (5.19)	23.9 (9.35)	24.0 (5.19)	12.5 (7.28)	21.3 (8.96)
Median (CV%)	25.0 (22.3)	22.0 (39.1)	25.0 (21.6)	12.0 (58.1)	22.0 (42.1)
[Min, Max]	[3.00, 31.0]	[4.00, 44.0]	[12.0, 31.0]	[2.00, 38.0]	[2.00, 44.0]
PPI used					
No PPI used	86 (76.8%)	163 (80.7%)	44 (91.7%)	90 (89.1%)	383 (82.7%)
PPI used	26 (23.2%)	39 (19.3%)	4 (8.3%)	11 (10.9%)	80 (17.3%)
PPI switch on					
Did not switch on PPI	86 (76.8%)	163 (80.7%)	44 (91.7%)	90 (89.1%)	383 (82.7%)
Switched on PPI	26 (23.2%)	39 (19.3%)	4 (8.3%)	11 (10.9%)	80 (17.3%)
PPI switch off					
Did not switch off PPI	86 (76.8%)	163 (80.7%)	44 (91.7%)	90 (89.1%)	383 (82.7%)
Switched off PPI	26 (23.2%)	39 (19.3%)	4 (8.3%)	11 (10.9%)	80 (17.3%)
PPI use by day					
No PPI used	95 (84.8%)	161 (79.7%)	43 (89.6%)	90 (89.1%)	389 (84.0%)
PPI taken on <=50% of days	4 (3.6%)	21 (10.4%)	4 (8.3%)	8 (7.9%)	37 (8.0%)
PPI taken on >50% of days	13 (11.6%)	20 (9.9%)	1 (2.1%)	3 (3.0%)	37 (8.0%)
PPI use by PK samples					
No PPI used	95 (84.8%)	171 (84.7%)	44 (91.7%)	94 (93.1%)	404 (87.3%)
PPI taken in <=50% of PK samples	4 (3.6%)	14 (6.9%)	3 (6.3%)	4 (4.0%)	25 (5.4%)
PPI taken in >50% of PK samples	13 (11.6%)	17 (8.4%)	1 (2.1%)	3 (3.0%)	34 (7.3%)

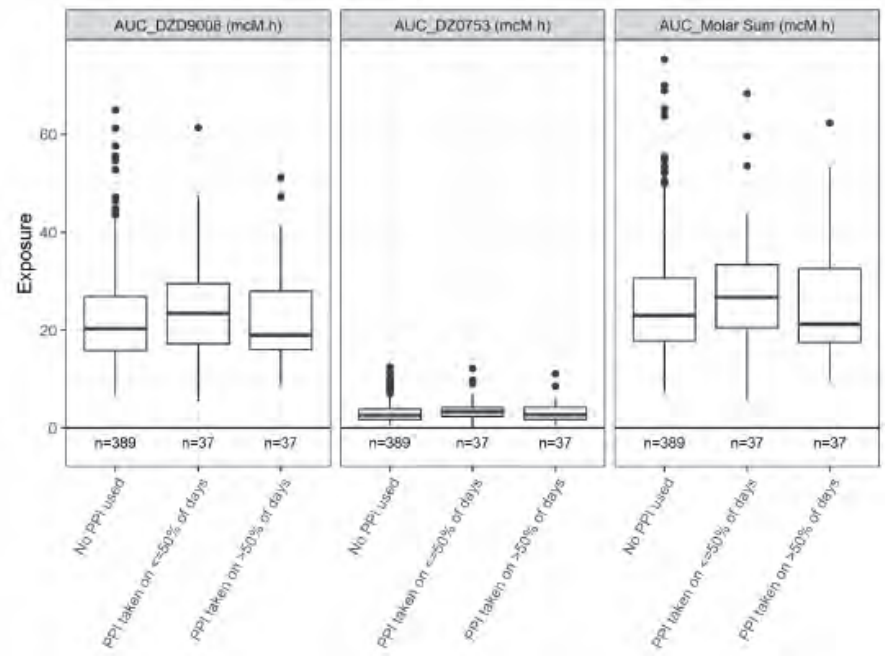
Source: Table 1. Evaluation of the impact of PPI on the PK of DZD9008 IR response received on 4/4/2025.

FDA Figure 20: Individual Predicted AUC by PPI Use

1. **Individual PPI Use:**

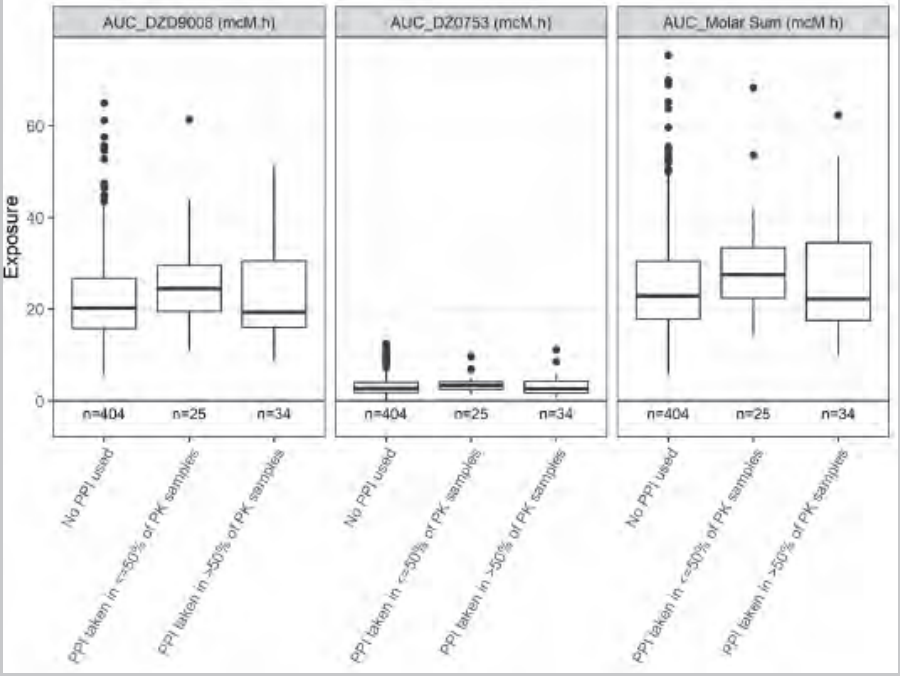


2. **PPI Use by Day**



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.

3. PPI Use by PK Samples



Source: Figures 4, 5, 6 Evaluation of the impact of PPI on the PK of DZD9008, IR response received on 4/4/2025.

Reviewer's Comments:

1. *The PopPK model adequately described the PK data of sunvozertinib (DZD9008) and its metabolite DZ0753 in both healthy volunteers and patients with a NSCLC. The PK of sunvozertinib was characterized by a two-compartment model with absorption characterized by 2 transit-compartments.*

2. *No clinically meaningful differences in sunvozertinib PK were observed based on correlations between individual predicted exposure and age, sex, race, smoking status, formulation, food status, PPI use, concomitant use of CYP3A4 inhibitors and inducers, renal or hepatic functions, indicating no dose adjustment is needed for these factors.*

3. *Apparent clearance and volume of distribution were influenced by health status and body weight, but the impact of body weight on exposure was less than the overall variability observed in NSCLC patients, supporting a fixed-dose approach.*

4. *Further investigation of PPI-related covariate impact on sunvozertinib exposure with additional PPI covariate data categories based on the full analysis dataset support the original population PK model findings that comedication usage of PPI does not have a*

clinically meaningful impact on sunvozertinib or DZ0753 exposure.

19.4.2 Exposure-Response Analysis

19.4.2.1 E-R Executive Summary

The FDA's Executive Summary:

- In this submission, the sunvozertinib E-R analyses for efficacy included 287 NSCLC patients treated with 200–300 mg sunvozertinib from WU-KONG1B and WU-KONG6. No statistically significant relationship was observed between drug exposure and objective response rate (ORR).
- Subgroup analyses (b) (4) However, given the limited sample size, these findings remain inconclusive.
- The E-R safety analysis used data from 463 NSCLC patients across 50–400 mg doses from WU-KONG1 (Parts A and B), WU-KONG2, and WU-KONG6. Higher exposure was associated with increased incidence of grade ≥3 treatment-emergent adverse events (TEAEs), particularly elevated CPK, diarrhea, and anemia. However, an increase of the dose from 200 mg to 300 mg QD led to a shallower increase of incidences of these identified TEAEs with limited clinical significance.
- In conclusion, the clinical pharmacology program adequately characterized the PK profile of sunvozertinib and supported the proposed 200 mg QD regimen in the general population.

19.4.2.2 E-R (efficacy) Assessment Summary

The Applicant's Position:

There was no statistically significant relationship between time-averaged exposure (TAE) of sunvozertinib and the probability of ORR by IRC for in patients with advanced NSCLC with EGFR exon20ins.

Table 7761: Summary of Key Findings in E-R (Efficacy) Analysis

General Information	
Goal of ER analysis	Explore the exposure-response relationship between exposure of sunvozertinib and ORR in NSCLC patients
Study Included	WU-KONG1B and WU-KONG6
Endpoint	IRC confirmed ORR

No. of Patients (total, and with individual PK)		N= 287 (WU-KONG1B: N=192 , WU-KONG6:N=95)
Population Characteristics (Table and Table)	General	Age median (range): 61 (29 - 88) years Weight median (range): 64 (33 - 118) kg male 113 (39.4%) female 174 (60.6%) Asian 212 (73.9%); white 71 (24.7%); Black 2 (0.7%); Other 1 (0.3%); unknown 1 (0.3%)
	Pediatrics (if any)	Not Applicable
Dose(s) Included		200 mg and 300 mg QD
Exposure Metrics Explored (range)		Time averaged exposure
Covariates Evaluated		Race, sex, age, ECOG, Body size (body weight and BMI), Tumor type or genetics, baseline brain metastasis

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	ORR as binary endpoints were analyzed by logistic regression models based on the following equation: $\log\left(\frac{p_i}{1-p_i}\right) = \text{Intercept} + \text{Slope} \times \text{Exposure}_i + \beta_1 X_{i1} + \cdots + \beta_p X_{ip}$ p_i is the probability of response (or adverse event (AE) for safety variables) for participant i, Intercept is the logit of the probability of response in the absence of DZD9008, Slope is the slope of the relationship between exposure and the logit of the probability of response, Exposure_i is the predicted exposure for participant i, $\beta_1 \ldots \beta_p$ is the vector of parameters for covariate effects, and $X_{i1} \ldots X_{ip}$ is the vector of covariate variables for participant i.	**Acceptable**
Model Parameter Estimates	Not Applicable	
Model Evaluation	Figure 21	Acceptable
Covariates and Clinical Relevance	The effect of TAE on ORR was not statistically significant based on the likelihood ratio test covariates were not evaluated.	
Simulation for Specific Population	Not Applicable	
Visualization of E-R relationships	Figure 21	Acceptable
Overall Clinical Relevance for ER	There was no statistically significant relationship between ORR and TAE.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not Applicable	

Table 7862 Summary of Baseline Characteristics and Laboratory Values in the E-R Efficacy Dataset (WU-KONG6 and WU-KONG1B)

	WU-KONG1B (N=192)	WU-KONG6 (N=95)	Overall (N=287)
Age (yrs)			
Mean (SD)	62.8 (10.5)	57.5 (10.3)	61.1 (10.7)
Median [Min, Max]	62.5 [35.0, 88.0]	58.0 [29.0, 79.0]	61.0 [29.0, 88.0]
Body weight (kg)			
Mean (SD)	65.3 (14.5)	63.8 (12.0)	64.8 (13.7)
Median [Min, Max]	64.0 [33.0, 118]	64.0 [38.0, 91.0]	64.0 [33.0, 118]
BMI (kg/m^2)			
Mean (SD)	24.5 (4.38)	24.1 (3.53)	24.4 (4.12)
Median [Min, Max]	24.1 [13.9, 39.4]	23.9 [17.2, 32.5]	23.9 [13.9, 39.4]
Missing	1 (0.5%)	1 (1.1%)	2 (0.7%)
BSA (m^2)			
Mean (SD)	1.69 (0.201)	1.68 (0.185)	1.69 (0.196)
Median [Min, Max]	1.68 [1.22, 2.29]	1.68 [1.26, 2.10]	1.68 [1.22, 2.29]
Missing	1 (0.5%)	1 (1.1%)	2 (0.7%)
Sex			
Male	75 (39.1%)	38 (40.0%)	113 (39.4%)
Female	117 (60.9%)	57 (60.0%)	174 (60.6%)
Race			
White	71 (37.0%)	0 (0%)	71 (24.7%)
Black or African American	2 (1.0%)	0 (0%)	2 (0.7%)
Asian	117 (60.9%)	95 (100%)	212 (73.9%)
Other (incl multiple)	1 (0.5%)	0 (0%)	1 (0.3%)
Unknown	1 (0.5%)	0 (0%)	1 (0.3%)
Region			
Asian	113 (58.9%)	95 (100%)	208 (72.5%)
Non-Asian	79 (41.1%)	0 (0%)	79 (27.5%)
First dose (mg)			
200 mg	85 (44.3%)	0 (0%)	85 (29.6%)
300 mg	107 (55.7%)	95 (100%)	202 (70.4%)
ECOG PS			
ECOG-0	71 (37.0%)	28 (29.5%)	99 (34.5%)
ECOG-1	121 (63.0%)	65 (68.4%)	186 (64.8%)
ECOG-2	0 (0%)	1 (1.1%)	1 (0.3%)
Unknown	0 (0%)	1 (1.1%)	1 (0.3%)
Brain metastasis at baseline			

No	144 (75.0%)	64 (67.4%)	208 (72.5%)
Yes	48 (25.0%)	31 (32.6%)	79 (27.5%)
Tumor type and tumor genetics			
769_ASV	41 (21.4%)	37 (38.9%)	78 (27.2%)
770_SVD	43 (22.4%)	17 (17.9%)	60 (20.9%)
Other	98 (51.0%)	41 (43.2%)	139 (48.4%)
Unknown	10 (5.2%)	0 (0%)	10 (3.5%)

Source: Applicant Table. Module 5.3.3.5/ER Report/Table 23.

