CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761416Orig1s000

MULTI-DISCIPLINE REVIEW

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	BLA
Application Number(s)	761416
Priority or Standard	Priority
Submit Date(s)	March 29, 2024
Received Date(s)	March 29, 2024
PDUFA Goal Date	November 29, 2024
Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	See electronic stamp date
Established Name	Zanidatamab-hrii
Trade Name	Zihera
Pharmacologic Class	bispecific HER2-directed antibody
Code name	ZW25
Applicant	Jazz Pharmaceuticals
Formulation(s)	300 mg lyophilized powder in a single-dose vial
Dosing Regimen	20 mg/kg intravenous injection every 2 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer, as detected by an FDA-approved test.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test

Table of Contents

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.

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.

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 Tables

Table of Figures

REVIEWERS OF MULTI-DISCIPLINARY REVIEW AND EVALUATION

Regulatory Project Manager	Rebecca Cohen
Pharmacology/Toxicology Reviewer(s)	Steven Zumbrun
Pharmacology/Toxicology Team Leader(s)	Matthew Thompson
Office of Clinical Pharmacology Reviewer(s)	Dapeng Cui (clinical), Da Zhang (pharmacometrics), Joseph Roman (pharmacogenomics)
Office of Clinical Pharmacology Team Leader(s)	Jason Moore (clinical), Youwei Bi (pharmacometrics), Sarah Dorff (pharmacogenomics)
Clinical Reviewer	Vaibhav Kumar
Clinical Team Leader	Sandra J. Casak
Statistical Reviewer	Sirisha L Mushti
Statistical Team Leader	Chi Song
Associate Director for Labeling (ADL)	Doris Auth
Cross-Disciplinary Team Leader	Sandra J. Casak
Division Director (DHOT)	Haleh Saber
Division Director (OCP)	Atiqur Rahman
Division Director (OB)	Shenghui Tang
Division Director (OOD)	Steven J. Lemery
Office Director (or designated signatory authority)	Paul Kluetz

ADDITIONAL REVIEWERS OF APPLICATION

OPQ	Emine Guven Maiorov/TL Jun Liu
Microbiology	Hamet Toure/TL Dharmasena Madushini
OPDP	Rebecca Falter/TL Emily Dvorsky
OSI	Courtney McGuire/ TL Michelle Fedowitz
OSE/DEPI	Kate Gelperin/ TL Steven Bird
OSE/DMEPA	Ngoc-Linh (Linh) Do/ TL Ashley Lowery

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

GLOSSARY

2L	Second-line
ADA	Antidrug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-\tau}$	Area under the plasma concentration-time curve over a dosing interval, where tau is the dosing interval
AUC_{∞}	Area under the concentration-time curve from time zero extrapolated to infinity
BLA	Biologics license application
BOR	Best overall response
BTC	Biliary tract cancer
CBR	Clinical benefit rate
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CisGem	Cisplatin plus gemcitabine
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Serum clearance
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration
CMC	Chemistry, manufacturing, and controls
COA	Clinical outcome assessments
cOR	Confirmed objective response
cORR	Confirmed objective response rate
CR	Complete response
CT	Computer tomography
C_{trough}	Trough concentration
$C_{trough,ss}$	Trough concentration at steady state
CV%	Percent coefficient of variation
CYP	Cytochrome P450
DART	Developmental and reproductive toxicity
DCO	Data cutoff
DOR	Duration of response
DMF	Drug master file
EC_{50}	Effective concentration that produces 50% of the maximum response
EC_{90}	Effective concentration that produces 90% of the maximum response
ECC	Extrahepatic cholangiocarcinoma
ECD	Extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EOP1	End of Phase 1

EQ-5D-5L	European Quality of Life 5-Dimensions 5-Level questionnaire
ER	Exposure-response
ESMO	European Society of Medical Oncology
EU	European Union
F	Female
FDA	Food and Drug Administration
FISH	Fluorescence in-situ hybridization
GBC	Gallbladder cancer
GEA	Gastroesophageal adenocarcinoma
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMR	Geometric mean ratio
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-related quality of life
IC_{50}	Concentration of drug (zanidatamab) where response/binding is reduced by 50%
IC_{90}	Concentration of drug (zanidatamab) where response/binding is reduced by 90%
ICC	Intrahepatic cholangiocarcinoma
ICR	Independent central review
IgG1	Immunoglobulin G isotype 1
IHC	Immunohistochemistry
IIV	Interindividual variability
IND	Investigational new drug application
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
IRR	Infusion related reaction
ISH	In-situ hybridization
IV	Intravenous
JZP598	Zanidatamab
K_D	Dissociation constant at equilibrium
K_m	amount of drug at 50% of maximum nonlinear elimination;
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
M	Male
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
N	Number of animals
NA	Not applicable
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NDA	New drug application
OBD	Optimal biologic dose
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFS	Progression-free survival

PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetics
PR	Partial response
PT	Preferred term
$t_{½}$	Terminal elimination half-life
TBIL	Total bilirubin
TK	Toxicokinetic
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
QTc	QT interval corrected for heart rate
QTcF	Corrected QT interval by Fredericia
QW	Weekly
RD	Recommended dose
SAE	Serious adverse event
SD	Stable disease
sHER2	Soluble human epidermal growth factor receptor 2
SOC	System organ class
StD	Standard deviation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
V_c	Central volume of distribution
V_p	Peripheral volume of distribution
VPC	Visual predictive check
V_{ss}	Volume of distribution at steady state
WRO	Written response only
ZW25	Zanidatamab

1. EXECUTIVE SUMMARY

1.1. Product Introduction

Zanidatamab is a cytolytic bispecific IgG1-like antibody that binds two distinct sites on HER2. Zanidatamab has complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) activity resulting in tumor growth inhibition and cell death in vitro and in vivo.

Zanidatamab for injection is supplied as a white lyophilized powder in single-dose vials for reconstitution and dilution. Each of reconstituted product contains 300 mg of zanidatamab.

The recommended dosage of zanidatamab is 20 mg/kg, administered as an intravenous infusion once every 2 weeks until disease progression or unacceptable toxicity.

Zanidatamab is a new molecular entity and has not been previously marketed.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team agrees that the BLA for Zihera (zanidatamab) for injection meets the statutory standards for approval under 21 CFR 314, Subpart H (accelerated approval) for the following indication:

treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

This approval recommendation is primarily based on safety and efficacy results of a single trial, Study ZWI-ZW25-203 / HERIZON BTC 01 (NCT04466891). Study 203 is an open label, non-randomized, single-arm, 2-cohort trial that evaluated the efficacy of zanidatamab in patients with locally advanced unresectable or metastatic biliary tract cancer (BTC) (including gallbladder, intra, and extrahepatic cholangiocarcinoma) and disease progression after prior therapy with at least one prior gemcitabine-based chemotherapy regimen for advanced disease. Cohort 1 assessed patients with HER2 amplification by in situ hybridization (ISH) and HER2 overexpression by immunohistochemistry (IHC) (2 or 3+). Cohort 2 enrolled patients with HER2 amplification by ISH and HER2 IHC 0 -1+. The approval is based on the results of a subset of 62 patients in Cohort 1 with HER2-amplified tumors and IHC 3+. The safety of zanidatamab is supported by data from all 87 patients enrolled in Study 203 and additional 153 patients with multiple solid tumors treated with zanidatamab 20 mg/kg every 2 weeks (total safety population 233 patients) in Study 101, a dose finding trial.

Study 203 demonstrated a clinically meaningful and durable objective response rate (ORR) in patients with previously treated, locally advanced or metastatic BTC with HER2 ISH-amplified IHC3+ tumors. In the studied population of 80 patients with HER2 ISH-amplified IHC 2-3+ BTC who received at least one dose of zanidatamab, the centrally reviewed estimated ORR was 41.3% (95% confidence interval [CI]: 30.4%, 52.8%) with a median duration of response (DOR) of 14.9 months (95% CI: 7.4, not estimable). However, 32 of the 33 responders had IHC3+ tumors; in the HER2-amplified IHC3+ subpopulation (n= 62), the ORR was 51.6% (95% CI: 38.6%, 64.5%) with a mDOR of 14.9 months (95% CI: 7.4, NE), while only one of the 18 patients with ISH-amplified IHC2+ BTC had a response (ORR: 5.6%, 95% CI: 0.1%, 27.3%).

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence. The results of Study 203 above were supported by results in a smaller group of patients evaluated in supportive Study ZWI-ZW25-101. In Study 101, among 14 patients with IHC3+ BTC, the ORR was 50% (95% CI: 23, 77). This "confirmatory evidence" from Study 101 is regarding the effect on the endpoint of ORR supporting the accelerated approval (and not to verify and describe clinical benefit).

Although the sample sizes in both trials were small, the patient population is rare in the US, and importantly, responses rate in the population was 51.6% (in Study 203) with a lower bound of the 95% CI of 38.6%. This effect would not be a chance finding as tumors generally do not shrink in the absence of therapy.

The review team considers the ORR and DOR results in Study 203 in patients with HER2 ISH-amplified IHC 3+ are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, and representative of a meaningful advantage over existing treatments for the proposed indication. The submitted data satisfies the requirements for accelerated approval.

To verify and describe the benefit of zanidatamab, FDA requested, and the Applicant agreed to a postmarketing requirement to conduct a randomized clinical trial comparing the efficacy and safety of zanidatamab in combination with standard-of-care therapy (cisplatin and gemcitabine ± an immune checkpoint inhibitor) against standard-of-care therapy alone for the first-line treatment of patients with advanced HER2-positive biliary tract cancer.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Zanidatamab is a bispecific IgG1-like antibody that binds two distinct sites on HER2,. Zanidatamab has complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) activity resulting in tumor growth inhibition and cell death in vitro and in vivo. Although zanidatamab is a new molecular entity, monoclonal antibodies targeting HER2 domains ECD4 and ECD2 have been available since 1998 and 2012 respectively.

Substantial evidence of the safety and effectiveness of zanidatamab for the treatment of adult patients with metastatic or locally advanced HER2, ISH amplified, IHC3+ biliary tract cancer is demonstrated by the results of a single multicenter, international, open-label, 2-cohort trial, Study ZWI-ZW25-203/ HERIZON BTC 01 (NCT04466891). This trial evaluated zanidatamab in patients with disease progression after prior treatment with systemic therapy for advanced disease. Cohort 1 of Study 203 assessed patients with HER2 amplification by ISH and HER2 overexpression by IHC (2 or 3+), while Cohort 2 enrolled patients with HER2 amplification by ISH and HER2 IHC 0 -1+. The approval is based on the results of a subset of 62 patients in Cohort 1 with HER2-amplified tumors and IHC 3+. The safety of zanidatamab is supported by data from all 87 patients enrolled in Study 203 an additional 153 patients with multiple solid tumors treated with zanidatamab 20 mg/kg every 2 weeks (total safety population 233 patients) in Study 101, a dose finding trial. All patients received zanidatamab until disease progression or intolerable toxicity.

The primary efficacy population was well distributed between regions (24% North America, 58% Asia, 18% Europe). Trial demographics were as follows: median age 64 years (range 32-79) and 49% of patients were age 65 or older; 56% female and 44% male; 65% Asian, 29% White; 6% Hispanic/Latino. All patients had a ECOG performance status of 0 (28%) or 1 (73%). Fifty-one percent of patients had gallbladder cancer, 29% had intrahepatic cholangiocarcinoma, and 20% had extrahepatic cholangiocarcinoma. The median number of prior lines of therapy was 1 and 41% of patients had received more than one prior line of therapy (range 1-7); all patients received prior gemcitabine treatment and 28% had received immune checkpoint inhibitors.

Study 203 demonstrated a clinically meaningful and durable overall response rate (ORR) in patients with previously treated, locally advanced or metastatic BTC with a HER2 amplification (ISH+) and ICH3+ BTC, a serious and life-threatening disease. In the 62 patients with IHC3+ who received at least one dose of zanidatamab, the estimated overall response rate (ORR) was 51.6% (95% CI 38.6%, 64.5%) with a mDOR of 14.9 months (95% CI 7.4, NE), while only one of the 18 patients with ISH-amplified IHC2+ BTC had a response (ORR 5.6%, 95% CI 0.1%, 27.3%).

Study 203 also provided the primary data to support the safety of zanidatamab for the proposed indication. An additional 153 patients with a

variety of HER2-amplified cancers treated with zanidatamab 20 mg/kg as a single agent in Study 101, a dose-finding trial, provided additional supportive safety data. Although assessment of a causal relationship between zanidatamab and treatment-emergent reactions was limited given the single arm design of the trials providing safety data, the adverse reactions observed in patients treated with zanidatamab were largely expected given the mechanism of action and the toxicity profile observed in preclinical studies. Among the 80 patients with BTC enrolled in Study 203, the most common (incidence ≥ 15%) adverse reactions were diarrhea, infusion-related reaction, abdominal pain, fatigue, rash, nausea, decreased appetite, and vomiting. Most frequent Grade 3-4 adverse events were diarrhea (10%) and fatigue (4%). Laboratory abnormalities in ≥ 30% of patients were hemoglobin decreased, leukocytes decreased, albumin decreased, AST/ALT increased, alkaline phosphatase increased, and sodium and potassium decreased.

Overall, the toxicity profile of zanidatamab is considered acceptable when considering the anti-tumor effects (i.e., durable responses) in patients with previously treated HER2+ ISH-amplified IHC3+ BTC, who have a poor life expectancy and limited treatment options. The risks of zanidatamab are toxicities that oncologists are well-trained to manage and overall are acceptable for a population with a serious and life-threatening condition.

Taken together, the review team concluded that the ORR and DOR results in Study 203 provide evidence of zanidatamab's effectiveness and recommends accelerated approval as the conditions of 21 CFR Subpart H have been met. FDA requested and Jazz has agreed to a postmarketing requirement (PMR) to conduct a randomized clinical trial comparing zanidatamab in combination with standard of care chemotherapy ± immune checkpoint inhibitors vs. standard of care chemotherapy ± immune checkpoint inhibitors to verify and describe the benefit of zanidatamab in patients with advanced or metastatic HER2-positive BTC. The trial is ongoing, and the target completion date is March 2029.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Biliary tract cancers (BTC) are adenocarcinomas arising from the epithelium of the biliary ducts (intrahepatic, perihilar, and distal cholangiocarcinoma), the gallbladder, or ampullary cancers. Incidence varies by geographic region, with low incidence in most high-income countries (0.35-2 per 100,000) but represent a major health problem in endemic areas (up to 40% higher in China and Thailand) (Valle J, 2021). Although surgery is the preferred treatment option for BTC, most patients have advanced-stage disease at the time of diagnosis, and only 20-35% or less are eligible for surgical resection with curative intent. For patients with advanced-stage or unresectable BTC, the median overall survival with standard of care chemotherapy and immune checkpoint inhibitors is approximately one year (Oh, Ruth He et al. 2022, Kelley, Ueno et al. 2023) The median overall survival in patients who had disease progression after systemic therapy is approximately 6 months (Lamarca, Palmer et al. 2021). Human epidermal growth factor receptor 2 (HER2 or ERRB2) is estimated to be overexpressed or amplified in 15-24% of gallbladder cancer (GBC), 8-13% of extrahepatic cholangiocarcinoma (EHCC), and 3-4.5% of intrahepatic cholangiocarcinoma (IHCC)(Lee, Chon et al. 2023). Retrospective data and subgroup analyses of clinical trials suggest that the presence of ERBB2 alterations is a negative prognostic factor (Lowery 2018, Valle J 2022).	Biliary tract cancers are serious and life-threatening diseases. HER2 positive status appear to be a negative prognostic factor.
Current Treatment Options	Current standard of care for (unselected) unresectable or metastatic BTC is based on the ABC-02 trial (Valle J, 2010), which compared the combination of cisplatin and gemcitabine vs. gemcitabine as a single agent, resulting in improved overall survival (median OS 11.7 months	Patients with refractory advanced or metastatic BTC have an unmet medical need. There is no approved standard of care for the second-line setting (except in select patients with

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	vs. 8.1 months in the gemcitabine/cisplatin and gemcitabine arms respectively; HR 0.64, 95% CI 0.52, 0.80; p <0.001). On September 2, 2022, FDA approved durvalumab (a PD-L1 monoclonal antibody) in combination with gemcitabine/cisplatin based on the TOPAZ-1 trial (IMFINZI USPI), which compared the combination of durvalumab with gemcitabine/cisplatin vs. gemcitabine/cisplatin, resulting in improved overall survival (median OS 12.8 months vs. 11.5 months in the durvalumab/gemcitabine/cisplatin and control arms respectively; HR 0.80, 95% CI 0.66, 0.97). On October 31, 2023, FDA approved pembrolizumab (a PD-1 monoclonal antibody) in combination with gemcitabine/cisplatin based on the KEYNOTE-966 trial (KEYTRUDA USPI), which compared the combination of pembrolizumab with gemcitabine/cisplatin vs. gemcitabine/cisplatin, resulting in improved overall survival (median OS 12.7 months vs. 10.9 months in the pembrolizumab/gemcitabine/cisplatin and control arms respectively; HR 0.83, 95% CI 0.72, 0.95). After disease progression on the standard gemcitabine/cisplatin regimen ± immune checkpoint inhibitors, treatment options are limited, and no treatment has received regular FDA approval for treatment of patients with relapsed BTC. In the randomized study ABC-06 exploring chemotherapy with fluorouracil/leucovorin in combination with oxaliplatin (FOLFOX) vs. standard of care for the second line treatment of patients with CCA, patients receiving FOLFOX had a median OS benefit of 6.2 months compared to 5.3 months with best supportive care (hazard ratio [HR] 0.69; 95% CI: 0.50-0.97; p = 0.031) (Lamarca et al. 2019). This OS difference is modest, accompanied by a 5% ORR and with toxicities associated with multiagent chemotherapy. Other regimens include irinotecan in combination with a fluoropyrimidine, a platinum	uncommon biomarker-positive tumors [e.g., MSI-H, FGFR2, IDH+, BRAF, NTRK]) and standard treatment offers limited benefit. Trastuzumab-deruxtecan has tissue agnostic approval in patients with previously treated HER2 positive disease; however, it has a different risk profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	plus fluoropyrimidine, gemcitabine in combination with a platinum or fluoropyrimidine, or regorafenib (NCCN 2024). Identification of molecular subgroups with associated targeted therapies is emerging; FDA approved trastuzumab deruxtecan (an antibody-drug conjugate targeting HER2) for the treatment of patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options. The ORR in 22 patients with HER2, IHC3+ BTC was 45.5% (95% CI 24.4%, 67.8%). Additional FDA-approved targeted therapies for patients with cholangiocarcinoma or BTC include agents for the treatment of tumors harboring FGFR2 gene fusions or other aberrations (pemigatinib, infigratinib, and futibatinib) and tissue agnostic indications for patients with NTRK gene fusions, RET fusions, BRAF V600 mutations, mismatch repair deficiencies and microsatellite instability-high or high tumor burden offer molecularly targeted therapies in the relapsed setting. At the time of this review, all these molecularly driven therapies are under accelerated approval.	
Benefit	The approval is supported by a single trial, Study ZWI-ZW25-203/ HERIZON BTC 01 (NCT04466891). Study 203 is an open label, non-randomized, single-arm, 2-cohort trial that evaluated the efficacy of zanidatamab in patients with locally advanced unresectable or metastatic BTC and disease progression after prior therapy with at least one prior gemcitabine-based chemotherapy regimen for advanced disease. Cohort 1 enrolled patients with HER2 amplification by ISH and HER2 overexpression by IHC 2 or 3+. Cohort 2 enrolled patients with HER2 amplification by ISH and HER2 IHC 0-1+. HER2 status was determined by central laboratory. Patients were eligible if they had histologically	The submitted data demonstrates the safety and effectiveness of zanidatamab for treatment of adults with HER2 ISH amplified IHC3+ metastatic or locally advanced unresectable biliary tract cancer with disease progression after prior gemcitabine-based systemic treatment for advanced disease. In these patients, the magnitude of effect on ORR and duration of responses was clinically

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	confirmed disease, measurable disease by RECIST 1.1, adequate organ and bone marrow function, bilirubin ≤ 1.5 x ULN, left ventricular ejection fraction ≥ 50%, and ECOG performance status of 0-1. Patients who received gemcitabine in prior adjuvant or neoadjuvant treatment were eligible if progression occurred < 6 months from completion of gemcitabine-containing adjuvant therapy. The primary endpoint was confirmed response as per Independent Central assessment (IRC). The main secondary endpoint was duration of response. Patients received zanidatamab 20 mg/kg intravenously every 2 weeks until disease progression or intolerable toxicity. Study 203 enrolled 80 patients in Cohort 1; 62 (77.5%) patients had ISH-amplified, IHC3+ tumors and 18 (22.5%) patients had IHC2+ tumors. Study participant demographics were as follows: median age 64 years (range 32-79) and 49% were age 65 or older; 56% female and 44% male; 65% Asian, 29% White. ECOG performance status was 0 (28%) or 1 (73%). Fifty-one percent of patients had gallbladder cancer, 29% had intrahepatic cholangiocarcinoma, and 20% had extrahepatic cholangiocarcinoma. Nine (11%) patients had Stage 3 disease and the remaining 71 (89%) patients had metastatic disease at study entry. Forty-one percent of patients had received more than one prior line of therapy for metastatic or locally advanced disease. In the studied population of 80 patients with HER2 ISH-amplified IHC 2-3+ BTC who received at least one dose of zanidatamab, the IRC reviewed estimated ORR was 41.3% (95% confidence interval [CI]: 30.4%, 52.8%) with a median duration of response (DOR) of 14.9 months (95% CI: 7.4, NE). However, 32 of the 33 responders had	meaningful in the context of a disease with estimated survival of approximately 6 months. The submitted evidence meets the statutory evidentiary standard for accelerated approval. Jazz has agreed to a postmarketing requirement to submit data from a randomized trial comparing zanidatamab in combination with standard of care chemotherapy ± immune checkpoint inhibitors vs. standard of care for the treatment of patients with HER2 positive BTC who have not received prior systemic therapy. The trial has initiated accrual and has a target completion date of March 2029.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	IHC3+ tumors; in the HER2-amplified IHC3+ subpopulation (n= 62), the ORR was 51.6% (95% CI 38.6%, 64.5%) with a mDOR of 14.9 months (95% CI 7.4, NE), while only one of the 18 patients with ISH-amplified IHC2+ BTC had a response (ORR 5.6%, 95% CI 0.1%, 27.3%). The approval is based on the results of a subset of 62 patients in Cohort 1 with HER2-amplified tumors and IHC 3+.	
Risk and Risk Management	Although assessment of a causal relationship between zanidatamab and adverse reactions was limited in the context of the single arm design of the trials providing safety data, the toxicity profile was consistent with the mechanism of action and the toxicity profile observed in preclinical studies and other drugs targeting the same pathway. The primary data supporting the safety of zanidatamab for the proposed indication was provided from data derived from 80 patients with previously treated, locally advanced or metastatic HER2-amplified tumors and IHC 3+ BTC who received at least one dose of zanidatamab in Study 203. The safety evaluation of zanidatamab was also supported by data from an additional 153 patients with a variety of HER2+ cancers treated with zanidatamab 20 mg/kg every 2 weeks in Study 101, a dose-finding and activity estimating trial. Among the 80 patients with BTC enrolled in Study 203, the most common adverse reactions and lab abnormalities (incidence ≥ 15%) were diarrhea, infusion-related reaction, abdominal pain, fatigue, rash, nausea, decreased appetite, and vomiting. Most frequent Grade 3-4 adverse events were diarrhea (10%) and fatigue (4%). Laboratory abnormalities in ≥ 30% of patients were hemoglobin decreased, leukocytes decreased, albumin decreased, AST/ALT increased, alkaline phosphatase increased, and sodium and potassium decreased.	The toxicity profile of zanidatamab is acceptable when assessed in the context of the life-threatening nature of advanced unresectable or metastatic BTC. No significant safety concerns were identified during review of this application that would require a new risk management plan, including a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of zanidatamab. Significant and serious adverse reactions for zanidatamab are predictable based on the antibody mechanism of action and toxicity profile of the agents in this class. These risks are adequately addressed in product labeling, and oncologists who treat patients with BTC are well-trained in the monitoring and treatment of these adverse reactions. The review team determined that standard postmarketing surveillance would be sufficient for continued assessment of the safety of pembrolizumab in patients with BTC.

1.4. Patient Experience Data

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

✓	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	✓	Clinical outcome assessment (COA) data, such as			
			✓	Patient reported outcome (PRO)	Section 8.1.2
			□	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:

Biliary Tract Cancer (including GBC, ICC, and ECC) is a rare (~1% of adult cancers) diagnosis with poor prognosis (Valle, 2017). Newly diagnosed patients undergo surgical intervention with curative intent (~15% to 40%; Jansen, 2020) or have unresectable disease requiring systemic interventions (60% to 85%). The relapse rate is high, even post-surgery (5-year survival rates: ~10% for Stage III disease and 0% for Stage IV disease per American Joint Committee on Cancer classification, Valle, 2017; Yoo, 2021).

Patients with alteration in ERBB2 that encodes the HER2 protein have a markedly shorter time to progression on first-line therapy than patients without this mutation (Lowery, 2018). Clinical studies suggest that HER2-targeted agents could reduce tumor burden in patients with HER2-amplified or HER2-expressing BTC (ORR, 23% to 26%; median DOR, 4.9 to 10.8 months), though these studies are limited by small sample size (25 to 39 patients), restricted geographical region, and non-uniform local HER2 testing (Javle, 2021; Lee, 2023; Ohba, 2022). Reports show HER2 overexpression in GBC (~19% to 25%), ECC (17%) and ICC (5%) (Valle, 2017).

Zanidatamab, a humanized, bispecific, IgG1-like antibody directed against HER2, is being developed as a potential new treatment for patients with HER2-expressing cancers. Zanidatamab binds to HER2 across a range of expression levels and induces formation of receptor clusters and receptor internalization resulting in downregulation. The Applicant is seeking approval for zanidatamab for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive BTC, based on HER2 protein overexpression and/or HER2 gene amplification in tumor specimens.

The FDA's Assessment:

Biliary tract cancers are predominantly adenocarcinomas arising from the biliary epithelium and classified based on their anatomical site of origin i.e., gallbladder or cystic duct (gallbladder carcinoma [GBC]) or biliary tree (intrahepatic cholangiocarcinoma [ICC] or extrahepatic cholangiocarcinoma [ECC]) (Bridgewater, Goodman et al. 2016, Banales, Marin et al. 2020).

FDA agrees with the Applicant's description of BTC as a rare malignancy, especially in the US; however there is significant heterogeneity in regional incidences of BTCs based on subtype and the prevailing endemic risk factors. The estimated annual incidence of cholangiocarcinoma in the US is 0.35 – 2 cases per 100 000 (Valle, Kelley et al. 2021), with the highest incidence globally occurring in China, South Korea, and Thailand (> 6 cases per 100 000) (Banales, Marin et al. 2020). Retrospective data from the United States Cancer Statistics (USCS) database identified 61,388 patients with cholangiocarcinoma between 2001 to 2015. Approximately 40% had

"distant disease" at presentation, 85% were White, 9% Black, and 6% Asian or Pacific Islander, with a slight male predominance (51% versus 49%) (Patel and Benipal 2019).

Gallbladder carcinoma has a differing epidemiology compared to cholangiocarcinoma, with the highest annual global incidence in Southern Chile (27 cases per 100 000) and northern India (21.5 cases per 100 000) (Valle, Kelley et al. 2021). The annual incidence in the US is estimated at 1.5 cases per 100 000, with the highest incidence in female North American Indians (7.1 cases per 100 000) and lowest in White American males (<5 cases per 100 000) (Hundal and Shaffer 2014). The median age at diagnosis of GBC in the US is 67 years with female predominance (66% versus 34%) (Duffy, Capanu et al. 2008). The Applicant cited the prognosis of patients with treated with curative intent; however, the drug development for this application has focused specifically on patients with advanced BTCs. FDA agrees with the Applicant's statement of poor prognosis in this patient with advanced BTCs.

Human epidermal growth factor receptor 2 (*HER2*), also referred to as *ERBB2,* is estimated to be overexpressed or amplified in 15-24% of GBC, 8-13% of EHCC, and 3-4.5% of IHCC (Lee, Chon et al. 2023), largely consistent with the estimates cited by the Applicant. Lowery et al. (cited by the Applicant) conducted a single center prospective next generation sequencing study of 195 patients with cholangiocarcinoma, with reduced overall survival seen in 8 patients with *ERBB2* alterations compared to wild type (Lowery, Ptashkin et al. 2018). Inferior outcomes were also reported in an exploratory analysis in patients with *ERBB2* amplification who received gemcitabine, cisplatin and durvalumab compared to patients receiving gemcitabine and cisplatin in the TOPAZ-1 trial (Valle, Qin et al. 2022).

The Applicant states that zanidatamab binds to HER2 across a range of expression levels, however 78% of patients enrolled into Cohort 1 of Study ZWI-ZW25-203 had HER2 immunohistochemistry (IHC) 3+ all of whom had HER2 amplification by in situ hybridization (ISH). Furthermore, as summarized in Section 8, only one of 18 patients with IHC2+ experienced a response. See Section 8 for further details.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

There are no approved agents for HER2-amplified or HER2-expressing BTC. The current treatment for these patients after a first-line gemcitabine-containing regimen is cytotoxic chemotherapy, which does not provide a satisfactory disease prognosis. Precision medicines, including those targeting IDH1 and FGFR2 are available but there is little to no overlap reported between HER2 and FGFR2 or IDH1 abnormalities (Lowery, 2018). The 2023 NCCN guidelines and ESMO guidelines include the combination of trastuzumab and pertuzumab as an option for pretreated HER2-positive advanced BTC (NCCN, 2023; Vogel, 2023). As data for currently recommended therapies in this disease setting show (Applicant – Table 1), significant and urgent unmet medical need exists for effective treatment options for patients with advanced/metastatic HER2-positive BTC who have progressed on prior systemic therapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of second line treatment options for patients with advanced BTC. The updated guidance from NCCN version 2.2024, has removed the Category 2B recommendation for pembrolizumab and lenvatinib cited in Table 1.

The current first line treatment options in the US for patients with advanced BTC, irrespective of HER2 status, include either durvalumab or pembrolizumab in combination with gemcitabine and cisplatin based on the findings TOPAZ-1 and KEYNOTE-966 (IMFINZI 2024, KEYTRUDA 2024).

The use of FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) with active symptom control in the second line setting was evaluated in ABC-06, a randomized control trial comparing FOLFOX to active symptom control alone (Lamarca, Palmer et al. 2021). ABC-06 demonstrated an improvement in overall survival in patients receiving FOLFOX (median OS 6.2 months [95% CI: 5.4, 7.6] versus 5.3 months [95% CI: 4.1, 5.8], a HR 0.69 [95% CI: 0.50, 0.97]). Although statistically meaningful, there is no consensus on the use of this regimen in the second line setting as the benefit is marginal when considering toxicities related to cytotoxic chemotherapy.