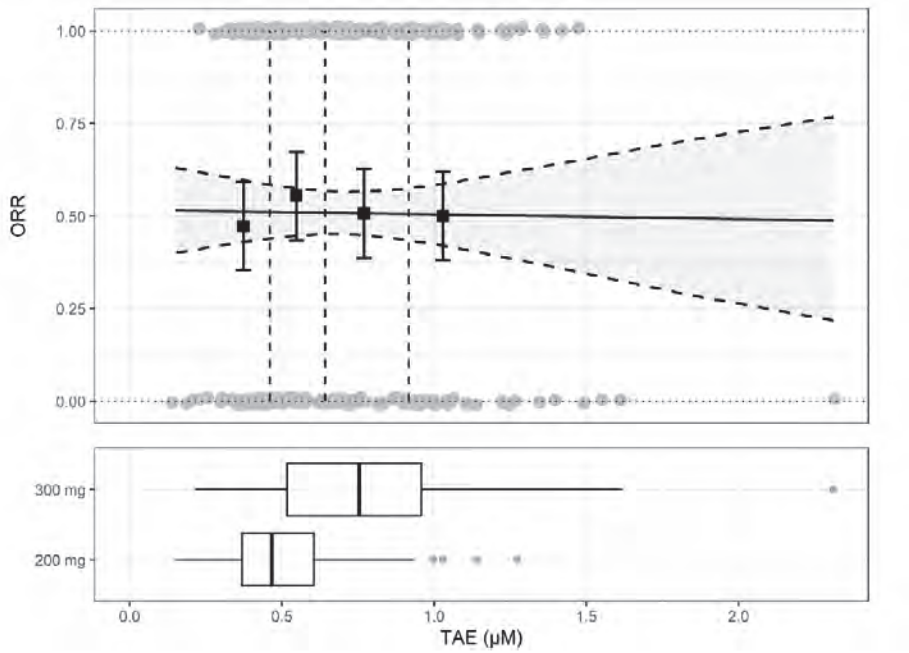
Table 7963 Covariant Distribution over TAE Quartiles for All Patients Included in the E-R Analysis of ORR (WU-KONG1B and WU-KONG6)

	Q1 (N=72)	Q2 (N=72)	Q3 (N=71)	Q4 (N=72)	Overall (N=287)
Age (yrs)					
Mean (SD)	61.1 (9.46)	63.7 (9.87)	60.7 (11.2)	58.8 (11.7)	61.1 (10.7)
Median [Min, Max]	60.5 [43.0, 85.0]	64.5 [38.0, 88.0]	61.0 [35.0, 83.0]	59.0 [29.0, 85.0]	61.0 [29.0, 88.0]
Body weight (kg)					
Mean (SD)	69.8 (13.9)	65.1 (14.0)	65.6 (12.4)	58.7 (12.1)	64.8 (13.7)
Median [Min, Max]	67.5 [46.0, 115]	63.0 [39.0, 118]	65.0 [38.0, 95.0]	56.5 [33.0, 84.0]	64.0 [33.0, 118]
BMI (kg/m^2)					
Mean (SD)	25.7 (3.98)	24.3 (3.94)	24.7 (4.08)	22.8 (3.98)	24.4 (4.10)
Median [Min, Max]	24.8 [18.0, 38.9]	24.4 [16.8, 39.4]	24.5 [15.4, 34.5]	22.5 [13.9, 35.0]	23.9 [13.9, 39.4]
Sex					
Male	27 (37.5%)	31 (43.1%)	29 (40.8%)	26 (36.1%)	113 (39.4%)
Female	45 (62.5%)	41 (56.9%)	42 (59.2%)	46 (63.9%)	174 (60.6%)
Race					
White	21 (29.2%)	23 (31.9%)	17 (23.9%)	10 (13.9%)	71 (24.7%)
Black or African American	0 (0%)	0 (0%)	1 (1.4%)	1 (1.4%)	2 (0.7%)
Asian	50 (69.4%)	49 (68.1%)	53 (74.6%)	60 (83.3%)	212 (73.9%)
Other (incl multiple)	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)	1 (0.3%)
Unknown	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Region					
Asian	49 (68.1%)	48 (66.7%)	52 (73.2%)	59 (81.9%)	208 (72.5%)
Non-Asian	23 (31.9%)	24 (33.3%)	19 (26.8%)	13 (18.1%)	79 (27.5%)
First dose (mg)					
200 mg	40 (55.6%)	26 (36.1%)	13 (18.3%)	6 (8.3%)	85 (29.6%)
300 mg	32 (44.4%)	46 (63.9%)	58 (81.7%)	66 (91.7%)	202 (70.4%)
ECOG PS					
ECOG=0	30 (41.7%)	30 (41.7%)	20 (28.2%)	19 (26.4%)	99 (34.5%)

ECOG≥1	42 (58.3%)	42 (58.3%)	51 (71.8%)	53 (73.6%)	188 (65.5%)
Brain metastasis at baseline					
No	56 (77.8%)	49 (68.1%)	53 (74.6%)	50 (69.4%)	208 (72.5%)
Yes	16 (22.2%)	23 (31.9%)	18 (25.4%)	22 (30.6%)	79 (27.5%)
Tumor type and tumor genetics					
769_ASV	15 (20.8%)	21 (29.2%)	19 (26.8%)	23 (31.9%)	78 (27.2%)
770_SVD	18 (25.0%)	18 (25.0%)	12 (16.9%)	12 (16.7%)	60 (20.9%)
Other	37 (51.4%)	31 (43.1%)	36 (50.7%)	35 (48.6%)	139 (48.4%)
Unknown	2 (2.8%)	2 (2.8%)	4 (5.6%)	2 (2.8%)	10 (3.5%)

BMI=body mass index; CV=coefficient of variation.
Source: Applicant Table. Module 5.3.3.5/ER Report/Table 24.

Figure 2121: Observed and Predicted ORR versus TAE in NSCLC Patients (WU-KONG1B and WU-KONG6)



Source: Applicant Figure. Module 5.3.3.5/ER Report/Figure 1.
Notes: Upper plot: The solid (dashed) curves show the model-predicted ORR (95% CI). The closed squares (error bars) show the observed ORR (95% CI based on the Pearson-Klopper method) for quartiles of TAE and are plotted at the median TAE of each quartile. The dashed vertical lines represent the quartile ranges. Gray circles indicate responders' and non-responders' TAE. Lower plot: boxplots showing the predicted TAE distribution by starting dose.
Abbreviations: CI=confidence interval, ORR=objective rate response, TAE=time-averaged exposure

19.4.2.3 E-R (safety) Assessment Summary

The Applicant's Position:

The exposure-safety analysis set comprised 463 NSCLC patients across the dose range of 50 mg to 400 mg QD. Higher exposure resulted in higher incidence of anemia and increased blood creatinine phosphokinase based on TAE, and anemia, grade 3 or higher diarrhea, and grade 3 or higher TEAE, and serious TEAE as

well as TEAE leading to dose discontinuation and modification based on AUCss. Increases in AE incidence predicted for increases in exposure corresponding to an increase in dose from 200 mg to 300 mg QD were not considered clinically meaningful.

Table 8064 Summary of Key Findings in E-R (Safety) Analysis

General Information			
Goal of ER analysis		Explore the exposure-response relationships between exposure of sunvozertinib and selected safety endpoints	
Study Included		WU-KONG1A, WU-KONG1B, WU-KONG2, and WU-KONG6	
Population Included		Patients with NSCLC	
Endpoint		Any grade or grade ≥ 3 diarrhea, rash, paronychia, anemia and increased blood creatinine phosphokinase, serious TEAE, TEAE leading to dose discontinuation or modification and TEAE with grade ≥ 3 were analyzed	
No. of Patients (total, and with individual PK)		463 all with PK data available	
Population Characteristics (Table)	General	Age median (range): 61 (29 - 96) years Weight median (range): 64 (30 - 118) kg male 195 (42.1%) female 268 (57.9%) Asian 353 (76.2%); white 102 (22.0%); Black 3 (0.6%); Other 3 (0.6%); Missing 2 (0.4%)	
	Organ impairment	Refer to Population PK analysis for organ impairment distributions	
	Pediatrics (if any)	Not Applicable	
	Geriatrics (if any)	Not Applicable	
Dose(s) Included		50 mg to 400 mg	
Exposure Metrics Explored (range)		Time-average exposure for concentration of sunvozertinib, up to the time of an event, or based on the period of dosing (i.e., until last dose) for participants not experiencing any event AUCss, steady state AUC corresponding to the initial dose of Sunvozertinib	
Covariates Evaluated		Race, sex, age, ECOG, Body size (body weight and BMI)	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Safety endpoints as binary endpoints were analyzed by logistic regression models based on the following equation: $\log\left(\frac{p_i}{1-p_i}\right) = \text{Intercept} + \text{Slope} \times \text{Exposure}_i + \beta_1 X_{i1} + \cdots + \beta_p X_{ip}$ pi is the probability of response (or adverse event (AE) for safety variables) for participant i, Intercept is the logit of the probability of response in the absence of DZD9008, Slope is the slope of the relationship between exposure and the logit of the probability of response, Exposure_i is	**Acceptable**

	the predicted exposure for participant i, β1 … βp is the vector of parameters for covariate effects, and Xi1 … Xip is the vector of covariate variables for participant i.	
Model Parameter Estimates	Check Module 5.3.3.5/E-R Report/Table 34 and Table 39 for details	Acceptable
Model Evaluation	For the endpoints with statistically significant relationship with exposures, the observed proportion are generally contained within the 95% CI of the model-predicted probabilities. Figure 22 and Figure 23	Acceptable
Covariates and Clinical Relevance	When using AUCss as exposure metric, age showed a significant effect on the E-R relationship for serious TEAE, TEAE leading to drug discontinuation, TEAE leading to dose modification, and TEAE with CTCAE grade 3 or higher, accounting for lower incidence in patients with lower ages. Race (Asian versus non-Asian) showed a significant effect on the E-R relationship for grade 3 or higher diarrhea, accounting for lower incidence in Asian Patients. However, as AUCss does not consider dose interruption or reduction, the effects of age and race should be interpreted with caution.	Acceptable
Simulation for Specific Population	Not Applicable	
Visualization of E-R relationships	Figure 22 and Figure 23	Acceptable
Overall Clinical Relevance for ER	For ≥ grade 3 anemia, increased CPK, and diarrhea, their predicted incidences are relatively low at both 200 mg and 300 mg (Table 48), and the incidence changes from 200 mg to 300 mg (8% to 11% for anemia, 12% to 15% for elevated blood CPK, and 7% to 9% for diarrhea) are of limited clinical significance. Although the predicted probabilities of TEAE with grade ≥ 3 is higher, relative differences between 200 mg and 300 mg may not be clinically meaningful.	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not Applicable	

Table 8165 Summary of Baseline Characteristics Stratified by Study in the E-R Safety Dataset

	WU-KONG1A (N=112)	WU-KONG1B (N=202)	WU-KONG2 (N=48)	WU-KONG6 (N=101)	Overall (N=463)
Age (yrs)					
Mean (SD)	61.1 (12.5)	62.9 (10.9)	55.5 (9.55)	57.3 (10.4)	60.5 (11.4)
Median [Min, Max]	61.5 [34.0, 96.0]	63.5 [35.0, 89.0]	55.0 [32.0, 82.0]	58.0 [29.0, 79.0]	61.0 [29.0, 96.0]
Body weight (kg)					
Mean (SD)	67.3 (15.6)	65.1 (14.6)	64.3 (13.7)	64.1 (11.7)	65.3 (14.2)
Median [Min, Max]	65.0 [39.0, 115]	64.0 [33.0, 118]	64.0 [30.0, 103]	64.5 [38.0, 91.0]	64.0 [30.0, 118]
BMI (kg/m2)					
Mean (SD)	25.1 (4.55)	24.4 (4.47)	23.7 (3.80)	24.1 (3.43)	24.5 (4.23)
Median [Min, Max]	24.6 [15.8, 40.3]	23.8 [13.9, 39.4]	23.1 [15.3, 32.1]	24.0 [17.2, 32.5]	24.1 [13.9, 40.3]
Missing	2 (1.8%)	1 (0.5%)	2 (4.2%)	1 (1.0%)	6 (1.3%)
Sex					
Male	51 (45.5%)	78 (38.6%)	23 (47.9%)	43 (42.6%)	195 (42.1%)
Female	61 (54.5%)	124 (61.4%)	25 (52.1%)	58 (57.4%)	268 (57.9%)
Race					
White	28 (25.0%)	74 (36.6%)	0 (0%)	0 (0%)	102 (22.0%)
Black or African American	1 (0.9%)	2 (1.0%)	0 (0%)	0 (0%)	3 (0.6%)
Asian	80 (71.4%)	124 (61.4%)	48 (100%)	101 (100%)	353 (76.2%)
Other (incl multiple)	2 (1.8%)	1 (0.5%)	0 (0%)	0 (0%)	3 (0.6%)
Missing	1 (0.9%)	1 (0.5%)	0 (0%)	0 (0%)	2 (0.4%)
First dose (mg)					
50 mg	3 (2.7%)	0 (0%)	3 (6.3%)	0 (0%)	6 (1.3%)
100 mg	6 (5.4%)	0 (0%)	3 (6.3%)	0 (0%)	9 (1.9%)
200 mg	26 (23.2%)	91 (45.0%)	3 (6.3%)	0 (0%)	120 (25.9%)
300 mg	71 (63.4%)	111 (55.0%)	25 (52.1%)	101 (100%)	308 (66.5%)
400 mg	6 (5.4%)	0 (0%)	14 (29.2%)	0 (0%)	20 (4.3%)
ECOG PS					
ECOG-0	47 (42.0%)	73 (36.1%)	13 (27.1%)	30 (29.7%)	163 (35.2%)
ECOG-1	65 (58.0%)	129 (63.9%)	34 (70.8%)	69 (68.3%)	297 (64.1%)
ECOG-2	0 (0%)	0 (0%)	1 (2.1%)	1 (1.0%)	2 (0.4%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (1.0%)	1 (0.2%)

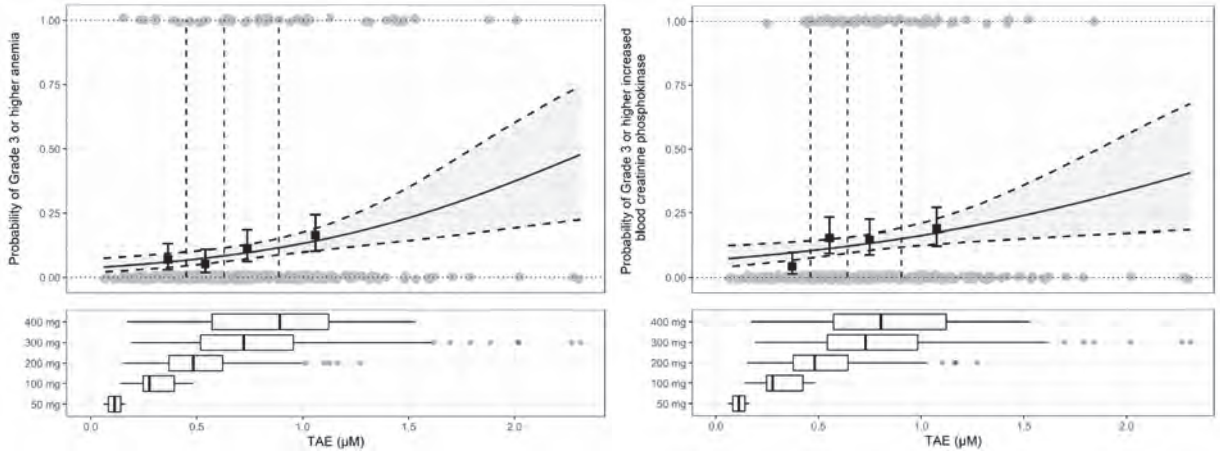
Source: Applicant Table. Module 5.3.3.5/E-R Report/Table 25.