Table 1: Current Treatment Options for 2L Advanced/Metastatic HER2-Positive BTC

Regimen	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA-Approved Treatments for 2L Advanced/Metastatic HER2-Positive BTC			
None			
Other Treatments for 2L Advanced/Metastatic HER2-Positive BTC			
Trastuzumab + pertuzumab NCCN Guidelines v3.2023 Useful in certain situations, recommendation category 2A	No labelled dosing in this setting. In the MyPathway study (Javle, 2021), patients received IV pertuzumab (840 mg loading dose then 420 mg Q3W) + trastuzumab (8 mg/kg loading dose then 6 mg/kg Q3W).	In 39 patients with treatment-refractory metastatic BTC with ERBB2 amplification and/or HER2 overexpression: ORR: 23% (95% CI, 11–39) Median DOR: 10.8 months (95% CI, 0.7–25.4 months) OS at 1 year: 50% (95% CI, 33-64)	Grade 3-4 TEAEs reported in 46% of patients, including elevated ALT and AST (13% each)
Other Treatments for 2L Advanced/Metastatic BTC Regardless of HER2 Expression			
mFOLFOX NCCN Guidelines v3.2023 Preferred regimen, recommendation category 2A	No labelled dosing in this setting. In the ABC-06 study (Lamarca, 2021), patients received IV oxaliplatin 85 mg/m^2, L-folinic acid (175 mg) or folinic acid (350 mg), 5-FU (400 mg/m^2 bolus), 5-FU (2400 mg/m^2 46-hour continuous infusion) every 14 days for up to 12 cycles.	In patients with advanced BTC after progression on CisGem: ORR: 5% (CR 1%, PR 4%) PFS at 6 months: 32.1% Median OS: 6.2 months (95% CI, 5.4-7.6 months)	Neutropenia Infections Peripheral neuropathy
FOLFIRI NCCN Guidelines v3.2023 Other recommended regimen, recommendation category 2A	No labelled dosing in this setting. In the study supporting NCCN recommendation (Caparica, 2019), patients received IV 5-FU 400 mg/m^2 bolus on Day 1 then 2400 mg/m^2 on a 48-hour infusion Days 1-2, leucovorin 200 mg/m^2 on Day 1, irinotecan 180 mg/m^2 on Day 1 every 14 days.	In patients with locally advanced or metastatic BTC who failed at least 1L of therapy: Median PFS: 1.7 months (95% CI, 0.66-2.67 months) Median OS: 5 months (95% CI, 2.77-7.20 months)	Myelosuppression Diarrhea Renal impairment/failure Embryo-fetal toxicity

Regimen	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
Regorafenib NCCN Guidelines v3.2023 Other recommended regimen, recommendation category 2A	No labelled dosing in this setting. In the study supporting NCCN recommendation (Sun, 2019), patients received 120 mg once daily for 21 days followed by 7 days off (28-day cycles).	In patients with advanced/unresectable BTC who failed at least 1L of therapy: Median PFS: 15.6 weeks (90% CI, 12.9-24.7 weeks)	Hepatotoxicity Hemorrhage Dermatological toxicity Hypertension Cardiac ischemia and infarction Reversible posterior leukoencephalopathy syndrome GI perforation or fistula Wound healing complications Embryo-fetal toxicity
Liposomal irinotecan + fluorouracil + leucovorin NCCN Guidelines v3.2023 Other recommended regimen, recommendation category 2B	No labelled dosing in this setting. In the study supporting NCCN recommendation (Hyung, 2023), patients received IV liposomal irinotecan (70 mg/m^2), leucovorin (400 mg/m^2 bolus), 5-FU (2400 mg/m^2 46-hour continuous infusion) every 14 days.	In Asian patients with advanced BTC after disease progression on CisGem: Median PFS: 4.2 months (95% CI, 2.8-5.3) Median OS: 8.6 months (95% CI, 5.4-10.5 months) OS at 6 months: 60.7% ORR: 12.5%	Neutropenia Pancytopenia Diarrhea Acute kidney injury
Nivolumab NCCN Guidelines v3.2023 Other recommended regimen, recommendation category 2B	No labelled dosing in this setting. In the study supporting NCCN recommendation (Kim, 2020), patients received IV nivolumab (240 mg) every 14 days for 16 weeks then IV nivolumab (480 mg) every 4 weeks.	In patients with advanced treatment-refractory BTC: ORR: 11% Median PFS: 3.68 months (95% CI, 2.30-5.69) Median OS: 14.24 months (95% CI, 5.98-not reached)	Hyponatremia Elevated alkaline phosphatase
Lenvatinib + pembrolizumab NCCN Guidelines v3.2023 Other recommended regimen, recommendation category 2B	No labelled dosing in this setting. In the study supporting NCCN recommendation (Lwin, 2020), patients received lenvantinib (20 mg/day) and pembrolizumab (200 mg Q3W) for 35 cycles.	In patients with advanced BTC who failed at least 1L of therapy: ORR: 10% (95% CI, 2-26%) Median DOR: 5.3 months (2.1 to 6.2 months)	Grade ≥ 3 AEs reported in 48% of patients and 6% of patients discontinued due to AEs

Abbreviations: 1L = first line; 2L = second line; AE = adverse event; 5-FU = 5-fluorouracil; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BTC = biliary tract cancer; CI = confidence interval; CisGem = cisplatin + gemcitabine; CR = complete response; DOR = duration of response; 5-FU = 5-fluorouracil; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; IV = intravenous; NCCN = National Comprehensive Cancer Network; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; Q3W = every 3 weeks; TEAE = treatment-emergent adverse events.

3. REGULATORY BACKGROUND

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Zanidatamab is not currently authorized in any market for any indication worldwide.

The FDA's Assessment:

FDA agrees.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Table 2: Key FDA Interactions for BTC

Date	Description of Regulatory Activity
29 Jun 2016	The initial IND for zanidatamab (b) (4) was submitted, containing the clinical protocol for Study ZWI-ZW25-101 (NCT02892123). On 28 Jul 2016 the study was allowed to proceed.
15 Jan 2019	An IND for zanidatamab (IND 142519) was submitted containing the clinical protocol for Study (b) (4) On 14 Feb 2019 the study was allowed to proceed.
4 Dec 2019	Type B (EOP1) Meeting to discuss the design of Study ZWI-ZW25-203.
12 Dec 2019	Fast Track Designation granted.
18 Dec 2019	Orphan Drug Designation granted.
21 Feb 2020	Clinical Study ZWI-ZW25-203 (NCT04466891) submitted to IND 142519.
27 Nov 2020	Breakthrough Therapy Designation granted.
12 May 2021	Type B Guidance Meeting to discuss development plan for BTC.
8 Sep 2021	Type B pre-Phase 3 Meeting to discuss proposed confirmatory trial design.
1 Sep 2022	Agreed iPSP Letter issued for BTC.
26 Jun 2023	Type B Guidance Meeting to discuss proposed confirmatory trial design.
2 Nov 2023	Type B pre-BLA (Clinical/Nonclinical) Meeting to seek FDA feedback on the Clinical and Nonclinical data package to be included in the original BLA for zanidatamab.
14 Nov 2023	Type B pre-BLA (CMC) WRO Meeting to seek FDA feedback on the CMC data package to be included in the original BLA filing for zanidatamab.

Abbreviations: BLA = biologic license application; BTC = biliary tract cancer; CMC = chemistry, manufacturing, and controls; EOP1 = End of Phase 1; FDA = Food and Drug Administration; HER2 = human epidermal growth factor receptor 2; IND = investigational new drug application; iPSP = initial Pediatric Study Plan; WRO = written response only.
Note: Additional meetings occurred on 12 Aug 2019, 2 Apr 2021, 22 Oct 2021, 22 Apr 2022 and 26 May 2023 to discuss CMC development.

Table 3: Key FDA Interactions for BLA 761416

Date	Description of Regulatory Activity
15 Dec 2023	Rolling Review Submission 1 of original BLA 761416 provided and included Module 4 Nonclinical and associated Module 2 Summary documents.
29 Mar 2024	Rolling Review Submission 2 provided and included the remaining components to complete original BLA 761416.

Abbreviations: BLA = biologic license application.

The FDA's Assessment:

FDA agrees with the timing of key FDA-Sponsor interactions. Further details of the regulatory interactions with the Sponsor for this drug development program are outlined in Table 4:

Table 4: FDA Analysis - Key FDA-Sponsor Interactions

Date	Description of Regulatory Interactions
29 June 2015	FDA issued written correspondence (b) (4) with advice on the first-in-human study in patients with HER2-positive solid tumors and overall development of zanidatamab.
4 Dec 2019	Type B (EOP1) Meeting to discuss the design of Study ZWI-ZW25-203 in patients with relapsed/refractory HER2-amplified BTC. FDA provided guidance on a development program and stated that if it is clear that zanidatamab approval was intended to be under the accelerated approval pathway on the basis of an intermediate clinical endpoint, confirmatory trials should be underway at the time of the marketing application.
27 Nov 2020	Breakthrough Therapy Designation was granted to zanidatamab for the treatment of patients with HER2 gene amplified, locally advanced (unresectable) or metastatic biliary tract cancer who have either received prior systemic chemotherapy for locally advanced (unresectable) or metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant systemic chemotherapy based on an ORR of 47% (95% CI 23, 72.2) with a median duration of response of 6.6 months, reported on 17 evaluable patients enrolled in the ZWI-ZW25-101 trial.
12 May 2021	Type B Guidance Meeting to discuss development plan for BTC. FDA provided feedback on questions relating to Chemistry, Manufacturing, and Controls (CMC) issues related to zanidatamab.
8 Sep 2021	Type B pre-Phase 3 Meeting to discuss proposed confirmatory trial design for Study ZWI-ZW25-302 a randomized, blinded, placebo controlled study for the first-line treatment of advanced BTC comparing zanidatamab or placebo in combination with gemcitabine and cisplatin.
1 Sep 2022	FDA issued an agreement letter on the Sponsor's iPSP (b) (4) .
10 May 2023	Type B Guidance Meeting: Zymeworks proposed submission of an application for the regular approval of Zymeworks in patients with HER2+ BTC based on the results of Study ZWI-ZW25-203. FDA disagreed with the adequacy of the data from Cohort 1 of Study ZWI-ZW25-203 to support traditional approval of zanidatamab for the treatment of HER2+ BTC, as based on the projected sample size for the intended use population, the conduct of a randomized controlled trial appears feasible. FDA further emphasized that any consideration for accelerated approval submission requires a proposal that describes the study that would provide verification of benefit and referred Zymeworks to the December 4, 2019, meeting minutes) and that the trial should be underway prior to, or within a specified time period after the date of approval of the applicable product. FDA also noted that although a randomized controlled trial of zanidatamab as an add-on to chemotherapy (Study ZWIZW25-302) was discussed with FDA on May 12, 2021, a status update to Study ZWI-ZW25-302 was not provided in the meeting package. (b) (4)

Date	Description of Regulatory Interactions
14 Jun 2023	Submission of letter notifying FDA of change in Sponsorship from Zymeworks to Jazz Pharmaceuticals Inc.
26 Jun 2023	Type B Guidance Meeting: Jazz confirmed that the previously proposed trial ZWI-ZW25-302 was not initiated and was no longer being planned. FDA reiterated advice on the need to have a confirmatory trial well underway and expressed concerns regarding the preliminary stage of planning for the proposed confirmatory study, given the intended timeline for BLA submission. FDA stated that submission of the planned BLA should occur when enrollment to the proposed confirmatory has commenced and when there is sufficient enrollment to indicate that the projected trial enrollment milestones and goals can be met based on the rate of trial accrual. [redacted] (b) (4)
31 Jul 2023	Jazz submitted the protocol for Study JZP598-302 to IND 142519.
2 Nov 2023	Type B pre-BLA (Clinical/Nonclinical) Meeting to seek FDA feedback on the clinical and nonclinical data package to be included in the original BLA for zanidatamab. FDA generally agreed with the proposed data package and requested a dedicated analysis of LVEF changes, cardiac events, diarrhea, and ILD/pneumonitis as well as submission of a 90-day safety update.
14 Nov 2023	Type B pre-BLA (CMC) WRO Meeting to seek FDA feedback on the CMC data package to be included in the original BLA filing for zanidatamab.

4. SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct inspections of two foreign clinical investigators (CIs), one domestic CI, the Applicant (Jazz Pharmaceuticals Ireland, Limited), and the imaging contract research organization (CRO), [redacted] (b) (4)

FDA inspected the following clinical sites:

- Site 0109 (Dr. James Harding, Memorial Sloan Kettering Cancer Center, New York, NY, US)

- Site 0302 (Dr. Jin Won Kim, Seoul National University Bundang Hospital, South Korea)
- Site 0306 (Dr. Hye J. Choi, Seoul, South Korea)

The inspection of Dr. Kim identified protocol deviations related to omission of required corticosteroid prophylaxis prior to zanidatamab administration in two patients who did not experience infusion-related reactions. The inspections of the other 2 clinical sites, (b) (4), and the Applicant revealed no significant discrepancies or regulatory violations. Based on the inspection results, OSI concluded that the data appear acceptable in support of the proposed indication. For further details, refer to the OSI review dated 10/4/2024.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) did not identify product quality issues that would preclude approval of zanidatamab-hrii under this BLA. Refer to the OPQ review of this application for additional information. No safety or efficacy concerns were identified during this review that related to Chemistry, Manufacturing, and Controls (CMC). OPQ recommended approval of BLA 761416 for ZIIHERA (zanidatamab-hrii) manufactured by (b) (4) OPQ stated in their review that the data submitted in the Application are adequate to support the conclusion that the manufacture of ZIIHERA (zanidatamab-hrii) is well-controlled and leads to a product that is pure and potent.

4.3. Clinical Microbiology

OPQ's Division of Microbiology Assessment reviewers did not identify issues that would preclude approval of zanidatamab-hrii.

4.4. Devices and Companion Diagnostic Issues

The HER2 status used for the efficacy analyses of Study 203 was determined by the Applicant based on central lab results. All patients in Study 203 were required to have in situ hybridization-positive (ISH+), followed by immunohistochemistry (IHC) testing. A total of 104 (94%) out of 111 IHC 3+ tumors had evidence of HER2 gene amplification, whereas only 34 (17%) out of 201 IHC 2+ tumors had evidence of HER2 gene amplification.

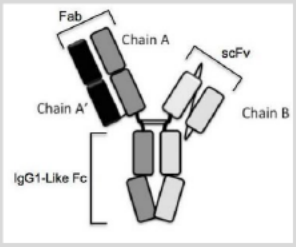
Ventana Medical Systems submitted supplemental Pre Market Application (sPMA) P990081/S054 for the PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody companion diagnostic test. As the current approval for zanidatamab is restricted to patients with IHC3+ tumors, the data in the sPMA submission supports the use of IHC as the test to select patients for zanidatamab treatment.

The companion diagnostic test will be approved concurrently with the zanidatamab approval.

5. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1. Executive Summary

Zanidatamab-hrii (also known as ZW25 and JZP598) is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. HER2 is a member of the EGFR/ErbB/HER family of oncogenes; activation leads to dimerization, autophosphorylation, and activation of downstream signaling pathways. Binding of zanidatamab-hriii with HER2 results in internalization leading to a reduction of the receptor on the tumor cell surface. Zanidatamab-hrii induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumor growth inhibition and cell death in vitro and in vivo. The established pharmacologic class of zanidatamab is bispecific HER2-directed antibody.



(Excerpted from Applicant's Submission)

In surface plasmon resonance (SPR) binding studies, zanidatamab bound human and cynomolgus monkey HER2 extracellular domain (ECD) with similar affinity. Zanidatamab did not bind in rodents, supporting the Applicant's use of cynomolgus monkey as a pharmacologically relevant species for toxicology assessments. In a panel of HER2-expressing cell lines, zanidatamab treatment resulted in antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC).

General toxicology and safety pharmacology were assessed in a 13-week GLP-compliant repeat-dose toxicology study in cynomolgus monkeys at zanidatamab doses up to 150 mg/kg per week. Adverse findings were limited to clinical observations which included watery/soft feces. No adverse safety pharmacology findings were observed. Zanidatamab exposure was generally dose proportional.

No reproductive and developmental toxicity studies were conducted with zanidatamab. The Applicant provided a weight of evidence (WoE) assessment for reproductive risk. Published literature has shown that the HER2 pathway plays an important part in normal growth and differentiation. Exposure to anti-HER2 agents during pregnancy is associated with severe, specific adverse pregnancy and fetal or newborn outcomes (Gougis, et al.[1]). Based on

[1] Gougis P, Grandal B, Jochum F, et al. Treatments During Pregnancy Targeting ERBB2 and Outcomes of Pregnant Individuals and Newborns. JAMA Netw Open. 2023;6(10):e2339934. Published 2023 Oct 2. doi:10.1001/jamanetworkopen.2023.39934

mechanism of action, zanidatamab can cause fetal harm when administered to a pregnant woman. In literature reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Females of reproductive potential are advised to use effective contraception during treatment with zanidatamab and for four months after the last dose. The recommended duration of contraception is based on five times the clinical half-life of 21 days.

There are no data on the presence of zanidatamab-hrii in human milk, the effects on the breastfed child, or the effects on milk production. Published data suggest human IgG is present in human milk but does not enter neonatal or infant circulation in substantial amounts. Treatment with zanidatamab-hrii should consider potential adverse effects, taking into account five times the clinical half-life of 21 days.

Fertility studies with zanidatamab-hrii have not been conducted. Dedicated fertility studies were not warranted.

Studies have not been conducted to evaluate the carcinogenic or mutagenic potential of zanidatamab-hrii. Genetic toxicity and carcinogenicity studies were not warranted.

There are no pharmacology/toxicology approvability issues with the submitted BLA for the proposed indication.

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 zanidatamab.

5.3. Pharmacology

Primary pharmacology

The Applicant's Position:

In vitro binding studies demonstrated that zanidatamab binds to HER2 ECD with a K_D of 0.74 nM and forms multimeric clusters following binding to HER2 in a *trans* configuration (binding dimerization domain [ECD2] and juxtamembrane extracellular domain [ECD4] of independent HER2 molecule) (ZW25-07). Zanidatamab binding to HER2 on the cell surface mediated HER2 internalization, downregulated cell surface HER2, and decreased levels of some signaling phosphoproteins. Zanidatamab mediated concentration-dependent CDC in HER2 IHC 3+ cancer cell lines (IC_{50} range 8.05 to 12.9 nM; IC_{90} range 12.37 to 25.09 nM) (ZW25-38 and JZP598-IR-1535). In the presence of PBMCs, zanidatamab mediated ADCC in HER2-expressing cell lines (EC_{50} range 0.097 to 0.89 nM; EC_{90} range 0.77 to 14.81 nM) (ZW25-37 and JZP598-IR-1535). Zanidatamab also mediated ADCP in HER2-expressing cell lines (EC_{50} range

0.023 to 0.35 nM; EC_{90} range 0.08 to 3.05 nM) (ZW25-36 and JZP598-IR-1535). The mean IC_{90} for ligand-dependent growth inhibition in a cell line representative of gastrointestinal tract malignancies with HER2 amplification and high HER2 expression (N87) was 200.5 nM (range: 118 to 355.3 nM) (JZP598-IR-1535).

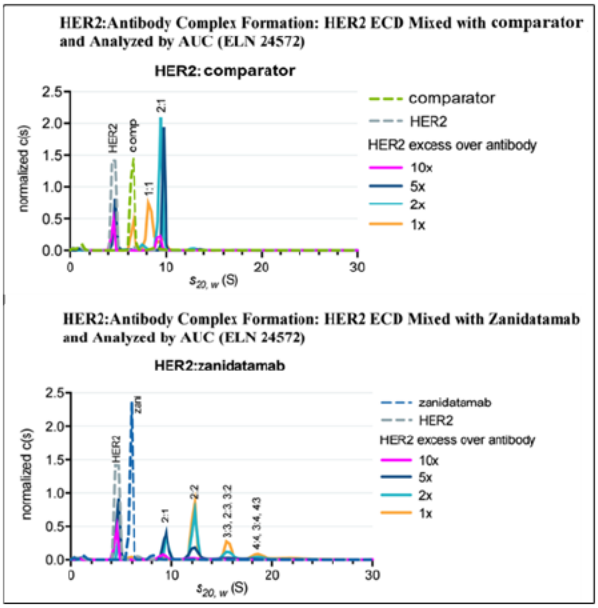
The FDA's Assessment:

The binding affinity of zanidatamab to human, cynomolgus monkey, dog, rat, and mouse HER2 ECD was evaluated via SPR. These data showed that zanidatamab bound human and monkey HER2 with similar affinity (Kd = 0.74 and 0.47 nM, respectively), bound dog HER2 >10-fold less (Kd = 4.07 nM) and did not bind rat or mouse HER2. These data support the use of cynomolgus monkeys as a pharmacologically relevant species for toxicity assessments.

HER2 Origin	*k_a (1/Ms)*	*k_d (1/s)*	*K_d (nM)*
Human	7.02E+04	5.22E-05	0.74
Cynomolgus Monkey	1.04E+05	4.91E-05	0.47
Canine	1.03E+05	4.19E-04	4.07
Rat	No binding	No binding	No binding
Mouse	No binding	No binding	No binding

(Excerpted from Applicant's Submission)

Using ultracentrifugation, the Applicant showed zanidatamab forms high molecular weight complexes.



AUC of mixtures of HER2 ECD with zanidatamab or a comparator at 10-, 5-, 2-fold excess and equimolar ratio of HER2 ECD. HER2 ECD and zanidatamab or comparator were also run separately and plotted together with their respective HER2:zanidatamab mixtures. Complexes larger than 2:1 became more prevalent when the excess of HER2 ECD was reduced. Complex stoichiometry larger than 2:1 is approximate. The comparator formed mainly heterodimers (1:1) and heterotrimers

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.

(2:1) with HER2 ECD and only trace amounts of higher order complexes were detected at reduced HER2 excess. Zanidatamab = zani; comparator = comp. HER2 ECD = HER2.

(Excerpted from Applicant's Submission – edited comparator name)

Zanidatamab demonstrated the ability to induce CDC in HER2-positive cancer cells, resulting in a decrease in viable cell numbers in multiple HER2 3+ cancer cell lines. No CDC activity was observed in cell lines expressing lower levels of HER2 (HER2 2+, HER2 1+, or HER2 0), and heat-inactivated human complement serum prevented CDC activity.

Cell line	HER2 IHC Overall Score	IC_{90} nM (95% CI)
HCC1954	3+	17.57 (undefined, 22.36)
AU565	3+	15.11 (undefined, undefined)
NCI-H2170	3+	18.01 (undefined, 36.92)
OE-19	3+	25.09 (undefined, 33.47)
BT-474	3+	15.80 (undefined)
SKBR3	3+	12.37 (10.04, undefined)
NCI-N87	3+	19.08 (undefined, 22.37)
JIMT-1	2+	Undefined
ZR-75-1	2+	Undefined
MDA-MB-175-VII	0	Undefined
MCF7	1+	Undefined

(Excerpted from Applicant's Submission)

Zanidatamab had ADCC activity against HER2-positive tumor cells with human PBMCs. This effect was observed across different PBMC donors, while no ADCC activity was seen in HER2-negative cell lines.

Cell line	HER2 IHC	EC_{50} nM (95% CI)		
		Experiment 1	Experiment 2	Experiment 3
NCI-N87	3+	14.81 (1.64, undefined)	1.19 (undefined)	0.77 (0.22, 5.62)
SKBR3	3+	1.23 (undefined)	0.73 (undefined, 1.70)	Undefined
JIMT-1	2+	1.17 (0.31, 12.72)	Undefined	Undefined
MDA-MB-468	0	Undefined	Undefined	Undefined

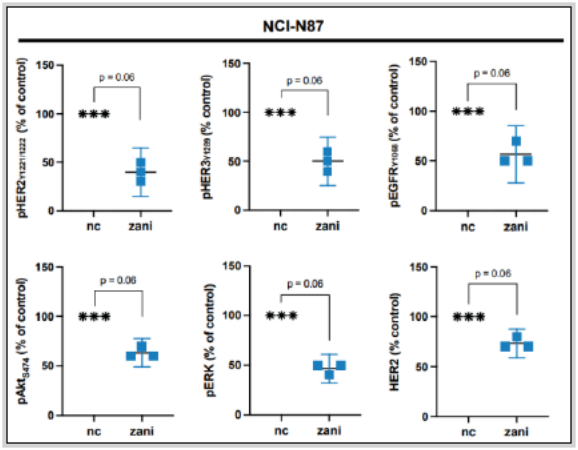
(Excerpted from Applicant's Submission)

Zanidatamab demonstrated concentration-dependent ADCP in cell lines with varying HER2 expression levels. No ADCP was detected in HER2-negative cells.

Cell line	HER2 IHC	EC_{50} nM (95% CI)		
		Experiment 1	Experiment 2	Experiment 3
NCI-N87	3+	1.67 (0.66, 5.98)	3.05 (1.147, 11.65)	0.08 (0.04, 0.31)
SKBR3	3+	8.76[a] (undefined)	13.45 (undefined)	0.27 (undefined)
JIMT-1	2+	Undefined	0.71 (undefined, 1.55)	5.99 (undefined)
MDA-MB-468	0	Undefined	Undefined	Undefined

(Excerpted from Applicant's Submission)

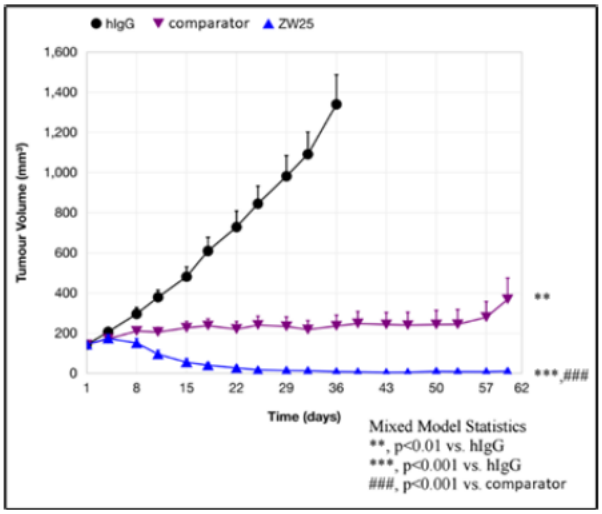
Zanidatamab treatment led to reductions in total HER2 levels in SK-BR-3, NCI-N87 cells, and JIMT-1 cells. Zanidatamab decreased phosphorylated HER2, HER3, EGFR, AKT, and ERK levels in NCI-N87 (below) and SK-BR-3 cells.



Zanidatamab mediated inhibition of pHER2, pHER3, pEGFR, pAKT, pERK and HER2 (adjusted p = 0.06) in NCI-N87 cells compared to negative control treated cells (24 h). Phospho-signaling was performed by immunoblotting. One sample two-sided t-test compared to negative control treated cells value of 100% with p values adjustment using Benjamini & Hochberg false discovery, comparisons with adjusted p values < 0.1 shown. Comparisons with p values < 0.05 considered significantly different. Data are mean ± 95% CI.

(Excerpted from Applicant's Submission)

Though a biliary tract cancer model was not submitted, zanidatamab has in vivo activity in HER2-expressing tumor models.



Zanidatamab treatment of HER2 3+ GXA3054 gastric cancer patient-derived xenograft nude mice. Mean GXA3054 tumor volume following intravenous administration of hIgG at 30 mg/kg (black circles), comparator at 30 mg/kg (purple downward triangle), or zanidatamab (ZW25) at 30 mg/kg (blue upward triangles) twice each week for 5 weeks (n = 10 mice/group). Data are graphed as mean tumor volume ±

standard error of the mean. Abbreviations: hIgG = human immunoglobulin G; HER2 = human epidermal growth factor receptor 2; ZW25 = zanidatamab (also known as JZP598)
Source: ZW25-29
(Excerpted from Applicant's Submission – edited comparator name)

Secondary Pharmacology

The Applicant's Position:

No secondary pharmacology studies were performed.

The FDA's Assessment:

Secondary pharmacology studies were not warranted.

Safety Pharmacology

The Applicant's Position:

Safety pharmacology assessment, including an assessment of zanidatamab's effect on the cardiovascular, respiratory, and central nervous systems, was part of the 13-week GLP-compliant general toxicology study in accordance with ICH S9 (ICH, 2009). No significant effects on the central nervous, respiratory, cardiovascular, and renal/urinary systems were noted when zanidatamab was administered to cynomolgus monkeys once weekly for up to 13 weeks. Zanidatamab displayed low immunogenic potential in a functional human PBMC proliferation assay.

Cynomolgus monkey serum samples from all dosing cohorts were evaluated for anti-zanidatamab antibodies (ADA). No zanidatamab-treated animals had detectable ADA in a confirmatory assay postdose, but the majority had serum concentrations of zanidatamab that exceeded the specific drug tolerance level of the confirmatory assay; thus, ADA may be present but undetectable due to high drug concentrations.

The FDA's Assessment:

The FDA generally agrees with the Applicant's Position. Stand-alone safety pharmacology studies were not performed; however, appropriate safety assessments were included in the 13-week repeat-dose toxicology study ZW25-04-13WTOX (2363-002). No test article-related adverse events were found in cardiovascular, respiratory, or central nervous system assessments.

5.4. ADME/PK

The Applicant's Position:

A series of PK and toxicology studies (with a TK component) of zanidatamab have been completed in cynomolgus monkeys. These studies included non-GLP single- and repeat-dose IV

administration studies and a GLP repeat-dose IV infusion study up to 13 weeks with doses ranging from 5 to 150 mg/kg. The cynomolgus monkey is considered a suitable species for characterizing the PK of zanidatamab as it binds both human and monkey HER2 molecules with similar subnanomolar affinity.

Following a single IV infusion of zanidatamab to monkeys at doses of 10 and 30 mg/kg, the systemic exposure to zanidatamab (in terms of AUC_{∞} and C_{max}) was approximately dose proportional over the three-fold increase in dose (ZW25-01-PKTol). The CL of zanidatamab was 0.518 and 0.394 mL/h/kg, and the V_{ss} of zanidatamab was 48.5 and 65.0 mL/kg at 10 and 30 mg/kg, respectively. The mean half-life of zanidatamab was 65.5 and 114 hours at 10 and 30 mg/kg, respectively.

Following QW IV infusion of zanidatamab to monkeys, the systemic exposure of zanidatamab generally increased in an approximately dose-proportional manner over the 30-fold increase in dose from 5 to 150 mg/kg (non-GLP study ZW25-02-28DTOX [2363-001] and GLP study ZW25-04-13WTOX [2363-002]). Mean accumulation of zanidatamab in monkey serum (as assessed by the ratio of $AUC_{0\text{-}168h\ Day\ 22,\ 50,\ or\ 85}/AUC_{0\text{-}168h\ Day\ 1}$) ranged from 1.65 to 3.15 across all 8 and 13-week dosing cohorts No zanidatamab-treated animals had detectable ADA in a confirmatory assay post-dose, but the majority had serum concentrations of zanidatamab that exceeded the specific drug tolerance level of the confirmatory assay; thus, ADA may be present but undetectable due to high drug concentrations.

Because zanidatamab is a monoclonal antibody, no specific distribution, metabolism, or excretion studies have been performed with zanidatamab. In addition, no drug interaction studies have been performed since it is not expected that zanidatamab will affect the activity or expression of CYP enzymes or drug transporters.

Table 5: ADME/PK Study Summary

Absorption	
Not applicable.	
Distribution	
In vivo tissue distribution studies have not been performed with zanidatamab.	
Metabolism	
No specific metabolism studies have been performed for zanidatamab.	
Excretion	
No specific excretion studies have been performed for zanidatamab.	
Summary PK parameters from pharmacokinetic studies	
Single Dose PK	
ZW25-01-PKTol. A Pharmacokinetic and General Tolerability Study of Zanidatamab in Female Cynomolgus Macaques Following Single Intravenous Injection (non-GLP).	
Species	Cynomolgus monkey
Number and Sex of Animals	2 F per group
Method of Administration	IV bolus (5 min)

Formulation Solution in [redacted] sucrose, pH [redacted]

Dose (mg/kg)	10	30
CL (mL/h/kg)	0.518	0.394
V_{ss} (mL/kg)	48.5	65.0
$t_{½}$ (h)	65.5	114
AUC_{∞} (h·ng/mL)	19,300,000	76,100,000

Abbreviations: AUC = area under the curve; CL = serum clearance; $t_{½}$ = terminal elimination half-life; V_{ss} = volume of distribution at steady state.
Data presented are the geometric means.

Repeat Dose PK

Study ZW25-04-13WTOX (2363-002). ZW25: A 13-Week Intravenous Infusion Toxicity Study With an 8-Week Interim Termination in Cynomolgus Monkeys With 8-Week Recovery Periods (GLP).

Species Cynomolgus Monkey
Method of Administration IV infusion (1 hour) administered once weekly
Formulation Solution in [redacted] sucrose, pH [redacted]

		Day 1		Day 50		Day 85	
Dose (mg/kg)	Gender	C_{max} µg/mL (CV%/N)	AUC_{0-168h} h·µg/mL (CV%/N)	C_{max} µg/mL (CV%/N)	AUC_{0-168h} h·µg/mL (CV%/N)	C_{max} µg/mL (CV%/N)	AUC_{0-168h} h·µg/mL (CV%/N)
5	M	145 (6.65 / 3)	6,910 (6.95 / 3)	128 (87.9 / 3)	12,800 (NA / 2)	–	–
	F	144 (7.83 / 3)	9,220 (3.13 / 3)	202 (6.14 / 3)	18,700 (7.67 / 3)		
50	M	1,840 (5.45 / 3)	96,200 (7.49 / 3)	3,760 (51.0 / 3)	278,000 (39.5 / 3)	–	–
	F	1,680 (7.36 / 3)	96,300 (3.61 / 3)	4,070 (32.9 / 3)	322,000 (28.4 / 3)		
150	M	4,890 (8.77 / 5)	288,000 (7.40 / 5)	7,190 (19.0 / 5)	542,000 (9.03 / 5)	–	–
	F	4,660 (6.64 / 5)	305,000 (4.80 / 5)	10,000 (21.6 / 5)	831,000 (32.4 / 5)		
5	M	182 (18.1 / 4)	9,550 (9.39 / 4)	–	–	265 (35.2 / 4)	19,700 (5.73 / 4)
	F	164 (7.53 / 4)	10,300 (9.74 / 4)			365 (34.9 / 4)	26,700 (12.6 / 4)
50	M	1,870 (28.1 / 4)	90,200 (14.5 / 4)	–	–	2,340 (7.07 / 4)	193,000 (16.2 / 4)
	F	1,560 (8.19 / 4)	101,000 (7.57 / 4)			2,580 (8.11 / 4)	213,000 (11.9 / 4)
150	M	4,400 (12.0 / 7)	289,000 (5.25 / 7)	–	–	6,220 (11.2 / 7)	508,000 (10.8 / 7)
	F	5,120 (23.4 / 7)	378,000 (28.4 / 7)			7,150 (17.8 / 7)	561,000 (12.8 / 7)

Abbreviations: AUC = area under the curve; C_{max} = maximum observed concentration; CV = coefficient of variation; F = female; M = male; N = number of animals.

Integrative summary Table of C_{max} and AUC parameters across toxicity studies

N/A

Tabulation of any exposure margins used in [redacted]

Safety Margin Calculation

	Cynomolgus Monkey	Human	Fold Safety Margin
Mean C_{max} after first dose (ng/mL)	4,760,000	461,100	10.3
Mean AUC[a] (h·ng/mL)	534,000,000	73,132,800	7.3

Abbreviations: AUC = area under the curve; C_{max} = maximum observed concentration; QW = once a week; Q2W = once every 2 weeks.
[a] For monkeys, value presented is mean $AUC_{0\text{-}168h}$ from Day 85 (approximately steady state). For humans, value presented is mean AUC_{∞} (approximately equivalent to $AUC_{0\text{-}\tau}$ at steady state) following the first dose. Cynomolgus monkeys received 150 mg/kg QW for 13 weeks and humans received 20 mg/kg Q2W. Human data from Study ZWI-ZW25-203, data cutoff date: 28 July 2023.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

5.5. Toxicology

The Applicant's Position:

A comprehensive series of non-GLP and GLP studies have been conducted. The program included tissue cross-reactivity studies in panels of human tissues and IV toxicology studies of up to 13 treatment cycles (13 weeks duration) performed in cynomolgus monkeys.