Table 8266 Covariate Distribution over AUC_{ss} Quartiles for All Patients Included in the E-R Safety Analysis

	Q1 (N=116)	Q2 (N=116)	Q3 (N=115)	Q4(N=116)	Overall (N=463)
Age (yrs)					
Mean (SD)	59.1 (10.7)	60.3 (10.6)	62.1 (12.0)	60.4 (12.1)	60.5 (11.4)
Median [Min, Max]	59.0 [32.0, 85.0]	61.0 [35.0, 82.0]	64.0 [34.0, 88.0]	61.0 [29.0, 96.0]	61.0 [29.0, 96.0]
Body weight (kg)					
Mean (SD)	70.1 (15.8)	68.1 (14.1)	62.9 (12.0)	60.2 (12.4)	65.3 (14.2)
Median [Min, Max]	69.5 [39.0, 118]	66.0 [44.0, 115]	62.0 [33.0, 95.0]	59.3 [30.0, 90.0]	64.0 [30.0, 118]
BMI (kg/m^2)					
Mean (SD)	25.7 (4.30)	25.4 (4.27)	23.6 (3.57)	23.2 (4.18)	24.5 (4.23)
Median [Min, Max]	25.2 [18.0, 39.4]	24.7 [17.9, 40.3]	23.4 [13.9, 33.3]	22.9 [13.9, 35.0]	24.1 [13.9, 40.3]
Missing	2 (1.7%)	0 (0%)	3 (2.6%)	1 (0.9%)	6 (1.3%)
Sex					
Male	50 (43.1%)	51 (44.0%)	45 (39.1%)	49 (42.2%)	195 (42.1%)
Female	66 (56.9%)	65 (56.0%)	70 (60.9%)	67 (57.8%)	268 (57.9%)
Race					
White	28 (24.1%)	32 (27.6%)	27 (23.5%)	15 (12.9%)	102 (22.0%)
Black or African American	0 (0%)	0 (0%)	1 (0.9%)	2 (1.7%)	3 (0.6%)
Asian	87 (75.0%)	83 (71.6%)	85 (73.9%)	98 (84.5%)	353 (76.2%)
Other (incl multiple)	0 (0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	3 (0.6%)
unknown	1 (0.9%)	0 (0%)	1 (0.9%)	0 (0%)	2 (0.4%)
First dose (mg)					
50 mg	6 (5.2%)	0 (0%)	0 (0%)	0 (0%)	6 (1.3%)
100 mg	8 (6.9%)	1 (0.9%)	0 (0%)	0 (0%)	9 (1.9%)
200 mg	64 (55.2%)	30 (25.9%)	20 (17.4%)	6 (5.2%)	120 (25.9%)
300 mg	37 (31.9%)	81 (69.8%)	92 (80.0%)	98 (84.5%)	308 (66.5%)
400 mg	1 (0.9%)	4 (3.4%)	3 (2.6%)	12 (10.3%)	20 (4.3%)
ECOG PS					
ECOG-0	56 (48.3%)	40 (34.5%)	41 (35.7%)	26 (22.4%)	163 (35.2%)
ECOG-1	59 (50.9%)	76 (65.5%)	73 (63.5%)	89 (76.7%)	297 (64.1%)
ECOG-2	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)	2 (0.4%)
Missing	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.2%)

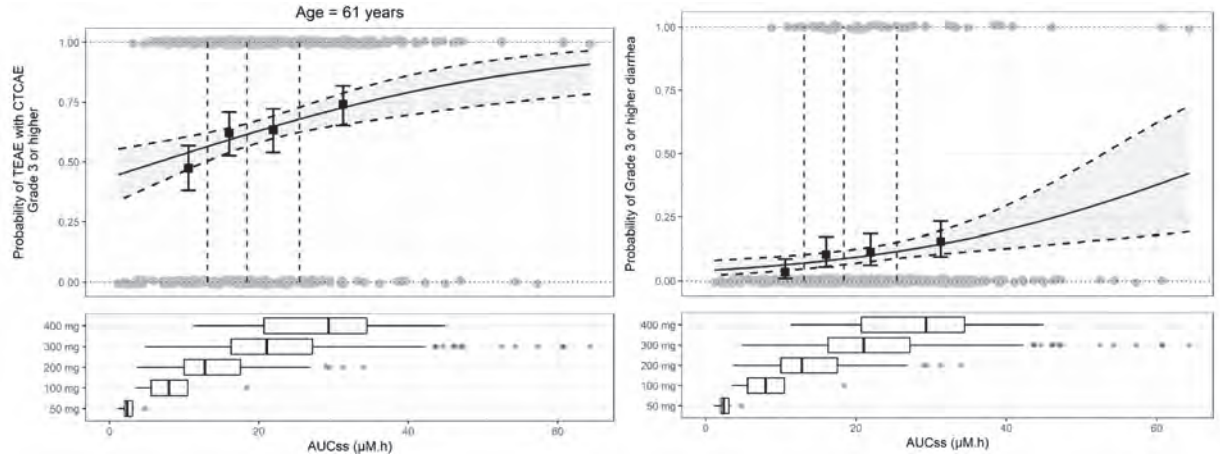
Source: Applicant Table. Module 5.3.3.5/E-R Report/Table 26.

Figure 2222: E-R Curves of Anemia with Grade ≥ 3 and Blood CPK Increased with Grade ≥ 3 versus Time-averaged Exposure in NSCLC Patients



Source: Applicant Figure. Module 5.3.3.5/E-R Report/Figure 3 and Figure 5.

Figure 2323: E-R Curves of TEAE with Grade ≥ 3 or Diarrhea with Grade ≥ 3 versus AUCss in NSCLC Patients



Source: Applicant Figure. Module 5.3.3.5/E-R Report/Figure 40 and Figure 32.

Table 8367: Predicted Probability (95% CI) for Significant AEs at Dose Regimens of 200 mg QD and 300 mg QD

Endpoint	Exposure Metrics	Predicted probability for 200 mg QD (95% CI)	Predicted probability for 300 mg QD (95% CI)
TEAE with grade ≥ 3	AUCss	0.569 (0.509, 0.625)	0.633 (0.584, 0.677)
Anemia with grade ≥ 3	TAE	0.0770 (0.0547, 0.108)	0.110 (0.0832, 0.144)
Blood CPK increased with grade ≥ 3	TAE	0.115 (0.0866, 0.151)	0.145 (0.114, 0.183)
Diarrhea with grade ≥ 3	AUCss	0.0717 (0.0489, 0.104)	0.0945 (0.0706, 0.126)

Source: Applicant Table. Module 5.3.3.5/E-R Report/Table 60, Table 9, Table 11 and Table 47.

19.4.2.4 Reviewer's Independent Analysis

E-R (Efficacy) Analyses

The objective of the E-R for efficacy analysis was to explore the exposure-response relationship between exposure of DZD9008 and ORR, using data from NSCLC patients with EGFR exon20ins in WU-KONG1B and WU-KONG6 (main analysis), with a sensitivity analysis based solely on WU-KONG1B.

Time-averaged exposure (TAE) of DZD9008 was used as the exposure metric. Logistic regression analysis showed no statistically significant association between TAE and ORR in either the main or sensitivity analysis (**FDA Table 84**, **Figure 24)**.

FDA Table 8468: Exposure Response Analysis for Efficacy Data

Study (N)	Objective Response Rate N (%)
WU-KONG1B (192)	88 (45.8)
WU-KONG6 (95)	56 (61.1)
Total (287)	146 (50.9)

N =number of subjects (% of total).

Source: Reviewer's Analysis

Sub-group E-R Efficacy Analysis

During the review, additional subgroup E-R efficacy analyses were conducted (b) (4)

(FDA Table 85).

These analyses used data from 174 patients randomized to 200 mg (N=85) or 300 mg (N=89) QD in WU-KONG1 Part B. Subgroups included the overall cohort, non-Asian patients, patients enrolled outside Asia, those with baseline brain metastases, and those previously treated with amivantamab. The selected subgroups were consistent with those in dose-efficacy analysis of 200 mg and 300 mg cohorts.

- E-R Analysis of ORR in Patients with Brain Metastases:

The distribution of TAE stratified by objective response status in patients with baseline brain metastases suggests a slight trend toward higher exposure in responders (**FDA Figure 24)**. Although a positive trend between exposure and tumor response was observed in this subgroup (**FDA Figure 25**), the effect of TAE on ORR was not statistically significant based on the likelihood ratio test (P = 0.307).

- E-R Analysis of ORR in Amivantamab-experienced Patients:

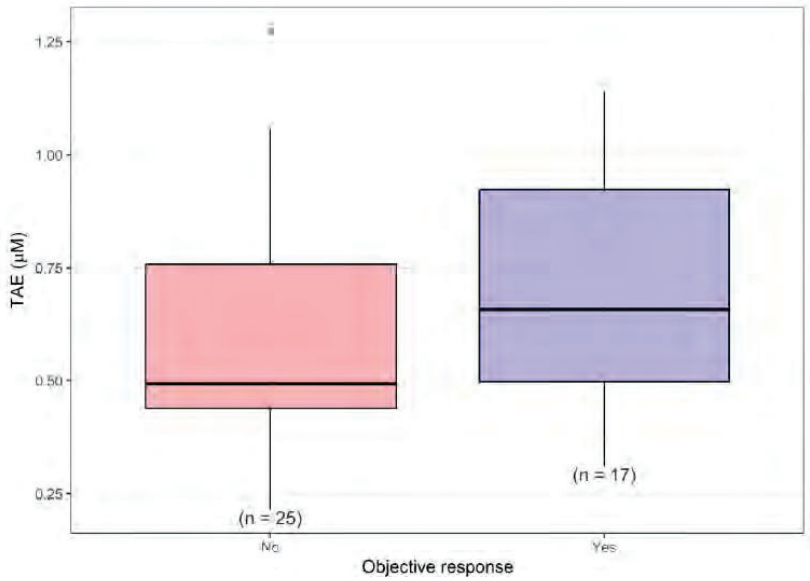
As shown in **FDA Figure 26**, the distribution of TAE stratified by objective response status in patients previously treated with amivantamab indicates higher exposure in patients with objective response. The effect of TAE on ORR was statistically significant based on the likelihood ratio test (P=0.017). Covariate evaluation revealed no statistically significant covariate effects on the E-R relationship after accounting for TAE. **FDA Figure 27** presents the observed and model-predicted ORR for patients previously treated with amivantamab in WU-KONG1B.

FDA Table 8569: Summary of ORR in Patients Randomized to 200 mg and 300 mg in WU-KONG1B

Study (N)	Objective Response Rate N (%)
200 mg-Rand (n=85)	39 (45.9%)
300 mg-Rand (n=89)	42 (47.2%)
Total (n=174)	81 (46.6%)

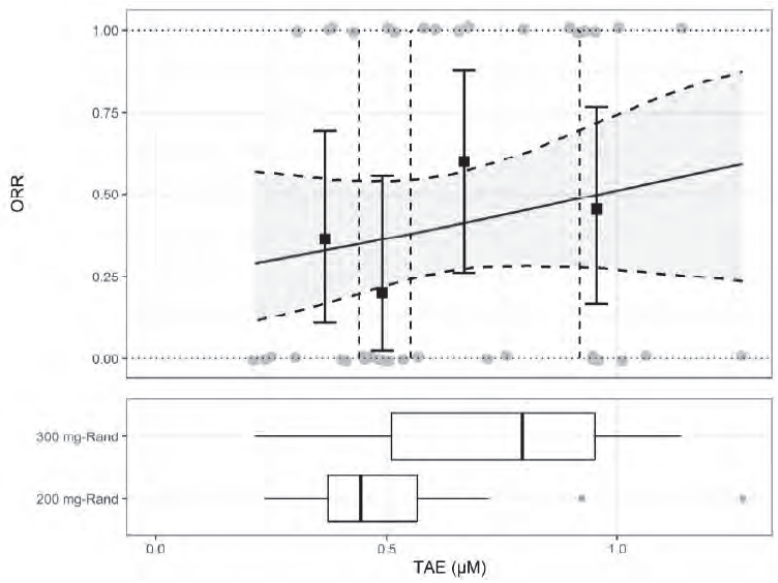
N =number of patients (% of total).
Source: Reviewer's Analysis

FDA Figure 2424: Boxplots Showing TAE Distribution by Response in Patients with Brain in WU-KONG1B