5.5.1. General Toxicology

The Applicant's Position:

The general toxicology program included an IV single-dose bolus study and multiple-dose infusion toxicology studies of up to 13 weeks in duration, with off-treatment assessments and safety pharmacology assessments of the central nervous system (neurobehavioral assessments), respiratory, and cardiovascular functions integrated into the pivotal studies. The cynomolgus monkey was selected as the most relevant species for toxicology testing based on considerations of sequence homology and affinity binding to HER2. Intravenous dosing was utilized in all pivotal toxicology studies since it is the intended route of administration in the clinic.

Table 6: General Toxicology Summary

ZW25: A 13-Week Intravenous Infusion Toxicity Study With an 8-Week Interim Termination in Cynomolgus Monkeys With 8-Week Recovery Periods/ZW25-04-13WTOX (2363-002)

Key Drug-related Adverse Findings:

- No adverse effects were observed at doses up to 150 mg/kg once weekly (QW), administered as IV infusions, for up to 13 weeks of treatment.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	Doses of 0 (vehicle control), 5, 50, and 150 mg/kg QW
Route of administration:	1 hour IV infusion
Formulation/Vehicle:	(b) (4) sucrose, pH (b) (4)
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3M and 3F per group (all doses) dosed for 8 weeks 2M and 2F per group (vehicle and 150 mg/kg QW) dosed for 8 weeks followed by 8 weeks off-treatment 4M and 4F (all doses) 13-week necropsy group 3M and 3F per group (vehicle and 150 mg/kg QW) dosed for 13 weeks followed by 8 weeks off-treatment.
Age:	2 years 11 months to 6 years 5 months
Satellite groups:	N/A

Abbreviations: IV = intravenous; F = female; GLP = Good Laboratory Practice; M = male; QW = weekly; ZW25 = zanidatamab.

No adverse effects were observed at any dose tested (up to 150 mg/kg QW) for animals in either the 8-week or 13-week dosing cohorts. Non-adverse effects associated with the administration of zanidatamab at all dose levels included a non–dose-dependent increase in the incidence of watery/soft feces compared with controls. In some animals, this finding correlated with a mild increase in blood urea nitrogen concentration at all dose levels, which may have been secondary to mild subclinical dehydration associated with watery/soft feces.

Systemic exposure ($AUC_{0\text{-}168h}$) and C_{max} for zanidatamab increased with increasing dose in an approximately dose proportional manner on Days 1, 50, and 85 of treatment (ie, following 1, 8, and 13 doses). An increase in systemic exposure was also evident after repeated administration of zanidatamab, once weekly, for 8 or 13 weeks.

A summary table of TK parameters is presented in Section 5.4.

The FDA's Assessment:

FDA generally agrees with the Applicant's position.

			DAY 57								DAY 92								DAY 141			
			0		5		50		150		0		5		50		150		0		150	
Organ/System	Finding	Severity	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Heart	Heart: mineralization, focal	Minimal																1				
	Heart: thrombus	Minimal						1														
GI	Large Intestine, cecum: hemorrhage	Minimal			1																	
		Mild					1															
	Large Intestine, cecum: inflammation	Minimal			1																	
	Large Intestine, colon: hemorrhage	Minimal																				1
	Stomach, fundus: hemorrhage	Minimal														1						
Skin	Skin: erosion/ulcer	Mild				1																
	Skin: exudate, epidermal surface	Mild				1																
	Skin: hemorrhage	Mild																			1	
	Skin: hyperplasia, epidermal	Minimal				1																
	Skin: inflammation, chronic	Minimal				1																
Thymus	Thymus: decreased lymphocytes, generalized	Minimal			1	1		1				2		2		2		3		1		
		Mild												1				1				
Gland	Mammary gland: hyperplasia, lobular	Mild																1				
	Thyroid gland: inflammation, chronic	Minimal			1			1														
Reproduction	Ovaries: mineralization	Minimal		1		3		1		1										1		
		Mild										2										
	Uterus with cervix: inflammation, acute	Minimal												1								
	Testes: degeneration/atrophy, seminiferous tubules, unilateral	Mild											1									
	Testes: dilation, seminiferous tubules, unilateral	Mild											1									
	Testes: fibrous hypoplasia, bilateral	Minimal			1																	
		Mild														1						

DAY 57 (n=3/group); DAY 92 (n=4/grp); DAY 141 (n=3/group)

Cell color references number of animals with finding

5.5.2. Genetic Toxicology

The Applicant's Position:

The range and type of genotoxicity studies routinely conducted for small-molecule study interventions are generally not applicable to biotechnology-derived products (ICH S6[R1]) and are generally not performed for products intended for use in patients with advanced cancer (ICH S9) (ICH, 2009; ICH, 2011). It is not expected that a HER2 dual targeting bispecific monoclonal antibody, such as zanidatamab, which binds to the ECD of HER2, would interact directly with deoxyribonucleic acid or other chromosomal material. Thus, mutagenicity studies are considered inappropriate and were not conducted.

The FDA's Assessment:

Genotoxicity studies were not warranted.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies have been conducted with zanidatamab. Based on its mechanism of action, zanidatamab is not expected to be carcinogenic. Additionally, zanidatamab is neither a

growth factor nor an immunosuppressant. Thus, given the intended patient population and lack of mechanistic concern, carcinogenicity studies are not planned with zanidatamab (ICH S9) (ICH, 2009).

The FDA's Assessment:

Carcinogenicity studies were not warranted.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

HER2 is expressed broadly in epithelial tissues of the developing fetus, including the placenta (Fock, 2015) and vital organs including the brain and heart (Quirke, 1989). Studies of embryonic development in mice homozygous for deletion or mutation in the kinase domain of the ERBB2 gene (coding for the HER2 protein) reveal that these changes produce embryonic lethality on Day 9.5 due to heart and brain malformations (Lee, 1995; Erickson, 1997; Chan, 2002). A literature search for publicly available clinical study reports revealed several case reports on the activity of HER2 function-blocking antibodies resulting in cases of oligohydramnios and oligohydramnios sequelae manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death (Yildirim, 2018; Xia, 2021). Human epidermal growth factor receptor 2 has been shown to be critically important in the development of the placenta (Fock, 2015).

On the basis of a weight-of-evidence analysis supported by published literature indicating that embryo-fetal toxicity is a likely class effect of HER2 binding antibodies (ICH S5(R3) Section 1.2.2) (ICH, 2020), Jazz proposes that zanidatamab should be considered an embryofetal toxicant. Consequently, the conduct of de novo developmental and reproductive toxicity (DART) studies is not warranted for zanidatamab.

The FDA's Assessment:

The FDA generally agrees with the Applicant's Position.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Table 7: Other Toxicology Studies Summary

Study Type	Investigations	GLP Compliant	Test System	Doses (mg/kg)	Noteworthy Findings	Study Number
Immunotoxicity	Hematology and histopathology assessed in 13-week	Yes	Cynomolgus monkeys	0 5 50 150	No changes indicative of immunotoxicity.	ZW25-04-13WTOX (2363-002)

Study Type	Investigations	GLP Compliant	Test System	Doses (mg/kg)	Noteworthy Findings	Study Number
	toxicology study					
Immunogenicity	ADAs assessed in 13-week toxicology study	Yes	Cynomolgus monkeys	0 5 50 150	No zanidatamab-treated animals had detectable ADA in a confirmatory assay postdose, but the majority had serum concentrations of zanidatamab that exceeded the specific drug tolerance level of the confirmatory assay; thus, ADA may be present but undetectable due to high drug concentrations.	ZW25-04-13WTOX (2363-002)
Photosafety testing	Not applicable	–	–	–	–	–
Other toxicology	Tissue cross-reactivity study (in vitro)	Yes	Human tissue cryosections (SKOV3 and Jurkat cells as positive and negative controls, respectively)	1.0 and 10.0 µg/mL	The pattern of zanidatamab staining was consistent with HER2 expression in normal human tissues reported in the literature.	ZW25-09-GLP-TCR

Abbreviations: ADA = antidrug antibody; GLP = Good Laboratory Practice; HER2 = human epidermal growth factor receptor 2.

Immunotoxicity: Cynomolgus monkeys receiving zanidatamab in the 13-week GLP toxicology study exhibited no evidence of immunotoxicity. Specifically, no changes in the hematology or histopathology endpoints were observed that raised concern about immunotoxicity. In addition, zanidatamab did not affect the proliferation of human PBMCs, suggesting that it has low immunogenicity. Therefore, no further assessment of immunotoxicity was conducted.

Immunogenicity: General immunogenicity testing was not conducted for zanidatamab. However, the GLP-compliant 13-week toxicology study included an assessment of ADAs following repeat dosing with zanidatamab as recommended in ICH S6(R1) guidance for biotechnology-derived pharmaceuticals (ICH, 2011). No zanidatamab-treated animals had detectable ADA in a confirmatory assay postdose, but the majority had serum concentrations of zanidatamab that exceeded the specific drug tolerance level of the confirmatory assay; thus, ADA may be present but undetectable due to high drug concentrations.

Photosafety testing: According to ICH S10, photosensitivity generally applies to small molecules and does not generally apply to peptides and proteins (ICH, 2012). Therefore, no further assessment of photosafety was performed.

Other: A GLP tissue cross-reactivity study was conducted to evaluate the tissue binding specificity of zanidatamab with cryosections of 36 normal human tissues. SKOV3, a human ovarian cancer cell line overexpressing HER2, was used as a positive control, and Jurkat cells, a T cell line that does not express HER2, were used as the negative control. The pattern of zanidatamab staining was consistent with HER2 expression in normal human tissues reported in the literature (Press, 1990; Liu, 2001). Of the tissues not identified in the published literature, only one, the spinal cord, exhibited membrane staining. The existence of the blood-spinal cord barrier should limit the in vivo exposure of the spinal cord to zanidatamab (Rossi, 2013).

Impurities and degradation products: The impurity profile of the GLP lot ((b) (4) was within the specifications, and impurities were at equivalent or greater levels compared with the impurities in the clinical lot. There were no impurities that would require qualification in toxicological studies.

The FDA's Assessment:

The FDA generally agrees with the Applicant's Position.

X X

Primary Reviewer Supervisor

6. CLINICAL PHARMACOLOGY

6.1. Executive Summary

The FDA's Assessment:

The Applicant is seeking approval of zanidatamab, a bispecific HER-2 directed antibody, for the treatment of adult patients with previously treated, unresectable or metastatic HER2-positive biliary tract cancer (BTC), as detected by an FDA-approved test. The proposed recommended dosage is 20 mg/kg administered as an intravenous (IV) infusion once every 2 weeks (Q2W) until disease progression or unacceptable toxicity.

The clinical pharmacology review focused on the adequacy of the clinical data to support the proposed dosing regimen and of the evaluation of immunogenicity.

FDA generally agrees with the proposed recommended dosage of zanidatamab 20 mg/kg Q2W in patients with unresectable or metastatic HER2-positive BTC. The proposed dosage was

selected based on the clinical efficacy and safety data as well as population pharmacokinetics (PopPK) and exposure-response (E-R) analyses for efficacy and safety. The dose finding and optimization are limited by the relatively small sample size for majority of dosage levels evaluated. However, the clinical efficacy and safety data together with the PopPK and E-R analyses provided evidence of clinically meaningful anti-tumor activity at the proposed recommended dosage in patients with advanced or metastatic BTC with HER2 amplification (ISH^+) and overexpression ($IHC3^+$).

The Applicant reported a low incidence (1.5%) of anti-drug antibody (ADA) in patients who received zanidatamab. However, the reported treatment-emergent ADA status was questionable because interference by soluble HER2 (sHER2) may potentially cause a higher rate of false-positive ADA at baseline compared to the post treatment samples. In addition, a substantial portion of ADA study samples had zanidatamab concentrations greater than the drug tolerance. A post-marketing commitment (PMC) will be issued to re-evaluate the incidence of ADA in the incurred samples following the development of a new immunogenicity assay.

Recommendations

The Office of Clinical Pharmacology reviewed the information contained in BLA 761416. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and/or comments are summarized in Table 8 and a Clinical Pharmacology PMC is summarized in Table 9.

Table 8: Key Clinical Pharmacology Review Issues by FDA

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of efficacy is provided by registrational Study ZWI-ZW25-203 conducted in patients with advanced or metastatic HER2-amplified BTC. The proposed dosing regimen, i.e., 20 mg/kg once every 2 weeks (Q2W), is supported by a favorable objective response rate of zanidatamab monotherapy. See Section 8.1.2 for details.
General dosing instructions	The recommended dosage of zanidatamab is 20 mg/kg administered as an intravenous (IV) infusion Q2W until disease progression or unacceptable toxicity.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Based on population pharmacokinetic (PopPK) analysis using data from studies ZWI-ZW25-101 and ZWI-ZW25-203, the following factors have no clinically meaningful effect on the exposure of zanidatamab: age (24 to 88 years), sex, race (White and Asian), mild and moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI), mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN

	or total bilirubin between 1 and 1.5 times ULN and any AST), or body weight (35 kg to 128 kg). The effect of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR < 15 mL/min) with or without hemodialysis, and moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) or severe (total bilirubin >3 ULN and any AST) hepatic impairment on the PK of zanidatamab is unknown.
Labeling	Overall, the Applicant's proposed labeling was acceptable with minor edits to the labeling format.

Table 9: Outstanding Clinical Pharmacology Issues

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Consideration for Design
☑ PMC ☐ PMR	The incidence and impact of anti-drug antibody (ADA) on zanidatamab PK, safety and efficacy were not adequately evaluated.	In Studies ZWI-ZW25-101 and ZWI-ZW25-203, soluble HER2 (sHER2) interfered with the evaluation for ADA which may increase the risk of false-positive ADA at baseline compared to the post treatment samples. In addition, a substantial portion of ADA study samples had zanidatamab concentrations greater than the drug tolerance. The reviewer's exploratory analysis indicated a trend of higher incidence of Grade 3-4 treatment emergent adverse event (TEAE) and serious AE (SAE) associated with post-treatment positive ADA.	Use a validated assay capable of sensitively detecting ADA responses in the presence of zanidatamab levels that are expected to be present in the serum at the time of patient sampling. Reanalyze the samples from Studies ZWI-ZW25-101 and ZWI-ZW25-203. Reevaluate the immunogenicity incidence and the effect of ADA on safety, PK, and efficacy of zanidatamab.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology package is derived from 2 studies with completed CSRs: Study ZWI-ZW25-101 (Study 101) and Study ZWI-ZW25-203 (Study 203) (Section 7). Study 101, the initial dose-finding study for zanidatamab, included participants with any locally advanced (unresectable) and/or metastatic HER2-expressing (HER2 1+, 2+, or 3+ by IHC) cancers who received zanidatamab monotherapy at doses ranging from 5 mg/kg to 15 mg/kg administered QW, 20 mg/kg to 30 mg/kg administered Q2W, and 30 mg/kg Q3W. Study 203 was a Phase 2b study of 20 mg/kg Q2W zanidatamab monotherapy in participants with HER2-amplified BTC.

In the Phase 1 dose escalation study (Study 101), zanidatamab PK exhibited nonlinear kinetics with more rapid CL at low doses. Following the first dose, as doses increased the geometric mean C_{max} was dose proportional while total systemic exposure ($AUC_{0-\infty}$) was greater than dose proportional. Exposure appeared less than dose proportional at 5 mg/kg QW. At steady-state, 10 mg/kg QW and 20 mg/kg Q2W had comparable geometric mean trough concentrations. Based on the PopPK Report, the data suggest that the target-mediated elimination pathway is likely saturated and in the linear range at the dose level of 10 mg/kg QW and above. The geometric mean accumulation indices based on $C_{trough,ss}$ was approximately 2.7 (20 mg/kg Q2W zanidatamab).

The PK of IV zanidatamab was characterized by a 2-compartment model with parallel linear and nonlinear CL pathways. The PopPK analysis used 3711 zanidatamab serum concentrations from 279 participants (192 from Study 101 and 87 from Study 203). Participants with BTC were predicted to have a CL of 0.0115 L/h, a V_c of 3.51 L, a V_p of 3.95 L, and a t½ of approximately 21 days. Based on the estimated t½, it would take approximately 3.5 months (ie, 5 half-lives) to reach steady-state following multiple-dose administration of zanidatamab.

The Applicant's Position:

Zanidatamab exhibits nonlinear PK following single doses from 5 mg/kg QW to 30 mg/kg Q2W. At steady-state, based on the PopPK analysis, the data suggest that the target-mediated elimination pathway is likely saturated and in the linear range at the dose level of 10 mg/kg QW and above. Zanidatamab geometric mean accumulation indices based on $C_{trough,ss}$ is approximately 2.7 (20 mg/kg Q2W dose level) and t½is approximately 21 days in participants with BTC.

The FDA's Assessment:

FDA generally agrees with the Applicant's position on the PK characteristics of zanidatamab. The clinical pharmacology program for the current BLA included the following assessments supported by data from two clinical studies.

- Dose escalation/expansion/confirmation:
  - Study ZWI-ZW25-101: Dose escalation and expansion study to evaluate zanidatamab monotherapy in participants with locally advanced unresectable and/or metastatic HER2-expressing solid tumors.
  - Study ZWI-ZW25-203: Open-label, single-arm, registrational study to evaluate the efficacy and safety of zanidatamab monotherapy in participants with advanced or metastatic HER2-amplified biliary tract cancers.
- PopPK analysis and E-R analysis (refer to Section 19.4 for details).

FDA agrees that the proposed recommended dosage of 20 mg/kg Q2W is approvable for the granted indication although the Applicant conducted limited dosage optimization (refer to the discussions in Section 6.2.2.1 and 6.3.2.2). The dosage was evaluated in a limited number of patients at few dosage levels; therefore, the E-R analysis heavily relies on the proposed recommended dosage of 20 mg/kg Q2W.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

In Part 1 of Study 101, 3 dosing schedules (QW, Q2W, and Q3W) for zanidatamab at doses ranging from 5 to 30 mg/kg were evaluated. The MTD of zanidatamab as monotherapy was not reached. The dose regimen of 5 mg/kg QW was not further evaluated since no cORR was observed at this dose level (N = 3). This is consistent with observed C_{trough} values following the first zanidatamab 5 mg/kg QW dose below the IC_{90} (25.0 µg/mL) (JZP598-IR-1535) for ligand-dependent cellular growth inhibition. Simulated clearance suggested that the target-mediated elimination pathway was likely saturated at 20 mg/kg Q2W, since it was comparable to that of the higher dose of 30 mg/kg Q2W (median CL_{ss} [10th to 90th percentiles]: 0.0123 [0.0079 to 0.0190] and 0.0115 [0.0076 to 0.0178] L/h for 20 and 30 mg/kg Q2W, respectively) further supporting the dose selection of 20 mg/kg Q2W. Recommended doses of 10 mg/kg QW and 20 mg/kg Q2W were selected for further evaluation in Part 2 of Study 101. Since 10 mg/kg QW and 20 mg/kg Q2W have comparable exposures, 20 mg/kg Q2W was selected for evaluation in pivotal Study 203 providing a less frequent dosing option.

In Study 203, zanidatamab 20 mg/kg Q2W demonstrated clinically meaningful anticancer activity with durable responses and clinically meaningful survival benefits in participants with HER2-amplified BTC who had received at least 1 prior therapy (Section 8.1.2). The exposure-efficacy relationship was evaluated in Study 203 participants with HER2-amplified BTC. The exposure-efficacy analysis showed a trend toward approaching a plateau for the probability of cOR assessed by ICR. As zanidatamab exposure (Cycle 1 C_{min}) increased, the probability of cOR increased and approached a plateau at the second quartile and beyond, suggesting that higher exposure/higher dose (ie, 25 mg/kg Q2W) is not expected to result in a greater probability of cOR. Conversely, zanidatamab exposure in the majority of patients following a lower dose (ie, 15 mg/kg Q2W) is expected to be in the lower quartiles which may

result in a lower probability of cOR. Following zanidatamab 20 mg/kg Q2W at steady state, 85.8% of patients would have trough levels associated with cOR of 41%. The relatively lower percentage of IHC 3+ in quartile 1 may have confounded the apparent low ORR in this quartile (the percentage of participants with IHC 3+ was 52.4%, 68.2%, 90.9%, and 72.7% in quartiles 1, 2, 3, and 4, respectively). Exposure-response analyses should be interpreted with caution due to the potential confounding effect of HER2 IHC status or other unmeasured factors, as well as the fact that the analyses were conducted on a single dose level.

The ER relationship for safety of zanidatamab was assessed for AEs classified as diarrhea, Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, IRRs, Grade ≥ 3 IRRs, and SAEs from 279 participants (pooled from Study 101 [N = 192] and Study 203 [N = 87]. No statistically significant ER safety relationship was found for any safety endpoints examined, except for diarrhea, where higher zanidatamab exposure was associated with an increased probability of diarrhea. Despite the apparent ER trend for diarrhea, there is no statistically significant ER relationship for Grade ≥ 3 diarrhea. In addition, there was a low incidence of TEAEs leading to treatment discontinuation (2 participants [2.3%] in Study 203). Overall, zanidatamab monotherapy was tolerable across the range of doses and cancer types evaluated, had an acceptable safety profile in the targeted BTC patient population with AEs that are manageable in the outpatient setting, and did not reveal new or unanticipated safety signals.

The Applicant's Position:

The dose regimen of 20 mg/kg IV administered Q2W for participants with HER2 positive BTC is supported by: 1) PK data indicating the selected dose achieves the desired target exposure, 2) saturated target-mediated elimination pathway, 3) acceptable clinical safety profiles with AEs that are manageable in the outpatient setting and supported by the exposure-safety analysis, and 4) a clinically meaningful efficacy profile supported by the exposure-efficacy analysis.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that clinical data and quantitative modeling data support the proposed recommended dosage of 20 mg/kg Q2W.

The maximum tolerated dose (MTD) was not reached in the dose escalation part of Study ZWI-ZW25-101. The safety profiles are generally comparable across the dosages evaluated (Table 10). In Study ZWI-ZW25-101 in patients with advanced or metastatic HER2 expressing solid tumors, the preliminary antitumor activity (based on the confirmed ORR) was generally observed across the range of dosages with highest activity at the proposed dosage of 20 mg/kg Q2W, although activity was evaluated in few patients at other dosages. In addition, the efficacy was confirmed in the registrational study ZWI-ZW25-203 in patients with advanced or metastatic BTC with HER2 amplification (ISH^+) and overexpression ($IHC3^+$) (Table 11).

Table 10: Summary of Key Safety Parameters in Studies ZWI-ZW25-101 and ZWI-ZW25-203

%	Study 101 Dose Escalation							Study 101 Dose Esxpansion	Pooled Studies 101 and 203
	5 mg/kg QW (N=3)	10 mg/kg QW (N=6)	15 mg/kg QW (N=7)	20 mg/kg Q2W (N=7)	25 mg/kg Q2W (N=6)	30 mg/kg Q2W (N=6)	30 mg/kg Q3W (N=11)	20 mg/kg Q2W (N=146)	20 mg/kg Q2W (N=233)
Treatment Emergent Adverse Events (TEAEs)	100	100	100	100	100	100	100	99	98
≥Grade 3 TEAE	33	33	43	29	33	33	9	43	50
SAE	0	33	43	29	17	0	0	22	34
TEAE leading to infusion interruption*	33	50	29	43	33	33	27	29	28
TEAE leading to discontinuation	0	0	0	14	0	0	9	3	3
TEAE leading to dose reduction	0	17	0	0	0	0	0	1	2
TEAE leading to interruption**	0	50	14	0	0	0	0	6	15

Table 11: Summary of Key Efficacy Parameters in Studies ZWI-ZW25-101 and ZWI-ZW25-203

%	Study 101 Dose Escalation							Study 101 Dose Esxpansion	Study 203 Cohort 1 HER2 IHC3+
	5 mg/kg QW (N=3)	10 mg/kg QW (N=4)	15 mg/kg QW (N=5)	20 mg/kg Q2W (N=7)	25 mg/kg Q2W (N=6)	30 mg/kg Q2W (N=6)	30 mg/kg Q3W (N=11)	20 mg/kg Q2W (N=145)	20 mg/kg Q2W (N=62)
Confirmed ORR (%)	0	25	20	29	17	0	9	29	52

6.2.2.2. Therapeutic Individualization

Data:

The PopPK analysis demonstrated that baseline covariates (including age, sex, race, ALT, AST, TBIL, NCI liver function group, eGFR, renal function categories, tumor size, HER2 expression, and sHER2 ECD concentration), did not have a significant influence on zanidatamab PK. Although baseline body weight, baseline ALB, baseline number of lesions, and cancer type were covariates impacting PK, they are not likely to have a clinically relevant impact on efficacy and safety, as the GMR values of PK exposures for all covariate groups were maintained within the bounds of 0.8 to 1.25 (other than GEA cancer type). The impact of severe renal impairment, end-stage renal disease (with or without dialysis), moderate (TBIL > 1.5 to ≤ 3 ULN and any AST) or severe (TBIL > 3 ULN and any AST) hepatic impairment on the PK of zanidatamab either was not studied or sufficient data were not available to draw definitive conclusions. No dose adjustment is necessary for zanidatamab in patients with BTC based on the evaluated covariates.

The Applicant's Position:

Based on the PopPK analysis, no clinically significant differences in the PK of zanidatamab were observed based on age (24 to 88 years), sex, race (White, Black, Asian), mild and moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI equation), mild hepatic impairment (TBIL ≤ ULN and AST > ULN or TBIL between 1 and 1.5 times ULN and any AST), tumor size (12 to 312 mm), HER2 expression (0 to 3+ by IHC), baseline sHER2 ECD concentration, and body weight (35.4 to 128 kg).

The clinical PK, efficacy, and safety data in participants with HER2-positive BTC, along with the findings of exposure-efficacy and exposure-safety relationships, support IV 20 mg/kg Q2W zanidatamab as a safe and effective dose for patients with BTC; dose modifications are not necessary based on the evaluated intrinsic or anticipated extrinsic factors.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Based on the PopPK analysis using data from Studies 101 and 203, the following factors have no clinically meaningful effect on the exposure of zanidatamab: age (24 to 88 years), sex, race (White and Asian), mild and moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI), mild hepatic impairment (total bilirubin ≤ upper limit of normal (ULN) and AST > ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or body weight (35 kg to 128 kg). Although the PopPK covariate analysis identified baseline body weight, albumin (ALB), baseline number of lesions, and cancer type as significant predictors of CL, as well as body weight and cancer type as significant predictors of Vc and cancer type as predictor of Vp, these covariates are unlikely to lead to clinically relevant differences in steady state zanidatamab exposures at the proposed dosing regimen of 20 mg/kg Q2W. Therefore, no dosage adjustments are recommended for the intrinsic and extrinsic covariates evaluated (refer to Section 19.4 for details of PopPK and E-R analyses).

6.2.2.3. Outstanding Issues

Data and The Applicant's position:

N/A

The FDA's Assessment:

As discussed in Section 6.3.1 below, the treatment-emergent ADA incidence reported by the Applicant was not reliable. A PMC will be issued requesting the Applicant to reanalyze the ADA samples from studies 101 and 203 using a validated assay and reevaluate the effect of ADAs on efficacy, PK, and safety of zanidatamab.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Zanidatamab is a humanized, IgG1-like, HER2-targeted bispecific antibody (binding and MOA in Section 5.3). The PK of IV zanidatamab in participants with BTC and various cancer types was characterized by a 2-compartment model with parallel linear and nonlinear CL pathways. From the PopPK analysis, participants with BTC were predicted to have a typical CL of 0.0115 L/h, a typical V_c of 3.51 L, a typical V_p of 3.95 L, and an estimated $t_{1/2}$ of approximately 21 days, taking approximately 3.5 months (ie, 5 half-lives) to reach steady-state following multiple-dose administration of zanidatamab (Section 6.2.1). Exposure-response analyses evaluated the zanidatamab exposure-efficacy relationship in participants with HER2-amplified BTC and exposure-safety relationships in participants with HER2-expressing cancers. Findings support the use of IV 20 mg/kg Q2W zanidatamab (Section 6.2.2.1).

The relationship between time-matched zanidatamab serum concentrations and ΔQTcF measurements was evaluated using linear regression (data from Study 101). The concentration-QT analysis dataset included 948 time-matched zanidatamab concentrations and QTcF measurements from 179 of 192 enrolled participants. The upper bound of the 2-sided 90% CI (or upper bound of the 1-sided 95% CI) for the effect on the QTcF interval did not exceed 10 ms (the threshold level of regulatory concern). Based on PopPK model-predicted 20 mg/kg Q2W and 30 mg/kg Q3W zanidatamab exposures (C_{max}) at steady state, neither the mean nor the upper bound of the 2-sided 90% CI for the change in QTcF from baseline exceed the regulatory concern of 10 ms.

Zanidatamab immunogenicity evaluations yielded overall treatment-emergent ADA incidence of 1.5% (4 of 268 evaluable participants: 1.6% [3 out of 183], in Study 101 and 1.2% [1 out of 85] in Study 203 [the 1 ADA positive participant was also NAb positive]). In Study 203, there was no apparent impact of anti-zanidatamab antibodies on the PK of zanidatamab: C_{trough} for the 1 participant with treatment-emergent ADAs (75.4 µg/mL) was similar to the geometric mean C_{trough} for the 74 participants in Cohort 1 without treatment-emergent ADAs (73.7 µg/mL, %CV 58.26). There was also no apparent impact of anti-zanidatamab antibodies on zanidatamab safety, although an inter-group comparison of AE incidences is not informative (only 1 participant with treatment-emergent ADAs in Study 203). The participant with

treatment-emergent ADAs experienced SAEs (including asthenia, acute kidney injury, obstruction gastric, and sepsis; all Grade 3, none considered related to zanidatamab per investigator assessment), and did not experience an IRR or diarrhea, the most frequently reported TEAEs with zanidatamab treatment.

No formal drug-drug interaction studies have been conducted with zanidatamab.

The Applicant's Position:

In participants with locally advanced (unresectable) and/or metastatic HER2-expressing cancers, 20 mg/kg Q2W Zanidatamab had no clinically relevant prolongation effect on QTc interval.

Zanidatamab is categorized as a low-risk molecule to elicit an immune response based on the immunogenicity risk factors assessment and the low incidence of ADAs observed to date across the clinical studies (1.5% [4 of 268 evaluable participants] overall; 1.6% [3 of 183 evaluable participants] in Study 101; 1.2% [1 of 85 evaluable participants] in Study 203). The 1 participant in Study 203 who was positive for treatment-emergent ADA was also positive for NAb (1.2%). There is no apparent impact of ADAs on PK or safety, based on the available data.

As an antibody, zanidatamab is not expected to impact CYP enzymes, target mechanisms related to proinflammatory cytokines, or any mechanisms unrelated to proinflammatory cytokines that may impact the PK of concomitant medicines.

The FDA's Assessment:

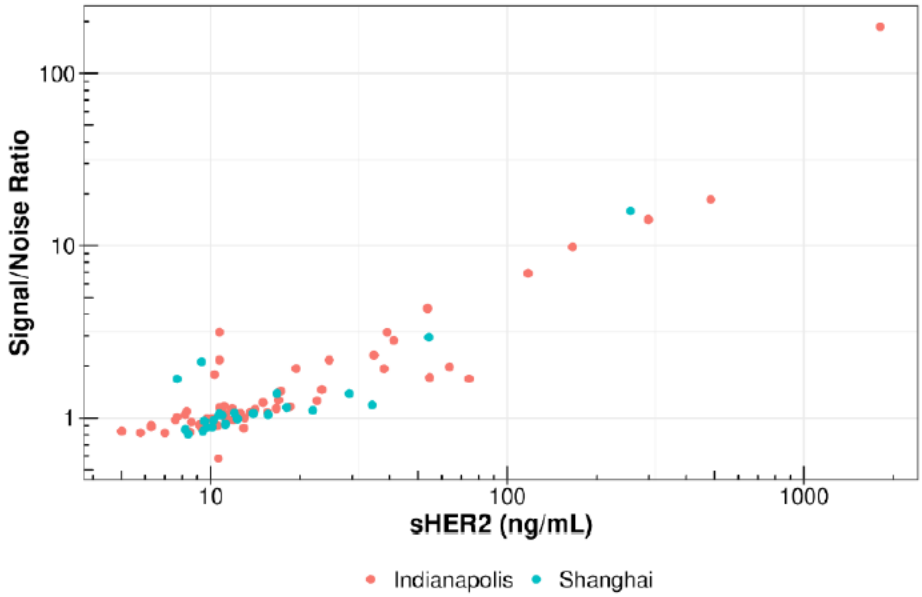
FDA generally agrees with the Applicant's characterization of zanidatamab clinical pharmacology. However, FDA disagrees with the following statements:

- "*Zanidatamab is categorized as a low-risk molecule to elicit an immune response. There is no apparent impact of ADAs on PK or safety, based on the available data.*"

The treatment-emergent ADA reported by the Applicant (i.e., 4 out of 268 [1.5%] evaluable participants) included treatment boosted ADA (i.e., pre-existing ADAs at baseline that are increased by 4-fold or higher after administration of zanidatamab) and treatment induced ADA (i.e., ADAs developed de novo [seroconversion] following administration of zanidatamab). However, two issues were identified in the ADA assay and study results:

1. There is a correlation between sHER2 levels and ADA^+ status (Figure 1) and titer, indicating that high sHER2 levels may interfere with the assay and result in false-positive ADA status and higher reported titer levels. Since sHER2 levels were higher at baseline compared to that following administration of zanidatamab, the reported "treatment-emergent" ADA is questionable due to the different extent of interference by sHER2 at baseline and post-treatment.