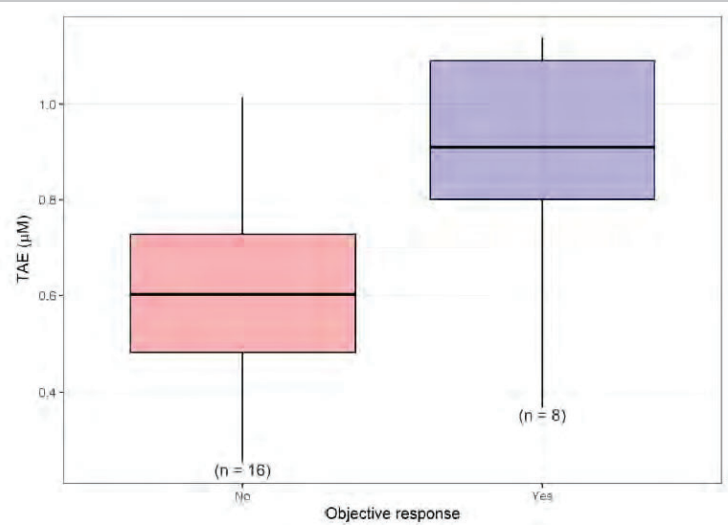
Source: Reviewer's Analysis

FDA Figure 2525: Observed Proportion and Predicted Probability of ORR Versus Time averaged Exposure for Patients with Brain Metastases



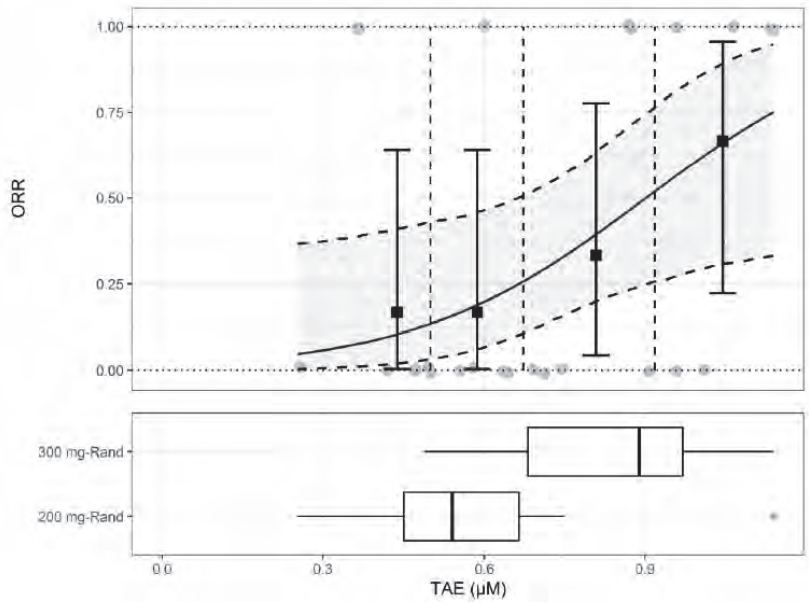
Source: Reviewer's Analysis

FDA Figure 2626: Boxplots Showing TAE Distribution by Response in Patients Previously Treated with Amivantamab in WU-KONG1B



Source: Reviewer's Analysis

FDA Figure 2727: Observed Proportion and Predicted Probability of ORR Versus TAE for Patients Previously Treated with Amivantamab



Source: Reviewer's Analysis

Reviewer's comments:

1. *The Sponsor's exposure-response analyses are generally acceptable. The E-R models developed for the efficacy endpoints of ORR are reproducible, and the conclusions are reasonable.*

2. *No statistically significant relationship was identified between TAE and ORR in the overall population treated with sunvozertinib at 200 mg or 300 mg QD, based on logistic regression analysis. This finding held true in both the primary analysis (WU-KONG1B and WU-KONG6) and the sensitivity analysis (WU-KONG1B).*

3. *Subgroup analyses* (b) (4) *However, given the limited sample size, these findings remain inconclusive.*

E-R (Safety) Analyses:

The objectives of this analysis were to evaluate the exposure-response relationship between exposure of DZD9008 and selected safety endpoints based on data from Studies WU-KONG1 (Part A and Part B), WU-KONG2 and WU-KONG6 (**FDA Table 86**).

FDA Table 8670: Exposure Response Analysis for Safety Data

Study Number/Phase	Population	Dose/Formulation	Analysis
WU-KONG1A (DZ2019E0001) (Phase 1)	NSCLC patients	50, 100, 200, 300 and 400 mg QD, tablets, oral	Exposure-Response of Safety
WU-KONG1B (DZ2019E0001) (Phase 2)	NSCLC patients	200 mg/300 mg QD, tablets, oral	Exposure-Response of Safety and Efficacy
WU-KONG2, DZ2019E0002 (Phase 1)	NSCLC patients	50, 100, 200, 300, and 400 mg QD, tablets, oral	Exposure-Response of Safety
WU-KONG6, DZ2020E0001 (Phase 2)	NSCLC patients	300 mg QD, tablets, oral	Exposure-Response of Safety and sensitivity analysis of Efficacy

NSCLC=non-small cell lung cancer; QD=once daily.

Time-averaged exposure (TAE) and steady-state area under the DZD9008 concentration-time curve (AUCss) for the concentration of DZD9008 (TAE) were evaluated as exposure metric in the safety E-R analyses.

Univariate logistic regression was used to assess the relationship between these exposure metrics and treatment-emergent adverse events (TEAEs). When exposure was a statistically significant predictor of response ($P < 0.05$, log-likelihood ratio test), further covariate analysis was conducted.

As a result, in addition to grade ⩾ 3 TEAEs, any grade anemia or blood creatine phosphokinase (CPK) increased were significantly related to TAE; Serious TEAE, TEAE leading to dose continuation, and TEAE leading to dose modification had a statistically significant relationship with AUCss.

No statistically significant relationship was identified with TAE or AUCss for any grade paronychia, and any grade and ⩾ grade 3 rash. Notably, apart from ⩾ Grade 3 diarrhea (predicted by AUCss), no significant E-R relationships were found for other EGFR-related adverse events such as rash and paronychia.

Reviewer's Comments:

1. *The Sponsor's exposure-response analyses for safety appear acceptable. The ER models developed for the safety endpoints are reproducible, and the conclusions drawn are generally reasonable.*

2. *Across the 50 to 400 mg dose range, a positive exposure-safety relationship was observed between the exposure indicator TAE and a higher incidence of anemia and increased blood CPK. Additionally, anemia, ≥ Grade 3 diarrhea, ≥ Grade 3 TEAEs, serious TEAEs, and TEAEs leading to dose discontinuation or modification were significantly associated with AUCss. These findings are consistent with the overall clinical safety profile.*

3. *Notably, while these exposure-safety relationships were identified across the broader dose range (50–400 mg), only a modest and shallow increase in the incidence of these TEAEs was observed within the clinically relevant 200–300 mg range.*

4. *In conclusion, the E-R analyses findings are consistent with the clinical observations and support the 200 mg QD is an effective dosage with acceptable safety profiles.*

19.4.3 Physiologically Based Pharmacokinetic Modelling Analyses

The FDA's Assessment:

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's Physiologically based Pharmacokinetic (PBPK) modeling analyses to predict the following:

DDI effect of moderate CYP3A4 inhibitors on the exposure of sunvozertinib

DDI effect of moderate CYP3A4 inducers on the exposure of sunvozertinib

DDI potential of sunvozertinib on the exposure of a CYP2D6 substrate

The Division of Pharmacometrics has reviewed the PBPK submission: Reports ASAT/7/B, ASAT/7/C, and AST/7/D and associated modeling and simulation files, and response to FDA's request for information dated March 13, 2025. The reviewer concluded the following:

PBPK analyses were adequate to predict the interaction effect of CYP3A modulators on sunvozertinib exposure at steady state. Coadministration of a moderate CYP3A inhibitor increased sunvozertinib AUCtau by 1.3-fold. Coadministration of a moderate CYP3A inducer decreased sunvozertinib AUCtau by approximately 44%; while a weak CYP3A inducer had not interaction effect on sunvozertinib PK.

Sunvozertinib predicted to have no to weak inhibitory effect on the PK of CYP2D6 substrates.

Methods

Sunvozertinib PBPK Model

The PBPK analyses were performed using the software Simcyp®.

The absorption and distribution of sunvozertinib were described using a mechanistic absorption model (Simcyp Advanced Dissolution, Absorption and Metabolism (ADAM) model) and a minimal PBPK model with single-adjustment compartment (SAC), respectively.

The fraction of sunvozertinib absorbed (fa) was estimated from in vitro solubility, dissolution and permeability data. Sunvozertinib exhibited pH-dependent solubility. In vitro dissolution profile for the tablet formulation in buffers at different pH values were used to describe both the fasted (pH 1.2) and fed (pH 4.5) profiles and used as model input parameters, without additional fitting.

Food had limited impact on oral bioavailability of sunvozertinib in healthy subjects. The AUCinf and Cmax increased by 21% and 16%, respectively, when sunvozertinib was given with a low-fat meal. However, food decreased GI adverse effects, thus, sunvozertinib is proposed to be taken with food.

The human mass balance study (DZ2021E0003) showed that 10.3% and 78.6% of sunvozertinib dose was excreted in urine and feces, respectively, with 5.6% and 7.3% of the dose as unchanged drug, respectively.

Two major plasma metabolites of sunvozertinib, DZ0753 (10.3%) and the cysteine conjugate M704 (12.2%), were identified (Report DZP/24). The formation of DZ0753 was completely inhibited by ketoconazole in vitro, suggesting CYP3A-mediated formation. Formation of metabolite M704 (M4) was not inhibited by ketoconazole (Report DZP/25).

In vitro phenotyping study indicated that CYP3A4/5 was the main CYP isoform responsible for sunvozertinib metabolism (Report ADME-DIH-180802-CYP Phenotyping). In vitro hepatocyte inhibition data and clinical DDI data with itraconazole were used to assign the relative contribution of CYP3A4 to the clearance of sunvozertinib. In human hepatocytes, the metabolism of sunvozertinib was inhibited by ketoconazole, with an estimated relative contribution of CYP3A (fmCYP3A) by 38.8% (Report DZP/25). If assuming the clinical CYP3A inhibition of sunvozertinib by itraconazole was complete and with negligible gut metabolism, the vivo fmCYP3A4 could be calculated as 33.7% based on this DDI data (Study DZ2021E0008). A mean fmCYP3A4 value of 36%, calculated from both in vitro and in vivo estimates of fmCYP3A4, was used in the model. Sunvozertinib elimination by glutathione conjugation was accounted for in the 'additional hepatic intrinsic clearance' (Report DZP/24).

In vitro study demonstrated that sunvozertinib was a reversible inhibitor of CYP2D6 (IC50=6.30 μM and CYP3A4 (IC50 = 18.2-21.1 μM). The CYP2D6 and CYP3A4 IC50 values were adjusted to Ki values of 3.2 μM and 9.1 μM, respectively, using the Cheng-Prusoff equation and used as model input parameters (Report ADME-DIH-180802-CYP Inhibition). The correction for unbound Ki was done using the measured unbound fraction in in vitro incubation (fumic=0.53, Report ADME-AZH-171115-Human Mic Fu). Two In vitro studies demonstrated that sunvozertinib was not a time-dependent inhibitor of CYP3A (Reports (b) (4) 205087, ADME-DIH-CYP KI/kinact, ADME-DIH-180802-CYP TDI) and CYP2D6 (Reports (b) (4) 225091 and ADME-DIH-180802-CYP TDI). The clinical DDI study (DZ2021E0009) with the sensitive CYP3A4

substrate midazolam demonstrated mild induction effect of sunvozertinib 300 mg (22% reduction in midazolam AUCinf). Thus, no CYP3A4 induction parameters of sunvozertinib was incorporated into the model given its modest in vivo effect and to lessen any potential impact of induction on the predicted CYP3A4 DDI risk with CYP3A modulators.

In vitro, sunvozertinib at 5 μM was determined to be a P-gp substrate (Report ADME-DIH-180802-P-gp Substrate). However, this pathway was not accounted for in the model because the active efflux transport of sunvozertinib by P-gp is anticipated to be minor due to the following reasons:

PK linearity was observed from 50 mg to 400 mg single dose, in both healthy subjects and cancer patients (Study DZ2021E0004, Part A and pooled analysis of Clinical Studies DZ2019E0001 and DZ2019E0002).

In vitro data suggested that sunvozertinib P-gp efflux is anticipated to be saturated at the therapeutic doses.

Mass balance data suggested that sunvozertinib is highly absorbed (<10% unchanged in feces in the human ADME Study DZ2021E0003, Reports 194/004 and 194/005).

Intestinal and/or hepatic P-gp mediated DDIs appeared minor based upon the weak DDI effect observed with itraconazole (dual CYP3A4 and P-gp inhibitor).

The input parameters for sunvozertinib PBPK model are listed in Table 75.

Table 8771. Input parameters for sunvozertinib PBPK model

PARAMETER	Value	Reference
Physicochemical and Binding Parameters		
Molecular Weight (g/mol)	584.09	Report (b) (4)-DIZA-18-4-10
Log P	4.25	Calculated from Log D (3.28), Report (b) (4)-DIZA-18-4-10
Compound type	Diprotic base	Report (b) (4)-DIZA-18-4-10
pKa	6.08, 8.30	
B:P	0.695	Report ADME-DIH-201112-1-Blood Partition
fu	Concentration dependent: 0.0653 – 0.110	Report ADME-DIH-180802-PPB
Main binding protein	AAG	Report ADME-DIH-180802-PPB
Absorption Model – ADAM Model		
fu_{gut}	1	Default
MDCKII P_{app} ($x10^{-6}$ cm/s)	7.56	Report ADME-DIH-180802-P-gp Substrate
Calibrator P_{app} ($x10^{-6}$ cm/s) propranolol	39.4	
$P_{eff,man}$ (pred) ($x10^{-4}$ cm/s)	0.526	Simcyp
Formulation type	Immediate Release	
Dissolution profiles Fasted stomach Fed stomach Small intestine	 pH 1.2 profile pH 4.5 profile pH 6.8 profile	DZD9008 Tablet 300mg Dissolution Results in different dissolution medium.xlsx
Distribution Model – Minimal PBPK Model		
V_{ss} (L/kg)	16.2	Phoenix modelling of Clinical Study DZ2021E0004, part B fasted data (Reference Appendix A, Section 8 from Report AST/7/D)
Q_{int} (L/h)	21.5	
V_{int} (L/kg)	8.47	
Elimination Parameters		
CL/F (L/h)	55.7	Clinical Study DZ2021E0004, part B fasted
fm_{CYP3A4}	0.36	Median of estimated *in vitro* and *in vivo* value
CYP3A4 CL_{int} (µL/min/pmol)	0.418	Retrograde model. CL/F= 55.7 L/h; fm CYP3A4= 36%, CL_R= 1.33 L/h, fa= 0.8, F_H= 0.8
Additional HLM CL_{int} (µL/min/mg)	92.5	
CL_R (L/h)	1.33	Clinical Study DZ2019E0001
Interaction Parameters		
CYP2D6 K_i (µM)	3.2	Calculated from IC_{50} using Cheng-Prusoff equation, Report ADME-DIH-180802-CYP Inhibition
CYP3A4 K_i (µM)	9.1	Calculated from nifedipine IC_{50} using Cheng-Prusoff equation, Report ADME-DIH-180802-CYP Inhibition
fu_{mic} @ 0.2 mg/mL, measured	0.530	Report ADME-AZH-171115-Human Mic Fu
P-gp K_i (µM)	8.6	From IC_{50} using Cheng-Prusoff equation, Report ADME-DIH-180802-P-gp Inhibition
fu_{inc}	1	Assumed

(Source: Response to FDA's Information Request).