Figure 1: Baseline Signal/Noise Versus Baseline sHER2 Levels in Study 203



Abbreviations: sHER2 = soluble human epidermal growth factor receptor 2.
Note: Data are plotted on a ln log scale.
Source: Data on file from bioanalytical laboratory S/N ratio; sHER2 Adismi dataset from Study 203

2. A larger portion of ADA samples from studies 101 and 203 (up to 71%) collected at C_{trough} had the concentrations of zanidatamab above the drug tolerance limits of the ADA assays (Table 12). As such, the ADA status of these samples may not be reliably detected and ADA incidence may be underestimated.

Table 12: Summary of Key ADA Assay Characteristics Related to Immunogenicity Assessment and the Summary Results of Corresponding C_{trough}

Validation report number	SC-15/343-002 (Full validation)	SC-21/343-016 (Partial validation)	8425-102 (Full validation)	8414-361 (Full validation)
Bioanalytical Site	(b) (4)			
Clinical study	101	101	203	203
Positive control (PCs) for anti-pertuzumab Ab	100 ng/mL	NA	20 ng/mL^	100 ng/mL
Positive control (PCs) for anti-trastuzumab Ab	30 ng/mL^	100 ng/mL	20 ng/mL^	100 ng/mL
Positive control type	Mouse monoclonal Ab vs. pertuzumab Human monoclonal Ab vs. trastuzumab			

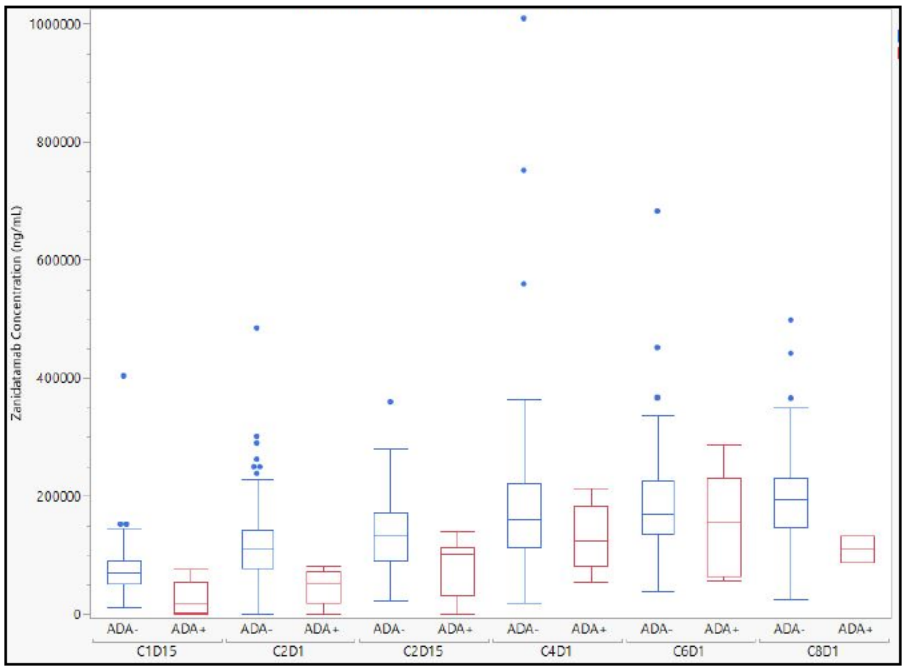
Drug tolerance*		• 117.25 µg/mL for anti-pertuzumab Ab • 70 µg/mL^ for anti-trastuzumab Ab	• 300 µg/mL for anti-pertuzumab Ab • NA for anti-trastuzumab Ab	• 100 µg/mL^ for both for anti-pertuzumab Ab and anti-trastuzumab Ab	• 188 µg/mL for anti-pertuzumab Ab • 171 µg/mL for anti-trastuzumab Ab
C_{trough} (µg/mL)	1st quartile	65.9		54.8	
	Median	106.1		123.0	
	3rd quartile	166.3		201.5	
	Max	752.0		1010.0	
% of samples with C_{trough} > drug tolerance of ADA assay for anti-pertuzumab Ab		45.5%	0.9%	58.7%^	29.0%
% of samples with C_{trough} > drug tolerance of ADA assay for anti-trastuzumab Ab		71.4%^	NA	58.7%^	33.3%

Due to the above concerns on the ADA assay, this reviewer conducted an exploratory analysis by including all 19 patients with post-treatment positive ADA regardless of the fold increase compared to baseline (i.e., N=14 from study 101 and N=5 from study 203). The analysis suggested that these 19 patients had greater incidence of Grade 3-4 TEAEs and SAEs (Table 13), as well as lower PK exposure compared to patients without post-treatment positive ADA (Figure 2).

Table 13: Percentage of Grade 3-4 TEAE and SAE in Patients with and without Post-treatment Positive ADA

%	Study 101		Study 203	
	Patients without post-treatment positive ADA (N=170)	Patients with post-treatment positive ADA (N=14)	Patients without post-treatment positive ADA (N=80)	Patients with post-treatment positive ADA (N=5)
Grade 3-4 TEAE	40	50	63	100
SAE	21	36	51	80

Figure 2: Trough Zanidatamab Concentrations in Patients with and without Post-Treatment Positive ADA



A PMC will be issued to reanalyze the ADA samples from studies 101 and 203 using a validated assay capable of sensitively detecting ADA responses and reevaluate the immunogenicity of zanidatamab and the effect of ADAs on efficacy, PK, and safety of zanidatamab.

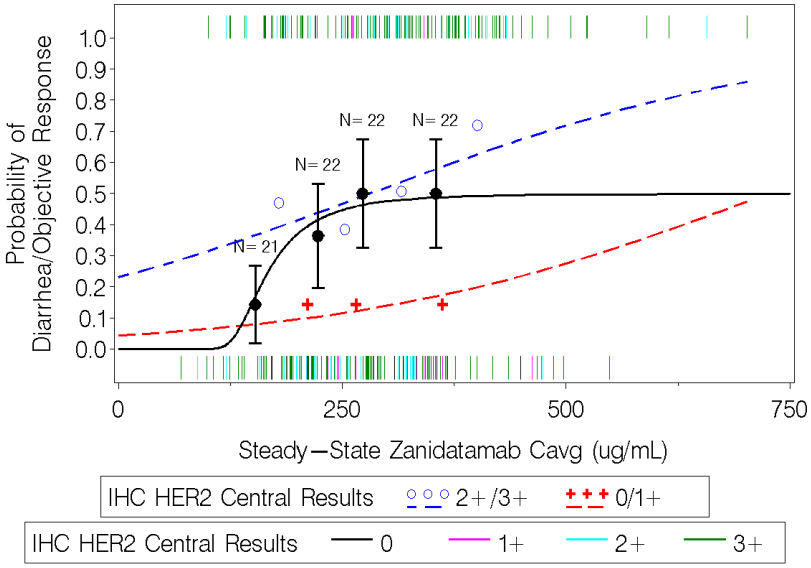
6.3.2. Clinical Pharmacology Questions

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

Data:

Along with the supportive evidence (Section 6.2.2.1), the clinical utility of zanidatamab is shown in Figure 3, which presents the correlation of zanidatamab concentration with both efficacy (probability of OR) and safety (probability of diarrhea). Zanidatamab C_{avg} at steady-state was used in the clinical utility plot for both efficacy and safety.

Figure 3. Clinical Utility Plot: Observed and Model-Predicted Probability of Diarrhea and Objective Responses Versus Zanidatamab Steady-State C_{avg}



Abbreviations: C_{avg} = average concentration; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry.
Note: The dashed lines represent the model-based predicted probability of diarrhea for each HER2 grouping. The open circles and plus signs represent the median steady-state C_{avg} values and associated observed probabilities of diarrhea. The hash marks at the top and bottom of the figure represent the individual steady-state C_{avg} values for subjects with and without diarrhea, respectively, color coded by HER2 IHC status. The black solid circles and bars represent the associated observed probabilities and 90% confidence interval of objective response at the median exposure of each quartile. The solid black line represents the model-predicted objective response.
Source: ER Report Figure 41.

The Applicant's Position:

In the clinical utility plot (Figure 3), the majority of participants (second quartile and beyond) had an exposure range that was on the plateau part of the efficacy curve (ie, with increasing exposure, there is no corresponding increase in efficacy). The clinical utility plot also shows that higher exposures may result in a higher probability of diarrhea. Conversely, lower exposure or lower doses than 20 mg/kg Q2W are predicted to be associated with a lower probability of efficacy. Consequently, 20 mg/kg Q2W is considered the optimal dose regimen for zanidatamab, which is expected to maximize the clinical benefit for patients with BTC.

Clinical efficacy supports clinical pharmacology data. In Study 203, zanidatamab 20 mg/kg Q2W demonstrated clinically meaningful benefit with durable responses and clinically meaningful survival in participants with HER2-amplified BTC who had received at least 1 prior therapy (Section 6.2.2.1).

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Evidence of effectiveness is provided by the results of the Study 203 (refer to Section 8.1.2). Supportive evidence is provided by the PK results, receptor occupancy (RO), popPK analysis and E-R analyses for safety and efficacy. An apparent E-R safety trend was observed for the occurrence of diarrhea (all grades); however, such trend was not observed for Grade ≥3 diarrhea. The E-R analysis of efficacy showed a trend that the probability of confirmed OR increased with higher zanidatamab exposure and approached a plateau at the second quartile and beyond. However, this positive exposure-efficacy trend should be interpreted with caution due to 1) the relatively lower percentage of participants with IHC 3^+ in the first quartile may potentially confounding the E-R assessment, and 2) the analysis was conducted using only one dosing regimen with limited total participants (refer to Section 19.4 for details of PopPK and E-R analyses).

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

Data:

The dose regimen of 20 mg/kg IV administered Q2W for participants with HER2 positive BTC is supported by: 1) PK data indicating the selected dose achieves the desired target exposure, 2) saturated target-mediated elimination pathway, 3) acceptable clinical safety profiles with AEs that are manageable in the outpatient setting and supported by the exposure-safety analysis, and 4) a clinically meaningful efficacy profile supported by the exposure-efficacy analysis, as described in Section 6.2.2.1).

The Applicant's Position:

Zanidatamab 20 mg/kg Q2W is considered the optimal dose regimen for zanidatamab, which is expected to maximize the clinical benefit for patients with BTC.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. During the dose escalation phase of Study 101, 3 dosing schedules (QW, Q2W, and Q3W) for zanidatamab at doses ranging from 5 to 30 mg/kg were evaluated and only the 20 mg/kg Q2W was further evaluated in dose expansion. The dose exploration and optimization are limited by the relatively small sample size at 5 mg/kg QW (n=3), 10 mg/kg QW (n=6), 15 mg/kg QW (n=7), 25 mg/kg Q2W (n=6), and 30 mg/kg Q2W (n=6), and 30 mg/kg Q3W (n=11). While there is lack of adequate dosage optimization, clinical efficacy and safety data together with the PopPK analysis and ER analyses for efficacy and safety provided evidence of anti-tumor activity of zanidatamab at 20 mg/kg Q2W in patients with advanced or metastatic BTC with HER2 amplification (ISH^+) and overexpression ($IHC3^+$). Hence, the Applicant's proposed recommended dosage of 20 mg/kg Q2W is acceptable. Refer to Section 6.2 for more details.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

A PopPK analysis was performed to evaluate the need for dose adjustment in special populations based on the participant's baseline covariates. Age, sex, race, AST, ALT, TBIL, NCI liver function group (normal to mild), eGFR, renal function categories (normal, mild, and moderate), tumor size, cancer type (other than GEA), HER2 expression, and sHER2 ECD concentration had no significant influence on the PK of zanidatamab. Although baseline body weight, ALB, and the number of lesions were statistically significant covariates, they are not expected to have a clinically relevant impact on zanidatamab PK exposure (Section 6.2.2.2) as the GMR values of PK exposures for all covariate groups were maintained within the bounds of 0.8 to 1.25.

The Applicant's Position:

Dose modifications are not necessary based on the evaluated intrinsic or anticipated extrinsic factors.

The FDA's Assessment:

FDA generally agrees with the Applicant's position (refer to Section 6.2.2.2 for the assessment and Section 19.4 for details of PopPK and E-R analyses).

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

Data:

No formal food-drug or drug-drug interaction studies have been conducted with zanidatamab.

The Applicant's Position:

As an IV antibody, extrinsic factors (eg, food, smoking, concomitant medications) are not expected to affect zanidatamab's PK. Hence, the effect of extrinsic factors on the PK has not been evaluated with dedicated studies or in the PopPK analysis. Zanidatamab is not expected to impact CYP enzymes or target mechanisms related or unrelated to proinflammatory cytokines that may impact the PK of concomitant medicines.

The FDA's Assessment:

FDA agrees with the Applicant's position.

X	X
Primary Reviewer	Team Leader

7. SOURCES OF CLINICAL DATA

7.1. Table of Clinical Studies

Data and the Applicant's position:

Data from primarily 2 clinical studies, summarized in Table 14, are relevant to this Application.

Table 14: Listing of Clinical Trials Relevant to this BLA

Study (Phase) NCT Number	Region (no. of centers)	Study Population	Design Study Objectives Safety Endpoints	Zanidatamab Treatment Regimen	Gender M/F (%) Median Age, yrs (range)	No. Enrolled/ Discontinued[a]/ Ongoing Follow-up Study Start
Pivotal ZWI-ZW25-203 (Phase 2b) NCT04466891	N Am (17) S Am (2) Europe (20) Asia (32)	HER2 gene-amplified, inoperable, and advanced or metastatic BTC **Cohort 1:** HER2 expression of IHC 2+ or 3+ and ISH+ **Cohort 2:** HER2 expression of IHC 0 or 1+ and ISH+	Design: Open-label, 2-cohort, single-arm Objectives: Antitumor activity, safety, PK, immunogenicity Efficacy Endpoints: cORR, DOR, PFS, DCR, CBR, OS Safety Endpoints: AEs, Change in clinical laboratory tests, concomitant medications, physical examination findings, ECOG PS, vital signs, ECG, and ECHO/MUGA scan	Monotherapy 20 mg/kg IV Q2W	**Cohort 1:** M/F: 44/56 Age: 64.0 (32, 79) **Cohort 2:** M/F: 71/29 Age: 62.0 (56, 77)	**Cohort 1:** 80/71/20 **Cohort 2:** 7/6/1 Start: Sep 2020
Supportive ZWI-ZW25-101 (Phase 1) NCT02892123	N Am (12) S Korea (5)	Locally advanced (unresectable) and/or metastatic HER2-expressing cancers Part 2 BTC Cohort: HER2 expression of IHC 3+ or IHC 2+ and ISH+	Design: Open-label, 3-part, single-arm • Part 1: monotherapy, 3+3 dose escalation, DLT evaluation • Part 2: monotherapy expansion cohorts at MTD, OBD, or RD • Part 3: not applicable to this application Objectives: Safety and tolerability, PK, immunogenicity, antitumor activity Efficacy Endpoints: cORR, DCR, PFS Safety Endpoints: DLTs, AEs, clinical laboratory values, ECG, ECOG PS, ECHO/MUGA scan, dose reductions	**Part 1:** Monotherapy • 5, 10, and 15 mg/kg IV QW • 20, 25, and 30 mg/kg IV Q2W • 30 mg/kg IV Q3W **Part 2:** Monotherapy • 10 mg/kg IV QW • 20 mg/kg IV Q2W	**Part 1:** M/F: 48/52 Age: 61.5 (27, 88) **Part 2:** M/F: 46/54 Age: 60.0 (24, 86)	**Part 1:** 46/44/2 **Part 2:** 146/135/11 Start: Sep 2016

Abbreviations: AE = adverse event; BLA = Biologics License Application; BTC = biliary tract cancer; CBR = clinical benefit rate; cORR = confirmed objective response rate; DCR = disease control rate; DLT = dose-limiting toxicity; DOR = duration of response; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; IV = intravenous; M/F = male/female; MTD = maximum tolerated dose; MUGA = multi-gated acquisition; N Am = North America; no = number; OBD = optimal biologic dose; OS = overall survival; PFS progression-free survival; PK = pharmacokinetic(s); Q2W = once every 2 weeks; Q3W = once every 3 weeks; QW = once a week; RD = recommended dose; S Am = South America; S Korea = South Korea; yrs = years.