The default population models for healthy volunteers (Sim-NEurCaucasian) and patients with cancer (Sim-Cancer) were used in the simulations. The CYP abundance values for the Sim-Cancer population are the same as those used in the Sim-NEurCaucasian population.

Model Verification

The exposure of sunvozertinib in healthy volunteers (HVs) after fasted single dosing was verified using PK data from Study DZ2021E0004, parts A and C.

Single and multiple fasted dosing in cancer patients was verified using PK data from Study DZ2019E0001.

Fed dosing in cancer patients was verified using the food effect data from Study DZ2019E0001.

Multiple dosing in cancer patients was verified using Clinical Study DZ2019E0001.

The key input parameter fmCYP3A was verified using clinical DDI data from Study DZ2019E0008 in healthy volunteers (US based study).

Model Application

Prediction of PK change of sunvozertinib in cancer patients following repeat oral doses of 200 mg QD and 300 mg QD for 18 days administered in the absence of fluconazole and following 18 days dosing with fluconazole 200 mg QD, under fed conditions.

Prediction of PK change of sunvozertinib in cancer patients following repeat oral doses of 200 mg QD and 300 mg QD for 18 days administered in the absence of efavirenz and following 15 days dosing with efavirenz 600 mg QD on day 4, under fed conditions.

Prediction of PK change of sunvozertinib in cancer patients following repeat oral doses of 200 mg QD and 300 mg QD for 18 days administered in the absence of dexamethasone and following 14 days dosing with dexamethasone 8 mg QD, under fed conditions.

Prediction of PK change of desipramine in extensive metabolizers of CYP2D6 in patients with cancer, following a single dose of 50 mg in the absence of sunvozertinib and following 18 days dosing with sunvozertinib 200 mg QD.

Results

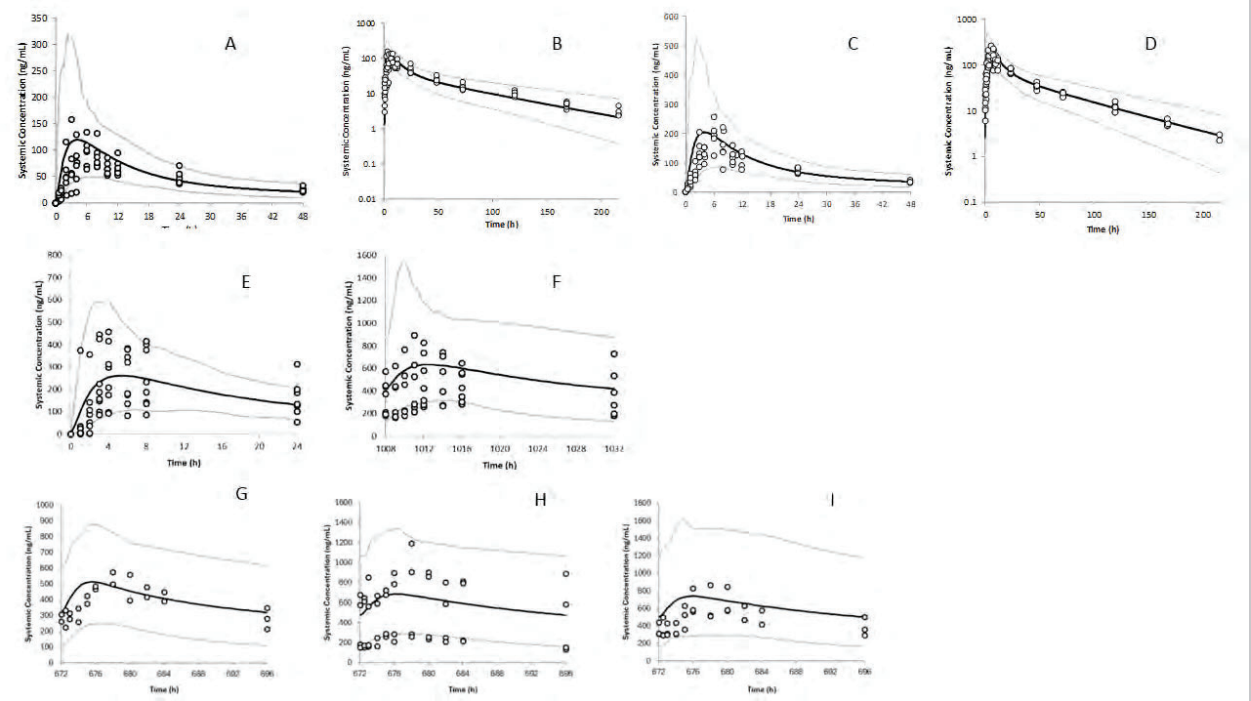
Predictive performance of PBPK model to describe sunvozertinib PK

The PBPK model of sunvozertinib reasonably predict the observed PK in healthy subjects following oral administration of single doses of 100, 200, 300 and 400 mg, under fasted and fed conditions (Study DZ2021E0004, parts A, B, C and D). Most of the predictions for AUCinf and Cmax had a prediction error ≤±25%, and all predictions had a PE value ≤±50% (Table 2). The predicted median Tmax was around 6 hours (min-max= 1.25 -11 hours) compared to observed median value of 6 hours (min-max= 6-8 hours). The predicted mean half-life for the 300 mg dose was 43.8 hours compared to observed mean value of 45.5 hours (PE=-4%).

Following administration of multiple doses of sunvozertinib 300 mg, under fed conditions to patients with cancer (Study DZ2020E0001), the predicted AUC and Cmax values on Days 1 and 44 had PE values ≤±25%. The predicted mean Ctrough was 419 ng/mL compared to observed mean value of 422 ng/mL hours (PE=-1%) (Table 2).

Overall, the percent prediction errors (%PE) for AUC and Cmax in healthy volunteers and cancer patients were ≤ ±63% across the dose range simulated (100 to 400 mg), except for the AUCinf from the 400 mg group in the Study DZ2019E0001, SAD in cancer patients (PE=137%) (Table 77. A comparison of the predicted versus observed plasma concentration-time profiles of sunvozertinib, following single and multiple oral dosing, is shown in Figure 28.

Figure 2828: Predicted and observed plasma concentration-time profiles of sunvozertinib



Linear (A,C) and log-linear (B,D) predicted (lines) and observed (circles; n = 6; Clinical Study DZ2021E0004, part A) plasma concentration-time profiles of sunvozertinib following a single 200 mg (A,B) and 300 mg (C,D) doses to healthy subjects under fasted conditions. Black line: mean for the predicted population (N = 60); grey lines: 5th-95th percentiles (n=6 per trial, 10 trials in total). (Source: simulation output files "3-dev-dzd9008-200mg-sd-dz0753" and "4-dev-dzd9008- 300mg-sd-dz0753").

(E, F) Predicted and observed plasma concentration-time profiles of sunvozertinib following 300 mg QD on Day 1 (E) and Day 44 (F) in cancer patients, under fed conditions. Predicted (lines) and observed (circles; n = 8; Clinical Study DZ2021E0001). Black line: mean for the predicted population (N = 80); grey lines: 5th-95th percentiles (n=8 per trial, 10 trials in total) (Source: simulation output file 10-ver-dzd9008-300mg-qd-dz0753-2020e0001-cancer).

(G, H, I) Predicted and observed plasma concentration-time profiles of multiple oral doses of 200 mg (G), 300 mg (H) and 400 mg QD (I) on Day 29 in cancer patients. Predicted (lines) and observed (circles; n = 3-7; Clinical Study DZ2019E0001, MAD). Black line: mean for the predicted population (N = 30-70); grey lines: 5th-95th percentiles (Source: Figure 8 of Response to FDA's IR).

Table 8872: Predicted and observed PK parameters of sunvozertinib following single and multiple doses

Sunvozertinib Dosage [Study], population	Cmax (ng/mL)			AUC (h.ng/mL)		
	Obs	Pred	%PE	Obs	Pred	%PE
100 mg SD [E0004, part C], HV	43.3	51.9	20	2512	2059	-18
100 mg SD [E0004, part A], HV	43.6	62.1	42	1990	2001	1
200 mg SD [E0004, part A], HV	96.7	117	21	4110	3751	-9
300 mg SD [E0004, part A], HV	191	199	4	5920	6083	3
400 mg SD [E0004, part A], HV	313	252	-19	10600	8407	-21
300 mg SD [E0004, part B], HV, fasted	158	168	7	5387	5726	6
300 mg SD [E0004, part B], HV, fed, low fat	183	173	-5	6531	5981	-8
300 mg SD [E0004, part D], HV, fasted	188	157	-16	6880	5785	-16
300 mg SD [E0004, part D], HV, fed high fat	208	162	-22	7470	6045	-19
300 mg SD [DZ2019E0001, FE] cancer, fasted	292	249	-15	10033	16386	63
300 mg SD [DZ2019E0001, FE] cancer, high fat	332	251	-24	12690	16800	32
200 mg QD [DZ2019E0001, SAD] cancer	257	202	-21	10021	9935	-1
300 mg QD [DZ2019E0001, SAD] cancer	461	258	-44	14544	15211	5
400 mg QD [DZ2019E0001, SAD] cancer	206	280	36	7290	17306	137
200 mg QD [DZ2019E0001, MAD] cancer	451	476	6	8190	8736	7
300 mg QD [DZ2019E0001, MAD] cancer	545	621	14	9690	12056	24
400 mg QD [DZ2019E0001, MAD] cancer	677	649	-4	12347	12643	2
300 mg QD Day 1 [DZ2020E0001] cancer, fed	261	255	-2	4241	4199	-1
300 mg QD Day 44 [DZ2020 E0001] cancer, fed	513	594	16	10111	11324	12

PK parameters are geometric mean values. AUC values represent: AUCinf for single dose (SD), AUCtau for multiple once daily (QD) dosing. %PE: = [(predicted value – observed value)/observed value] x 100 (Source: Table 9 of Report AST/7/C, and Response to FDA's IR dated March 13, 2025).

Predictive performance of sunvozertinib PBPK model to recover the DDI data with strong CYP3A modulators

The relative contribution of the CYP3A4 pathway to the total clearance of sunvozertinib (fmCYP3A4) was derived from in vitro inhibition study with ketoconazole. An estimated fmCYP3A4 value of 38.8% was calculated (Report DZP/25). Based on the clinical DDI data with the strong CYP3A inhibitor itraconazole, an estimated fmCYP3A value of 33.7% was estimated. A mean fmCYP3A4 value of 36% was used in the sunvozertinib PBPK model.

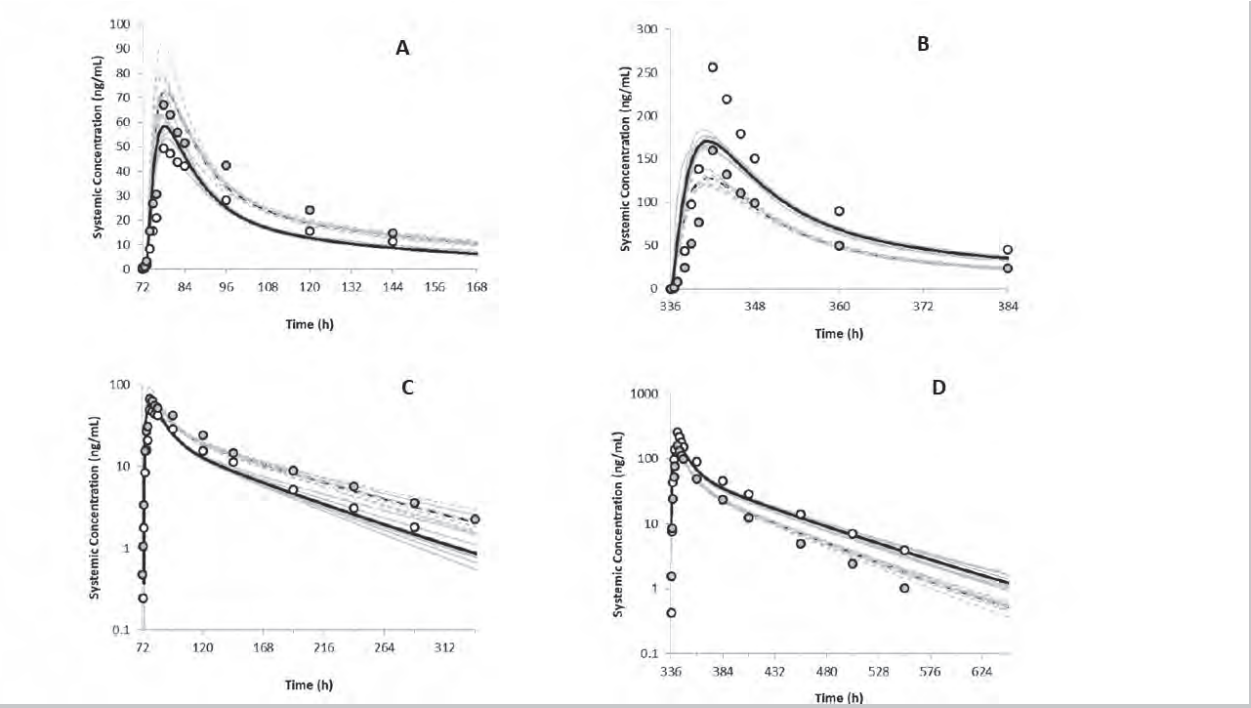
The fmCYP3A4 value was evaluated using the clinical DDI data with itraconazole and the strong CYP3A inducer carbamazepine. The predicted and observed AUCinf and Cmax values and corresponding geometric mean ratios (GMRs) for sunvozertinib in the absence and presence of itraconazole or carbamazepine are listed in Table 78. A comparison of predicted and observed PK profiles of sunvozertinib in both arms of the clinical DDI study is illustrated in Figure 29.

Table 8973. Predicted and observed Cmax and AUC values of sunvozertinib the absence and presence of strong CYP3A modulators

DDI Scenario	Cmax (ng/mL)		AUCinf (h.ng/mL)		Cmax ratio (90%CI)		AUCinf ratio (90%CI)	
	Obs	Pred	Obs	Pred	Obs	Pred	Obs	Pred
Strong CYP3A inhibitor								
sunvozertinib 100 mg SD	51.0	56.8	2420	2103	1.32 (1.21-1.43)	1.24	1.51 (1.45-1.57)	1.51
+ itraconazole (200 mg QD)	67.2	70.5	3650	3172				
Strong CYP3A inducer								
sunvozertinib 300 mg SD	248	167	7390	5971	0.62 (0.57-0.68)	0.76	0.52 (0.48-0.56)	0.68
+ carbamazepine (300 mg BID)	155	127	3850	4084				

PK data are geometric means. Cmax and AUC ratios are expressed as with/without modulator. Observed: Study DZ2021E0008 parts A and B (Source: CSR DZ2021E0008 and simulation output files of the report AST/7/C).

Figure 2929.: Predicted and observed plasma PK profiles of sunvozertinib co-administered with strong CYP3A modulators



Linear (A) and log-linear (B) predicted (lines) and observed (circles; n = 19; Clinical Study DZ2021E0008 part A plasma concentration-time profiles of sunvozertinib following a single 100 mg dose in the absence of itraconazole (solid line) and on the 4th day of 14 days of dosing of itraconazole 200 mg QD (dashed line) to healthy subjects under low fat fed conditions. The grey lines represent mean values of simulated individual trial and the black lines portray the mean data of the simulated population (n = 190) (Source: Figures 7 of the report AST/7/C).

Linear (C) and log-linear (D) predicted (lines) and observed (circles; n = 20; Clinical Study DZ2021E0008 part B) plasma concentration-time profiles of DZD9008 following a single 300 mg dose of sunvozertinib in the absence of carbamazepine (solid line, open circles) and on the 15th day of 27 days of dosing of carbamazepine (dashed line, filled circles) to healthy subjects under fed conditions. The grey lines represent mean values of simulated individual trial and the black lines portray the mean data of the simulated population (n = 200). (Source Figure 17 of the report AST/7/C).

The elimination of sunvozertinib decreased following coadministration with itraconazole. The observed sunvozertinib CL/F decreased around 50% with itraconazole coadministration (sunvozertinib alone range: 27.9 L/h to 65.4 L/h; with itraconazole: 14.0 L/h to 40.7 L/h), while the model predicted a CL/F decrease of around 45%. Likewise, the observed mean t1/2 increased from 60.4 hours (sunvozertinib alone) to 70.8 hours (with itraconazole). The model predicted mean t1/2 increase from 51.5 hours (sunvozertinib alone) to 57 hours (with itraconazole). The elimination of sunvozertinib increased slightly following coadministration with carbamazepine. The observed mean t1/2 decreased from 51 hours (sunvozertinib alone) to 45.5 hours (with carbamazepine). The model predicted mean t1/2 decrease from 50 hours (sunvozertinib alone) to 46.9 hours (with carbamazepine).

Prediction of the DDI effect of CYP3A modulators on the PK of sunvozertinib

Simulations were conducted to predict the effect of moderate CYP3A inhibitors or inducers on the PK of sunvozertinib following multiple sunvozertinib doses of 200 mg and 300 mg QD in cancer patients. The predicted geometric mean ratios of AUCtau and Cmax for sunvozertinib in the absence and presence of a CYP3A modulator are listed in Table 79.

Table 9074. Predicted PK changes of sunvozertinib by co-administration of CYP3A modulators

CYP3A modulator	Sunvozertinib dosage			
	200 mg QD*		300 mg QD	
	Cmax GMR	AUCtau GMR	Cmax GMR	AUCtau GMR
Fluconazole 200 mg QD Moderate CYP3A inhibitor	1.26	1.29	1.27	1.30
Efavirenz 600 mg QD Moderate CYP3A inducer	0.60	0.56	0.62	0.58
Dexamethasone 8 mg QD Weak CYP3A inducer	0.89	0.87	0.87	0.86

Data are geometric means ratios of Cmax and AUC, calculated as with/without modulator. (Source: simulation output files of report AST/7/C and *reviewer's independent analysis).

After multiple-dose administration of sunvozertinib 200 mg QD or 300 mg QD, a weak interaction effect was predicted with concomitant use of the moderate CYP3A inhibitor fluconazole. Both GMRs for sunvozertinib Cmax and AUCtau were around 1.3.

Similarly, PBPK predicted a weak interaction effect (AUC GMR ≥20 - <50%) with concomitant use of a moderate CYP3A inducer. Sunvozertinib Cmax and AUCtau decreased by approximately 40% with concomitant use of the moderate CYP3A inducer efavirenz. No DDI effect was predicted with the weak CYP3A inducer dexamethasone (Cmax and AUC GMRs < 20%).

Prediction of interaction effect of sunvozertinib on the PK of a CYP2D6 substrate

Sunvozertinib was determined to be a reversible inhibitor of CYP2D6, with no time-dependent inhibition potential. Simulations were conducted to evaluate the potential for drug-interaction of sunvozertinib (200 mg QD) with the sensitive CYP2D6 substrate desipramine (50 mg SD) in cancer patients who are extensive metabolizers (EM) of CYP2D6. No DDI effect on desipramine

was predicted (both AUCinf and Cmax GMRs of desipramine were 1.0, when used concomitantly with sunvozertinib).

A sensitivity analysis was also performed to evaluate the impact of uncertainty on the in vitro to in vivo extrapolation (IVIVE) of CYP2D6 inhibition constant (Ki) on the predicted interaction effect. The specific fold-reduction of CYP2D6 Ki evaluated on the sensitivity analysis was selected based on an analysis comparing of fold-difference in CYP2D6 Ki between measured in vitro values and values used in PBPK models for established CYP2D6 inhibitors (see additional comments below).

DDI risk assessment simulations were then conducted reducing the in vitro measured CYP2D6 Ki,u value of 3.2 µM (fumic=0.53) by 13-fold and 40-fold. Reducing the Ki,u values resulted in a shift towards weak interaction effect on desipramine. The desipramine AUCinf and Cmax ratios were equal or less than 1.5 and 1.25, respectively, when used concomitantly with sunvozertinib.

Overall, PBPK analysis predicted no to weak inhibitory effect of sunvozertinib on CYP2D6 substrates in cancer patients who are EM of CYP2D6.

Additional comments:

In response to an FDA request (Type B IND meeting), the Applicant provided an independent analysis to demonstrate the performance of PBPK analysis in predicting DDI due to competitive inhibition of CYP2D6. For CYP2D6 substrates, the desipramine model reasonably captured the PK profiles of desipramine following a single IV or oral dose in CYP2D6 extensive metabolizers or poor metabolizers. The predictive DDI performance with desipramine as CYP2D6 substrate was evaluated with various inhibitors of CYP2D6 (namely, the strong inhibitor bupropion, fluoxetine, paroxetine, moderate inhibitors cinacalcet and mirabegron and weak inhibitor ritonavir. Overall, the analysis had a reasonable predictive performance with a prediction error equal or less than ±25%.

The IVIVE of CYP2D6 inhibition parameters was also evaluated. The difference between the in vitro inhibition constant (IC50/Ki) and the optimized Ki used by PBPK model could provide the basis for degree of model uncertainty and range for sensitivity analysis on Ki. In this Applicant's analysis, the IC50 values for all tested CYP2D6 inhibitors were generated in the same laboratory, with same protocol as those for sunvozertinib. The fold-differences between in vitro and model CYP2D6 Ki values ranged from 0.2 to 13, except for bupropion and its metabolite which had a maximum fold- difference of 55-fold (different commutations of Ki values for bupropion and metabolite could be used to predict the clinical DDI with desipramine).

The FDA PBPK team has also previously evaluated the IVIVE of CYP2D6 inhibition parameters (refer to (b) (4) PBPK review for further details). This analysis concluded the in vitro CYP2D6 Ki value of an inhibitor needed to be reduced by 2- to 40-fold to reproduce the observed interaction effects of such inhibitors on the exposure of CYP2D6 substrates.

Discussion of the effect of food on sunvozertinib absorption and enterocyte concentrations

The fraction of sunvozertinib absorbed per intestinal segment was evaluated for both fed and fasted conditions. Differences between fed and fasted state were small. The mean total fraction of sunvozertinib absorbed in the fasted or fed state was 0.80 or 0.79 respectively. A large proportion of the oral dose was absorbed in the colon, followed by the jejunum.

The concentration driving the DDI simulations for sunvozertinib as a perpetrator and victim is the unbound enterocyte concentration of sunvozertinib (fugut x concentration in enterocytes). The value of fugut was assumed to be 1 (most conservative scenario). Enterocyte concentrations in each intestinal segment were highest in the fasted state compared to the fed state. The sunvozertinib enterocyte concentrations in jejunum I for example was around 3 -fold higher in fasted state (Report AST/7/D).

DDI simulations were conducted also under fasted state to evaluate the impact of the unbound enterocyte concentration in the intestine on the DDI predictions. For sunvozertinib as CYP3A4 victim, minimal differences on the predicted DDI effect of fluconazole and efavirenz on the PK of sunvozertinib (200 mg QD) were noted when simulations were conducted under fasted or fed conditions (reviewer's independent analysis). Similarly, for sunvozertinib as CYP2D6 perpetrator, minimal difference on the predicted DDI effect of sunvozertinib on desipramine was noted between fasted and fed state simulations (reviewer's independent analysis).

Conclusions

PBPK analyses were adequate to predict the interaction effect of CYP3A modulators on sunvozertinib exposure at steady state. Coadministration of a moderate CYP3A inhibitor increased sunvozertinib AUCtau by 1.3-fold. Coadministration of a moderate CYP3A inducer decreased sunvozertinib AUCtau by approximately 44%; while a weak CYP3A inducer had not interaction effect on sunvozertinib PK.

PBPK analysis predicted no to weak inhibitory effect of sunvozertinib on CYP2D6 substrates.

19.4.4 Summary of Bioanalytical Method Validation and Performance

The FDA's Assessment

Plasma and urine concentration of sunvozertinib and/or its metabolite DZ0753 were determined using the following methods at three bioanalytical laboratories (Table 91).

Table 91: Table 75: Summary of Bioanalytical Methods of Sunvozertinib and DZ0753 Used in Clinical Studies

Method	Matrix/ Anticoagulant	Analytes	Testing Laboratory	Validation Report	Clinical Study Applied and Bioanalytical Analysis Report
DZD9HPP	Plasma/K_2EDTA	sunvozertinib	(b) (4)	8402771 report 8402771 report addendum 01	WU-KONG1A: 8402773_Part A interim report 01 8402773_Part A report WU-KONG11: 8466962 report WU-KONG12: 8471126 report (sunvozertinib only)
DZ9DHPP	Plasma/K_2EDTA	sunvozertinib and DZ0753		8496187 report	WU-KONG1B none China site: 8402773_Part B report WU-KONG27: 8525061 report
9DZDHPP	Plasma/K_2EDTA	sunvozertinib		8410058 report 8410058 report addendum 01	WU-KONG2: 8410062 report
DZ9DHPP	Plasma/K_2EDTA	sunvozertinib and DZ0753		8485757 report 8485757 report addendum 01	WU-KONG1B China site:8511693 report WU-KONG6: 8471073 interim report 01 8471073 interim report 02 8471073 final report WU-KONG12: 8485758 report (DZ0753 only) WU-KONG19: 8515812 report
(b) (4) US-SML-0670	Plasma/K_2EDTA	sunvozertinib and DZ0753		DZL21589-21589X-B report DZL21589-21589X-B report amendment 01	WU-KONG7: DZL21589-21589X-C report
DZD9HPQ	Plasma: DPBS (50:50)	sunvozertinib and DZ0753		8523801 report	WU-KONG27: 8523802 report
DZD9HUP	Urine	sunvozertinib		8402772 report	WU-KONG1: 8402775 report WU-KONG11: 8466962 report
9DZDHUP	Urine	sunvozertinib		8410059 report 8410059 report addendum 01	WU-KONG2: 8410062 report

Source: Applicant table from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods

The methods were internally transferred and validated between laboratories as described below.

Assays for sunvozertinib and/or its metabolite DZ0753 in human plasma

- Sunvozertinib: An initial assay (Method DZD9HPP) for measuring sunvozertinib only in the human plasma was developed at (b) (4) for samples collected outside of China. The assay was then internally transferred to and validated by (b) (4). (Method 9DZDHPP) for samples collected in China. Cross-laboratory validation was performed and demonstrated the equivalence of the methods used between the two laboratories.
- Sunvozertinib and DZ0753: After metabolite DZ0753 was identified, an assay (Method DZ9DHPP) for measuring both sunvozertinib and DZ0753 in human plasma was developed by (b) (4), and then transferred to (b) (4) and validated by both laboratories. Cross-laboratory validation was performed between (b) (4), and then between (b) (4), which demonstrated the equivalence of the method used among the three laboratories.

- Cross-assay validation studies were also performed between the dual analytes sunvozertinib/DZ0753 assay and the single analyte sunvozertinib assay at (b) (4) sites. The results demonstrated the equivalence of the two assays for sunvozertinib.

Assay for sunvozertinib in human urine

- An assay (Method DZD9HUP) for sunvozertinib in human urine was developed by (b) (4), and then transferred to and validated by (b) (4) (Method 9DZDHUP). The results of a cross-laboratory assay validation study performed between (b) (4) demonstrated assay equivalence between the two laboratories.

The Office of Clinical Pharmacology review team has assessed the adequacy and acceptability of the above bioanalytical methods used in clinical studies. The bioanalytical method validation results and performance in the pivotal clinical study WU-KONG 1B and supportive clinical studies WU-KONG 1A and WU-KONG 6 are summarized in Table below. The bioanalytical method validation and performance in the Phase 1 clinical trial WU-KONG 2 (China) and clinical pharmacology studies WU-KONG 7, WU-KONG 11. WU-KONG 12, WU-KONG 19 and WU-KONG 27 are not included in the current review, including method validation reports and performance for DDI substrates/biomarkers (digoxin, rosuvastatin, midazolam, 1'-hydroxymidazolam and coproporphyrin I). However, the reviewer has determined that the bioanalytical method validation and performance for these studies are acceptable.

Table 927677: Summary of Sunvozertinib Method Performance in Human Plasma at (b) (4)

Bioanalytical method validation report name, amendments, and hyperlinks	Report: Method DZD9HPP, Validation of a Method for the Determination of DZD9008 in Human Plasma by HPLC with MS/MS Detection Report Number: 8402771 report and 8402771 report addendum 01
Method description	Sample processing was performed by protein precipitation using a sample volume of 25 µL. [$^2H_6$] -DZ0586 was added as an internal standard for sunvozertinib in calibration standards, quality control (QC), and clinical samples. Separation between sunvozertinib and interfering endogenous compounds was achieved by LC using an ACE Excel 2 C18 column (50 x 2.1 mm, 2 µm) and 100:0.2:0.2 Water: 1M Ammonium Formate: Formic Acid as mobile phase A, 75:25:0.2 Acetonitrile: Methanol: Formic Acid as mobile phase B. After gradient elution, a triple quadrupole mass spectrometer (API 4500, AB Sciex) equipped with a turbo ion spray source was used for detection in positive ion mode.
Materials used for calibration curve & concentration	Sunvozertinib dissolved in DMSO:methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 1, 2, 5, 25, 125, 500, 900 and 1000 ng/mL
Validated assay range	1 ng/mL~1000 ng/mL
Material used for QCs & concentration	Sunvozertinib dissolved in DMSO: methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 1, 3, 30, 400 and 800 ng/mL

Minimum required dilutions (MRDs)	N/A		
Source & lot of reagents (LBA)	DMSO/Methanol/Acetonitrile/Formic Acid/Ammonium Formate Source and lot information documented in raw data		
Regression model & weighting	Linear regression, $1/x^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8 calibrators in 4 runs	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.0% to 2.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 6.2%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: 1, 3, 30, 400 and 800 ng/mL	-3.9% to 1.5%	Yes
	Inter-batch %RSD QCs: 1, 3, 30, 400 and 800 ng/mL	≤ 11.2%	Yes
	Total Error (TE)	N/A	N/A
Selectivity & matrix effect	6 lots tested, -8.8% to 2.0% observed bias, precision (%RSD) 4.4%.		Yes
Interference & specificity	Passed acceptance criteria: • ≤ 5.0% of ISTD response in the control zero sample • ≤ 20.0% of the mean (acceptable) LLOQ calibration standard response		Yes
Hemolysis effect	6 replicates at 2 concentrations, 9.5% to 10.7% observed bias, precision (%RSD) 3.5% to 7.1%		Yes
Lipemic effect	6 replicates at 2 concentrations, 10.3% to 12.8% observed bias, precision (%RSD) 2.7% to 3.5%		Yes
Dilution linearity & hook effect	8000 ng/mL at dilution 10X, -12.4% observed bias, precision (%RSD) 7.1%		Yes
Bench-top/process stability	Bench-top stability: 24 hours on wet ice Processed sample stability: 167 hours refrigerated (2- 8°C) Processed sample viability: 210 hours refrigerated (2- 8°C) Stability in blood: 2 hours at room temperature and 2 hours on wet ice		Yes
Freeze-Thaw stability	4 cycles at -10°C to -30°C (wet ice thaw) 4 cycles at -60°C to -80°C (wet ice thaw)		Yes
Long-term storage	559 days at -10°C to -30°C 735 days at -60°C to -80°C		Yes
Parallelism	N/A		N/A
Carry over	No significant carryover of the analyte and ISTD was observed. (≤ 20.0% of the mean (acceptable) LLOQ		Yes

	calibration standard response and ≤5.0% of ISTD response in the control zero sample) with two exceptions. In analytical run 17 and run 21, interference peaks >20.0% of the peak area of the mean utilized LLOQ were observed for sunvozertinib in one carryover sample. The potential peak area contribution from carryover was reviewed, and it was confirmed that the carryover observed was significant to in requiring one LQC sample from run 17 to be deactivated but did not affect the integrity of all other data generated in those runs.	
Method Performance in Study WU-KONG1A		
Assay passing rate	73 of 83 runs met acceptance criteria; incurred sample reanalysis (ISR) passing rate: 88.9%	Yes
Standard curve performance	• Cumulative bias range: -1.4% to 1.0% • Cumulative precision: %RSD ≤ 6.3%	Yes
QC performance	• Cumulative bias range: -0.8% to 7.7% • Cumulative precision: %RSD ≤ 8.4%	Yes
Method reproducibility	12.2% of total number of samples analysed as ISR samples, 88.9% of the ISR results had a relative % difference within ±20%, which was within the acceptance criteria	Yes
Study sample analysis/ stability	The calibrator and QC pools were used within the established storage stability. The study samples were stored at -60°C to -80°C and analysed within 584 days of collection, which was within the established long-term stability.	

Source: Reviewer modified table from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 789379: Summary of Sunvozertinib and DZ0753 Method Performance in Human Plasma at (b) (4)

Bioanalytical method validation report name, amendments, and hyperlinks	Report: Method DZ9DHPP, Validation of a Method for the Determination of DZD9008 and DZ0753 in Human Plasma by HPLC with MS/MS Detection Report Number: 8496187 report
Method description	Sample processing was performed by protein precipitation using a sample volume of 25 µL. [$^2H_6$] -DZ0586 was added as an internal standard for sunvozertinib in calibration standards, quality control (QC), and clinical samples. Separation between sunvozertinib and interfering endogenous compounds was achieved by LC using an ACE Excel 2 C18 column (50 x 2.1 mm, 2 µm) and 100:0.2:0.2 Water: 1M Ammonium Formate: Formic Acid as mobile phase A, 75:25:0.2 Acetonitrile: Methanol: Formic Acid as mobile phase B. After gradient elution, a triple quadrupole mass spectrometer (API 4500, AB Sciex) equipped with a turbo ion spray source was used for detection in positive ion mode.

Materials used for calibration curve & concentration	Sunvozertinib dissolved in DMSO:methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 1, 2, 5, 20, 100, 500, 900 and 1000 ng/mL DZ0753 dissolved in DMSO:methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 0.5, 1, 2.5, 10, 50, 250, 450 and 500 ng/mL		
Validated assay range	Sunvozertinib: 1 ng/mL~1000 ng/mL DZ0753: 0.5 to 500 ng/mL		
Material used for QCs & concentration	Sunvozertinib dissolved in DMSO: methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 1, 3, 30, 400 and 800 ng/mL DZ0753 dissolved in DMSO:methanol (50:50) and spiked into control human plasma (K2EDTA) at concentrations of 0.5, 1.5, 15, 200 and 400 ng/mL		
Minimum required dilutions (MRDs)	N/A		
Source & lot of reagents (LBA)	DMSO/Methanol/Acetonitrile/Formic Acid/Ammonium Formate Source and lot information documented in raw data		
Regression model & weighting	Linear regression, $1/x^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8 calibrators in 3 runs	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Sunvozertinib: -3.0% to 3.0% DZ0753: -2.0% to 3.0%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	Sunvozertinib: ≤ 5.0% DZ0753: ≤ 7.5%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** Sunvozertinib QCs: 1, 3, 30, 400 and 800 ng/mL DZ0753 QCs: 0.5, 1.5, 15, 200 and 400 ng/mL	Sunvozertinib: 0.0% to 1.0% DZ0753: -2.6% to 4.0%	Yes
	Inter-batch %RSD Sunvozertinib QCs: 1, 3, 30, 400 and 800 ng/mL DZ0753 QCs: 0.5, 1.5, 15, 200 and 400 ng/mL	Sunvozertinib: ≤ 9.2% DZ0753: ≤ 9.8%	Yes
	Total Error (TE)	N/A	N/A
Selectivity & matrix effect	Normal human plasma: 6 lots tested • sunvozertinib: -7.3% to 4.9% observed bias, precision (%RSD) ≤ 4.6% • DZ0753: -11.3% to 3.3% observed bias, precision (%RSD) ≤ 6.5% Hepatic impairment plasma: 1 lot tested		Yes

	• sunvozertinib: -3.0% to 0.9% observed bias, precision (%RSD) ≤ 4.9% • DZ0753: -4.7% to 3.0% observed bias, precision (%RSD) ≤ 3.7%	
Interference & specificity	Passed acceptance criteria: • ≤ 5.0% of ISTD response in the control zero sample • ≤ 20.0% of the mean (acceptable) LLOQ calibration standard response	Yes
Hemolysis effect	No hemolysis effect observed	Yes
Lipemic effect	No lipemic effect observed	Yes
Dilution linearity & hook effect	Sunvozertinib: • 8000 ng/mL at dilution 10X, 0.6% observed bias, precision (%RSD) 1.2% • 800 ng/mL at dilution 2X, -1.1% observed bias, precision (%RSD): 3.1% DZ0753: • 4000 ng/mL at dilution 10X, -1.3% observed bias, precision (%RSD) 3.2% • 400 ng/mL at dilution 2X, -0.8% observed bias, precision (%RSD): 4.0%	Yes
Bench-top/process stability	Data referred to (b) (4) full validation study 8485757 (Table 63)	Yes
Freeze-Thaw stability	Data referred to (b) (4) full validation study 8485757 (Table 63)	Yes
Long-term storage	Data referred to (b) (4) full validation study 8485757 (Table 63)	Yes
Parallelism	N/A	N/A
Carry over	No significant carryover of the analyte and ISTD was observed. (≤ 20.0% of the mean (acceptable) LLOQ calibration standard response and ≤5.0% of ISTD response in the control zero sample) with one exception. In run 3, an interference peak >20.0% of the peak area of the mean utilized LLOQ was observed for sunvozertinib and DZ0753 and reviewed by the Responsible Scientist, the review confirmed that the carryover observed did not affect the integrity of the data.	Yes
Method Performance in Study WU-KONG1B		
Assay passing rate	Sunvozertinib: 35 of 39 runs met acceptance criteria; incurred sample reanalysis (ISR) passing rate: 89.2% DZ0753: 35 of 43 runs met acceptance criteria; incurred sample reanalysis (ISR) passing rate: 88.2%	Yes
Standard curve performance	Sunvozertinib: • Cumulative bias range: -4.2% to 2.6% • Cumulative precision: %RSD ≤ 7.5%	Yes

	DZ0753: • Cumulative bias range: -3.2% to 2.4% • Cumulative precision: %RSD ≤ 6.7%	
QC performance	Sunvozertinib: • Cumulative bias range: -5.3% to -0.3% • Cumulative precision: %RSD ≤ 8.5% DZ0753: • Cumulative bias range: -7.3% to -0.5% • Cumulative precision: %RSD ≤ 12.3%	Yes
Method reproducibility	Sunvozertinib: 8.7% of total number of samples analysed as ISR samples, 89.2% of the ISR results had a relative % difference within ±20%, which was within the acceptance criteria DZ0753: 9.1% of total number of samples analysed as ISR samples, 88.2% of the ISR results had a relative % difference within ±20%, which was within the acceptance criteria	Yes
Study sample analysis/ stability	Sunvozertinib and DZ0753: The calibrator and QC pools were used within the established storage stability. The study samples were stored at -60°C to -80°C and analysed within 584 days of collection, which was within the established long-term stability.	

Source: Reviewer modified table from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 9480. Summary of Sunvozertinib and DZ0753 Method Performance in Human Plasma at (b) (4)

Bioanalytical method validation report name, amendments, and hyperlinks	Report: Method DZ9DHPP, Validation of a Method for the Determination of DZD9008 and DZ0753 in Human Plasma by HPLC with MS/MS Detection Report Number: 8485757 report and 8485757 report addendum 01
Method description	Sample processing was performed by protein precipitation using a sample volume of 25 µL. [$^2H_6$] -DZ0586 was added as an internal standard for sunvozertinib in calibration standards, quality control (QC), and clinical samples. Separation between sunvozertinib and interfering endogenous compounds was achieved by LC using an ACE Excel 2 C18 column (50 x 2.1 mm, 2 µm) and 100:0.2:0.2 Water: 1M Ammonium Formate: Formic Acid as mobile phase A, 75:25:0.2 Acetonitrile: Methanol: Formic Acid as mobile phase B. After gradient elution, a triple quadrupole mass spectrometer (API 4500, AB Sciex) equipped with a turbo ion spray source was used for detection in positive ion mode.
Materials used for calibration curve & concentration	Sunvozertinib dissolved in DMSO:methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 1, 2, 5, 20, 100, 500, 900 and 1000 ng/mL DZ0753 dissolved in DMSO:methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 0.5, 1, 2.5, 10, 50, 250, 450 and 500 ng/mL
Validated assay range	Sunvozertinib: 1 ng/mL~1000 ng/mL DZ0753: 0.5 to 500 ng/mL

Material used for QCs & concentration	Sunvozertinib dissolved in DMSO: methanol (50:50) and spiked into control human plasma (K_2EDTA) at concentrations of 1, 3, 30, 400 and 800 ng/Ml DZ0753 dissolved in DMSO:methanol (50:50) and spiked into control human plasma (K2EDTA) at concentrations of 0.5, 1.5, 15, 200 and 400 ng/mL		
Minimum required dilutions (MRDs)	N/A		
Source & lot of reagents (LBA)	DMSO/Methanol/Acetonitrile/Formic Acid/Ammonium Formate Source and lot information documented in raw data		
Regression model & weighting	Linear regression, $1/x^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8 calibrators in 3 runs	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	Sunvozertinib: -1.4% to 1.2% DZ0753: -2.0% to 2.8%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	Sunvozertinib: ≤ 6.7% DZ0753: ≤ 5.1%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** Sunvozertinib QCs: 1, 3, 30, 400 and 800 ng/mL DZ0753 QCs: 0.5, 1.5, 15, 200 and 400 ng/mL	Sunvozertinib: -3.9% to -0.2% DZ0753: -4.6% to -2.7%	Yes
	Inter-batch %RSD Sunvozertinib QCs: 1, 3, 30, 400 and 800 ng/mL DZ0753 QCs: 0.5, 1.5, 15, 200 and 400 ng/mL	Sunvozertinib: ≤ 7.8% DZ0753: ≤ 6.8%	Yes
	Total Error (TE)	N/A	N/A
Selectivity & matrix effect	Normal human plasma: 6 lots tested • sunvozertinib: -2.1% to 9.9% observed bias, precision (%RSD) ≤ 7.1% • DZ0753: -1.2% to 13.8% observed bias, precision (%RSD) ≤ 6.7%		Yes
Interference & specificity	Passed acceptance criteria: • ≤ 5.0% of ISTD response in the control zero sample • ≤ 20.0% of the mean (acceptable) LLOQ calibration standard response		Yes
Hemolysis effect	6 replicates at 2 concentrations, • Sunvozertinib: -1.4% to 0.3% observed bias, precision (%RSD) 3.6% to 4.6% • DZ0753: -3.3% to -2.0% observed bias, precision (%RSD) 2.4% to 2.9%		Yes

Lipemic effect	6 replicates at 2 concentrations, • Sunvozertinib: -1.4% to 11.7% observed bias, precision (%RSD) 4.8% to 7.9% • DZ0753: -3.0% to 1.3% observed bias, precision (%RSD) 3.1% to 7.6%	Yes
Dilution linearity & hook effect	Sunvozertinib: • 8000 ng/mL at dilution 10X, -2.9% observed bias, precision (%RSD) 2.4% • 2500 ng/mL at dilution 10X, 0.4% observed bias, precision (%RSD): 1.5% DZ0753: • 4000 ng/mL at dilution 10X, -5.8% observed bias, precision (%RSD) 1.8% • 1250 ng/mL at dilution 10X, 0.0% observed bias, precision (%RSD): 2.0%	Yes
Bench-top/process stability	sunvozertinib and DZ0753: Bench-top stability: 6 hours at room temperature: Bench-top stability: 24 hours on wet ice: Processed sample stability: 167 hours refrigerated (2-8°C) Processed sample viability: 179 hours refrigerated (2-8°C) Stability in blood, 2 hours at room temperature and 2 hours on wet ice	Yes
Freeze-Thaw stability	sunvozertinib and DZ0753: 3 cycles at -10°C to -30°C (thawed at room temperature) 3 cycles at -60°C to -80°C (thawed at room temperature) 5 cycles at -10°C to -30°C (thawed on wet ice) 5 cycles at -60°C to -80°C (thawed on wet ice)	Yes
Long-term storage	sunvozertinib: • LQC and HQC level: 104 days at -10°C to -30°C 754 days at -60°C to -80°C • DQC1 level at 2500 ng/mL: 251 days at -10°C to -30°C 495 days at -60°C to -80°C DZ0753: • LQC and HQC level: 295 days at -10°C to -30°C 754 days at -60°C to -80°C • DQC1 level at 1250 ng/mL: 251 days at -10°C to -30°C 495 days at -60°C to -80°C	Yes
Parallelism	N/A	N/A

Carry over	No significant carryover of the analyte and ISTD was observed. (≤ 20.0% of the mean (acceptable) LLOQ calibration standard response and ≤5.0% of ISTD response in the control zero sample).	Yes
Method Performance in Study WU-KONG 6		
Assay passing rate	12 of 12 runs met acceptance criteria; incurred sample reanalysis (ISR) passing rate: 100%	Yes
Standard curve performance	Sunvozertinib: • Cumulative bias range: -2.8% to 7.0% • Cumulative precision: %RSD ≤ 4.4% DZ0753: • Cumulative bias range: -4.0% to 8.0% • Cumulative precision: %RSD ≤ 6.6%	Yes
QC performance	Sunvozertinib: • Cumulative bias range: -2.0% to 0.3% • Cumulative precision: %RSD ≤ 5.3% DZ0753: • Cumulative bias range: -4.0% to -0.7% • Cumulative precision: %RSD ≤ 6.4%	Yes
Method reproducibility	10.5% of total number of samples analyzed as ISR Sunvozertinib: 100% met acceptance criteria DZ0753: 100% met acceptance criteria	Yes
Study sample analysis/ stability	Sunvozertinib and DZ0753: The calibrator and QC pools were used within the established storage stability. The study samples were stored at -60°C to -80°C and analysed within 350 days of collection, which was within the established long-term stability.	
Method Performance in Study WU-KONG 1B		
Assay passing rate	11 of 11 runs met acceptance criteria; incurred sample reanalysis (ISR) passing rate: 100%	Yes
Standard curve performance	Sunvozertinib: • Cumulative bias range: -1.0% to 1.0% • Cumulative precision: %RSD ≤ 6.2% DZ0753: • Cumulative bias range: -2.4% to 1.6% • Cumulative precision: %RSD ≤ 6.7%	Yes
QC performance	Sunvozertinib: • Cumulative bias range: -0.0% to 1.3% • Cumulative precision: %RSD ≤ 5.5% DZ0753: • Cumulative bias range: 0.0% to 0.7% • Cumulative precision: %RSD ≤ 6.1%	Yes
Method reproducibility	10% of total number of samples analyzed as ISR Sunvozertinib: 100% met acceptance criteria DZ0753: 100% met acceptance criteria	Yes
Study sample analysis/ stability	Sunvozertinib and DZ0753: The calibrator and QC pools were used within the established storage stability. The study samples were stored at -60°C to -80°C	

	and analysed within 538 days of collection, which was within the established long-term stability.

Source: Reviewer modified table from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 958182: Summary of Sunvozertinib Method Performance in Human Urine at (b) (4)

Bioanalytical method validation report name, amendments, and hyperlinks	Report: Method DZD9HUP, Validation of a Method for the Determination of DZD9008 in Human Urine by HPLC with MS/MS Detection Report Number: 8402772 report		
Method description	Sample processing was performed by protein precipitation using a sample volume of 25 µL. [$^2H_6$] -DZ0586 was added as an internal standard for sunvozertinib in calibration standards, QC samples, and clinical samples (treated with 2-Propanol). Separation between sunvozertinib and interfering endogenous compounds was achieved by LC using an ACE Excel 2 C18 column (50 x 2.1 mm, 2 µm) and 100:0.2:0.2 Water: 1M Ammonium Formate: Formic Acid as mobile phase A, 75:25:0.2 Acetonitrile: Methanol: Formic Acid as mobile phase B. After gradient elution, a triple quadrupole mass spectrometer (API 4500, AB Sciex) equipped with a turbo ion spray source was used for detection in positive ion mode.		
Materials used for calibration curve & concentration	Sunvozertinib dissolved in DMSO:methanol (50:50) and spiked into control human urine at concentrations of 1, 2, 5, 25, 125, 500, 900 and 1000 ng/mL		
Validated assay range	1 ng/mL~1000 ng/mL		
Material used for QCs & concentration	Sunvozertinib dissolved in DMSO: methanol (50:50) and spiked into control human urine at concentrations of 1, 3, 30, 400 and 800 ng/mL		
Minimum required dilutions (MRDs)	N/A		
Source & lot of reagents (LBA)	DMSO/Methanol/Acetonitrile/Formic Acid/Ammonium Formate Source and lot information documented in raw data		
Regression model & weighting	Linear regression, $1/x^2$		
Validation parameters	**Method validation summary**		**Acceptability**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8 calibrators in 3 runs	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.5% to 3.5%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 6.0%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: 1, 3, 30, 400 and 800 ng/mL	-1.0% to 3.0%	Yes
	Inter-batch %RSD	≤ 6.8%	Yes

	QCs: 1, 3, 30, 400 and 800 ng/mL		
	Total Error (TE)	N/A	N/A
Selectivity & matrix effect	6 lots tested, 5 lots passed which met the acceptance criteria - 3.4% to 21.0% observed bias, precision (%RSD) 7.8%		Yes
Interference & specificity	Passed acceptance criteria: • ≤ 5.0% of ISTD response in the control zero sample • ≤ 20.0% of the mean (acceptable) LLOQ calibration standard response		Yes
Hemolysis effect	N/A		Yes
Lipemic effect	N/A		Yes
Dilution linearity & hook effect	8000 ng/mL at dilution 10X, -4.1% observed bias, precision (%RSD) 2.1%		Yes
Bench-top/process stability	Bench-top stability: 24 hours at room temperature. Processed sample stability: 192 hours refrigerated (2-8°C) Processed sample viability: 207 hours refrigerated (2-8°C)		Yes
Freeze-Thaw stability	5 cycles at -10°C to -30°C 5 cycles at -60°C to -80°C		Yes
Long-term storage	594 days at -10°C to -30°C 594 days at -60°C to -80°C		Yes
Parallelism	N/A		N/A
Carry over	No significant carryover of the analyte and ISTD was observed. (≤ 20.0% of the mean (acceptable) LLOQ calibration standard response and ≤5.0% of ISTD response in the control zero sample).		Yes
Method Performance in Study WU-KONG1A			
Assay passing rate	11 of 11 runs met acceptance criteria; ISR passing rate: 95.0%		Yes
Standard curve performance	• Cumulative bias range: -2.6% to 2.0% • Cumulative precision: %RSD ≤ 8.3%		Yes
QC performance	• Cumulative bias range: -3.7% to -0.8% • Cumulative precision: %RSD ≤ 8.4%		Yes
Method reproducibility	32.3% of total number of samples analyzed as ISR samples, 95.0% of the ISR results had a relative % difference within ±20%, which was within the acceptance criteria.		Yes
Study sample analysis/ stability	The calibrator and QC pools were used within the established storage stability. The study samples were stored at -60°C to -80°C and analysed within 556 days of collection, which was within the established long-term stability.		

Source: Reviewer modified table from Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods

19.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Not Applicable.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Brian Christmas, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	**Select one:** x Authored x Approved
	Signature: Brian J. Christmas -S Digitally signed by Brian J. Christmas -S Date: 2025.06.30 08:59:54 -04'00'			
Nonclinical Reviewer	Asurayya Worrede, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	**Select one:** x Authored x Approved
	Signature: ASURAYYA WORREDE -S Digitally signed by ASURAYYA WORREDE -S Date: 2025.06.30 10:11:00 -04'00'			
Nonclinical Supervisor	Claudia Miller, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	**Select one:** x Authored x Approved
	Signature: CLAUDIA MILLER -S Digitally signed by CLAUDIA MILLER -S Date: 2025.06.30 09:16:43 -04'00'			
Nonclinical Deputy Division Director (Acting)	Tiffany Ricks, Ph.D.	CDER/OND/OOD/DHOT	Sections: 5, 19.1	**Select one:** Authored x Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S Date: 2025.06.30 11:32:41 -04'00'			
Clinical Pharmacology Reviewer	Siyan Zhu, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4.4	**Select one:** X Authored _ Approved
	Signature: Siyan Zhu -S Digitally signed by Siyan Zhu -S Date: 2025.06.30 11:21:05 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Master Pharmaco kineticist	Jeanne Fourie-Zirkelbach, Ph.D.	CDER/OTS/OCP/DCPII	Sections: 6, 19.4.4	**Select one:** _ Authored X Approved
	Signature: JEANNE FOURIE ZIRKELBACH -S Digitally signed by JEANNE FOURIE ZIRKELBACH -S Date: 2025.06.30 08:32:55 -04'00'			
Division of Pharmacometrics (DPM) Reviewer	Da Zhang	CDER/OTS/OCP/DPM	Sections: 19.4.1, 19.4.2	**Select one:** X Authored _ Approved
	Signature: DA ZHANG -S Digitally signed by DA ZHANG -S Date: 2025.06.30 09:22:09 -04'00'			
Division of Pharmacometrics (DPM) Team Leader	Jiang Liu	CDER/OTS/OCP/DPM	Sections: 19.4.1, 19.4.2	**Select one:** Authored X Approved
	Signature: JIANG LIU -S Digitally signed by JIANG LIU -S Date: 2025.06.30 10:02:23 -04'00'			
Division of Pharmacometrics (DPM) PBPK Reviewer	Manuela Grimstein	CDER/OTS/OCP/DPM	Sections: 19.4.3	**Select one:** X Authored _ Approved
	Signature: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2025.06.30 09:54:18 -04'00'			
Division of Pharmacometrics PBPK Team Leader	Yuching Yang	CDER/OTS/OCP/DPM	Sections: 19.4.3	**Select one:** Authored X Approved
	Signature: Yuching Yang -S Digitally signed by Yuching Yang -S Date: 2025.07.01 14:16:14 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman	CDER/OTS/OCP/DCP II	Sections: 6, 19.4	**Select one:** Authored X Approved
	Signature: NAM A. RAHMAN -S Digitally signed by NAM A. RAHMAN -S Date: 2025.07.01 12:40:27 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Katie Chon	CDER/OOD/DO2	Sections: 1, 2, 3, 4, 7, 8, 9, 10, 12, 13, 19.2	**Select one:** _X_ **Authored** ___ Approved
	Signature: WONME K. CHON -S Digitally signed by WONME K. CHON -S Date: 2025.07.01 14:21:11 -04'00'			
Clinical Team Leader		CDER/OOD/DO2	Sections: see CTDL	**Select one:** ___ Authored ___ Approved
	Signature: see CDTL signature			
Statistical Team Leader	Flora Mulkey	CDER/OTS/DBV	Sections: 1, 8.1, 8.3	**Select one:** _X_ Authored _X_ Approved
	Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S Date: 2025.06.30 09:33:44 -04'00'			
Division Director (OB/DBV)	Shenghui Tang	CDER/OTS/DBV	Sections: 1, 8.1, 8.3	**Select one:** ___ Authored _X_ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2025.06.30 11:28:05 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura	CDER/OOD	Section: 11	**Select one:** ___x Authored ___ Approved
	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2025.06.30 08:46:06 -04'00'			
Cross-Disciplinary Team Leader (CDTL)		CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored ___ Approved
	Signature: see DARRTS electronic signature			
Supervisory Associate Director (Clinical)	Paz Vellanki	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored ___ Approved
	Signature: see DARRTS electronic signature			

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

/s/

PAZ J VELLANKI
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