[a] Discontinued from study treatment.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the clinical studies used for the risk-benefit assessment in this BLA.

The supportive Study ZWI-ZW25-101 (Study 101) entitled "Phase 1 trial of ZW25 in patients with locally advanced (unresectable) and/or metastatic HER2-expressing cancers" is a 3-part dose escalation and expansion study. Parts 1 and 2 have been outlined by the Applicant above. Part 3 is evaluating the safety, tolerability, and preliminary efficacy of zanidatamab as part of a combination regimen, and the findings are not applicable to this application.

The efficacy assessments were based on data from Cohort 1 of the Phase-2b study ZWI-ZW25-203 (Study 203). Cohort-1 enrolled patients with advanced or metastatic BTC (including ICC, ECC, and GBC) with HER2 amplification by ISH and HER2 overexpression by IHC (i.e., IHC 2+ or 3+).

The safety assessments included data from both Study ZWI-ZW25-203 and Study ZWI-ZW25-101.

8. STATISTICAL AND CLINICAL EVALUATION

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Study ZWI-ZW25-203 (Study 203)

Trial Design

The Applicant's Description:

Study 203 is a pivotal, multicenter, open label, single arm study that evaluated antitumor activity of zanidatamab monotherapy in participants with HER2 amplified, inoperable and advanced or metastatic BTC, including ICC, ECC, and GBC. Two cohorts of participants were enrolled:

- Cohort 1 (primary efficacy population), composed of participants with HER2 amplification by ISH and HER2 overexpression by IHC (ie, IHC 2+ or 3+)
- Cohort 2, composed of participants with HER2 amplification by ISH and HER2 IHC 0 or 1+

Enrolled participants received zanidatamab, 20 mg/kg IV Q2W until a protocol-defined treatment discontinuation criterion was met. Disease response was evaluated once every 8 weeks by CT or MRI. Participants who discontinued treatment with zanidatamab entered the 30-day safety follow up period and survival follow up. Participants who discontinued treatment for reasons other than disease progression continued to have scans until disease progression or start of new therapy.

The FDA's Assessment:

FDA generally agrees with the Applicant's description. Study 203 is a non-randomized study consisting of two cohorts as described above. Enrollment into a cohort was determined based on central confirmation of HER2 IHC expression.

Eligibility Criteria

The Applicant's Description:

Participants had histologically or cytologically confirmed, inoperable and advanced or metastatic BTC with at least 1 measurable target lesion by RECIST version 1.1. All participants received at least 1 prior gemcitabine containing systemic chemotherapy regimen for advanced disease and had disease progression after or developed intolerance to the most recent prior therapy. Prior to enrolment, new or archival tumor tissue was provided for HER2 amplification and HER2 protein expression testing at a central laboratory using ISH and IHC assays. A key exclusion criterion was any prior treatment with a HER2-targeted agent.

The FDA's Assessment:

FDA generally agrees with the Applicant's description. Patients who received gemcitabine-based therapies in the neoadjuvant or adjuvant setting with disease progression within 6 months of either surgical resection or completion of adjuvant treatment were eligible for this study. The eligibility criteria specified that all patients must have centrally confirmed HER2 amplification by an ISH assay. All patients had central assessment of HER2 expression by an IHC assay, however this was not a prespecified eligibility criteria.

Patients were required to have a left ventricular ejection fraction (LVEF) ≥ 50% and individuals with QTcF > 470 ms were excluded.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was cORR by RECIST version 1.1 assessed by ICR. The secondary efficacy endpoints were DOR, DCR, CBR, PFS by RECIST version 1.1 assessed by both ICR and investigator, and OS. The surrogate endpoint cORR is reasonably likely to predict the clinical benefit of zanidatamab on HER2-positive BTC and is suitable to support an Accelerated Approval pathway.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the primary and secondary efficacy endpoints for Study 203. However, time-to-event endpoints are not interpretable in single-arm studies and disease control rate of clinical benefit rate suitable for assessment of treatment effect and therefore considered exploratory. In regards to the suitability of ORR to support accelerated

approval, the adequacy of the results is based on the disease setting, magnitude, and duration of response in a prespecified and adequate sample size.

Statistical Analysis Plan and Amendments

The Applicant's Description:

This was a single-arm, open-label study. No statistical hypotheses were tested. Descriptive analyses were performed on the following data sets:

- Safety: all participants who received any amount of zanidatamab.
- Efficacy: all participants who received any amount of zanidatamab.
- Response evaluable: all participants in the safety analysis set with measurable disease at baseline and at least 1 evaluable post-baseline disease assessment (per RECIST version 1.1) or who discontinued study treatment due to death or unequivocal clinical progression.

The primary efficacy analysis was based on the Cohort 1 Efficacy Analysis Set. There were no differences between the planned and actual analyses. Data as of 28 July 2023 are presented in this application.

The cORR, CBR, and DCR and corresponding two-sided, exact Clopper-Pearson binomial 95% CI were calculated. The time to first confirmed objective response was calculated as the time from the first dose of study treatment to the earliest date a participant had a confirmed objective response (CR or PR).

Kaplan-Meier plots and estimates of the quartiles and their corresponding two-sided 95% CI were computed for DOR, PFS, and OS using the Brookmeyer and Crowley method with log-log transformation. Participants who were alive and had not progressed at the time of the analysis were censored at the time of their last tumor assessment that was a CR, PR, SD, or non-CR/non-PD. Censoring rules were prespecified in the Statistical Analysis Plan.

The proportion of participants with PFS and OS at defined time points was also provided. Two-sided 95% CIs for these landmark PFS estimates were based on the Greenwood estimator. The following sensitivity analyses were performed to assess the robustness of the estimates of PFS using the same statistical methods described above for the analysis of PFS:

- clinical progression was treated as an event in addition to radiographic progression and death.
- participants who initiated a new therapy prior to experiencing disease progression were considered to have had an event (PD) at the time of new therapy.
- participants who died or progressed after 2 or more consecutive missed or non-evaluable tumor assessments were considered to have had PD on the date of the first missed visit.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of analysis methods for primary and secondary endpoints. However, time-to-event endpoints (e.g., PFS and OS) are not interpretable

in single-arm studies and therefore considered exploratory.

Protocol Amendments

The Applicant's Description:

The original protocol (dated 13 February 2020) was amended 4 times. These amendments did not impact integrity of the study or affect interpretation of study results.

- Amendment 1 (26 April 2020): Revised HRQoL assessments. Clarified AESI definitions, instructions for zanidatamab IV infusion, missed doses, and IRR reporting procedures.
- Amendment 2 (23 July 2020; China only): Added extensive PK sampling procedures for the first 10 participants with additional IDMC meetings for safety in these participants.
- Amendment 3 (21 April 2021): Clarified inclusion/exclusion criteria, extended radiographic follow-up, permitted brain CT, clarified schedule for ECHO/MUGA, added extensive PK assessments, revised AESI definitions, clarified guidance for managing AEs, updated safety reporting to include SAEs associated with progression of underlying disease and clarify reporting time period, added biomarker assessments.
- Amendment 4 (08 September 2023): Administrative updates to reflect current sponsor, medical monitor, investigational product synonyms, and study registration numbers.

The FDA's Assessment:

There were three amendments to protocol for Study 203 submitted to FDA. The dates the protocol amendments were received by FDA, and further details of the pertinent revisions made are outlined below. The Amendment dated July 23, 2020, cited by the applicant above was not submitted to FDA as a separate protocol amendment, with details for the China only revisions included in Protocol Amendment #2 below.

- Amendment #1 (Submitted May 7, 2020):

  FDA agrees with the summary of revisions cited by the Applicant above. In this amendment the revisions specified that absolute decreases of ≥ 10 percentage points below baseline LVEF will be considered an AESI. The Applicant removed EORTC QLQ-C30 and QLQ-BIL21 questionnaires from the HRQoL assessments and specified that disease-related pain will now be assessed using the BPI short form rather than the QLQ-BIL21 pain score.

- Amendment #2 (Submitted May 3, 2021):

  The revisions cited by the Applicant as Amendment 2, were combined with Amendment 3 and included the more extensive pharmacokinetic sampling of the initial 10 patients enrolled in China and 20 patients enrolled in the rest of the world.

  There were no substantial changes to the eligibility criteria. The Applicant added non-infectious pulmonary toxicities, LVEF decrease of ≥ 10% from baseline or absolute value < 50% and/or Grade 2 or higher heart failure to the AESI definitions. The schedule of

assessments stated that the first post baseline ECHO/MUGA scan was to be performed prior to Cycle 3 infusion.

The dose modification and adverse event management for nausea, vomiting, diarrhea, and rash was expanded to provide greater guidance for investigators especially in the event of Grade 3 or 4 toxicities. The Applicant also revised the guidance to permanently discontinue zanidatamab in the event absolute LVEF decrease ≥ 16% or Grade 2 or higher symptomatic congestive heart failure. Permanent discontinuation upon the occurrence of Grade 2 or higher ILD was added.

The Applicant revised the dose modification guidance from "Optional dose reduction to 15 mg/kg" to "consider dose reduction after discussion with the medical monitor."

- Amendment #3 (Submitted February 9, 2024)

The revisions included administrative updates following the change of Sponsor from Zymeworks to Jazz Pharmaceuticals. Inc.

8.1.2. Study Results – Pivotal Study ZWI-ZW25-203

Compliance with Good Clinical Practices

The Applicant's Position:

As a global, multicenter study, Study 203 was designed and conducted in accordance with the ICH guidelines (including ICH-E17), the US CFR governing the protection of human patients, IRBs, and international treatment guidelines for patients with BTC at the time of study design.

The FDA's Assessment:

FDA acknowledges the Applicant's position and confirms that a statement regarding the conduct of Study 203 in compliance with the International Council for Harmonization (ICH) guidelines for current Good Clinical Practice (GCP) was stated in the protocol.

Financial Disclosure

Data and the Applicant's Position:

Financial disclosure information is located in Section 19.2.

The FDA's Assessment:

See Section 19.2. No conflicts of interest were reported.

Patient Disposition

Data and the Applicant's position:

A total of 80 participants were enrolled in Cohort 1, all of whom were included in the safety and efficacy analysis data sets. At the time of the DCO, 9 (11.3%) participants continued to receive study treatment, and 71 (88.8%) participants had discontinued treatment, primarily due to radiographic progression (65 [81.3%] participants). Eleven (13.8%) participants who had discontinued treatment remained on study for survival follow-up, none of whom continued to undergo radiographic follow-up. The median duration of follow-up was 21.9 months (range, 16 to 34 months). As of the DCO, data are sufficiently mature to assess the primary endpoint of cORR, which is not expected to change with further follow-up.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary. A summary of patient's disposition in Cohort 1 stratified by IHC expression level in Study 203 is outlined in Table 15.

Table 15: FDA Analysis - Patient disposition in Cohort 1 stratified by IHC expression.

Zanidatamab 20 mg/kg (Cohort 1)	**IHC 3+**	**IHC 2+**
Treated	**62 (100%)**	**18 (100%)**
Treatment Discontinued	53 (85%)	18 (100%)
Treatment Ongoing	9 (15%)	0
Reason for Treatment Discontinuation[a]		
Disease Progression[b]	50 (81%)	17 (94%)
Adverse Event	2 (3%)	0
Physician/Patient Decision	1 (2%)	1 (6%)
Patient Died during Study	37 (60%)	15 (83%)

Source: FDA Analysis ADSL Dataset
Abbreviations: IHC: immunohistochemistry
[a] Includes Radiographic and Clinical Progression (N=1 for each IHC 2+ and IHC 3+ for clinical progression)
[b] Percentages calculated from Number Treated

All patients with HER2 IHC 2+ in Cohort 1 had discontinued treatment as of the data cutoff (DCO) July 28, 2023, whereas 9 (15%) of patients with HER2 IHC 3+ continued to receive treatment as of the DCO. Two patients with HER2 IHC3+ discontinued treatment due to an adverse event (decreased left ventricular fraction [N=1], pneumonitis [N=1]).

Protocol Violations/Deviations

Data:

As of the DCO, 19 (23.8%) participants had an important protocol deviation, defined as those that might significantly impact the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being. The majority were related to compliance with the treatment regimen (11.3%), procedural deviations (5%), or dosing error (3.8%).

The Applicant's Position:

None of the deviations led to treatment discontinuation or withdrawal from the study, and none affected interpretation of the primary endpoint or other study results.

The FDA's Assessment:

There were 771 protocol deviations/violations in total across Cohort 1 and 2 for Study 203, with the majority (N=743 [96%]) being non-important protocol deviations.

In total there were 28 protocol violations or deviations that were classified as important. Following an information request sent by FDA, the Applicant provided further details of protocol deviations that are summarized below.

- 10 participants had important protocol deviations related to treatment compliance other than dosing errors. This includes 7 patients who did not have the appropriate reduction in infusion rate following a preceding IRR, with 2 of these patients experiencing a second IRR at subsequent dosing.
- Pretreatment prophylaxis was not administered per protocol for 4 participants.
- Four patients did not have correct scheduling of their on-treatment Echo/MUGA, among these patients 1 had a Grade 3 decline in LVEF detected on Cycle 3 Day 1. The patient recovered from the decline in LVEF and was subsequently able to continue zanidatamab treatment. The same patient had a dosing error, where zanidatamab should have been held at the Cycle 6 Day 1 dose.

The protocol violations do not alter the efficacy findings that were reported in Cohort 1 of Study 203. The protocol violations may have increased the risks at the individual patient level, however, the associated adverse reactions i.e., Grade 3 LVEF reduction and Grade 2 IRR were identified and do not significantly change the safety assessment in this application. Overall, the reported protocol deviations/violations do not significantly alter the risk-benefit assessment within Study 203.

Table of Demographic Characteristics

Data:

Table 16: Demographic Characteristics (Study 203 Safety Analysis Set)

		Study 203 Cohort 1 (N=80)
Age at informed consent (years)	Mean (StD)	62.5 (9.56)
	Min, Max	32, 79
Sex, n (%)	Female	45 (56.3)
	Male	35 (43.8)
Race[a], n (%)	American Indian or Alaska Native	1 (1.3)
	Asian	52 (65.0)
	White	23 (28.8)
	Not reportable[b]	2 (2.5)
	Unknown	2 (2.5)
ECOG performance status, n (%)	0	22 (27.5)
	1	58 (72.5)

ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; StD = standard deviation.
[a] Participants may select more than one race category.
[b] Collection and/or reporting of this information is prohibited by local and/or regional laws or regulations.
Source: ZWI-ZW25-203 CSR Table 10.

The Applicant's Position:

Given the rarity of BTC and a further reduced subset of patients with HER2 expressing tumors, a broad range of clinical sites (university vs local clinics) in wide geographic locations were consciously included for enrollment into this study. Cohort 1 participants were representative of the target indication population with previously treated, unresectable locally advanced or metastatic HER2-positive BTC, which has a higher prevalence in Asian populations. There was representation of different racial and ethnic groups across the global regions. While BTC as a whole is reported to be more common in men, the GBC subtype of BTC is more common in women and is the subtype of BTC with the highest rate of HER2-positivity. Study 203 has a high percentage of participants with GBC, and as a result, has a greater representation of women than might otherwise be expected by overall disease demographics.

The FDA's Assessment:

The FDA analysis of patient demographics stratified by IHC 3+ versus 2+ is outlined in Table 17.

Table 17: FDA Analysis - Patient Demographics in Cohort 1 Stratified by Central IHC Expression

Zanidatamab 20 mg/kg (Cohort 1)	IHC 3+	IHC 2+
	N=62	N=18
Age		
Median (min, max) years	64 (38, 79)	65 (32, 79)
< 65 years (%)	33 (53)	8 (44)
≥ 65 years (%)	29 (47)	10 (56)
Gender		
Male (%)	28 (55)	7 (39)
Female (%)	34 (45)	11 (61)
Region (%)		
North America	15 (24)	3 (17)
Asia	36 (58)	14 (24)
Europe	11 (18)	1 (6)
Race (%)		
American Indian or Alaska Native	1 (2)	0
Asian	38 (61)	14 (78)
White	19 (31)	4 (22)
Not reportable/Unknown	4 (6)	0
Ethnicity (%)		
Hispanic or Latino	5 (8)	0
Non-Hispanic or Latino	55 (88)	17 (94)
Unknown/ Not Reported	2 (3)	1 (6)
ECOG PS (%)		
0	20 (32)	2 (11)
1	42 (68)	16 (89)

Source: FDA Analysis ADSL Dataset
Abbreviations: ECOG PS: Eastern Cooperative Oncology Group Performance Status; IHC: Immunohistochemistry

The demographics of patients with IHC 3+ are generally consistent with the demographics of all patients enrolled into Cohort 1. FDA has outlined the epidemiology of advanced BTC stratified by primary site (GBC versus cholangiocarcinoma) in Section 2. FDA does not agree with the Applicant's statement that the enrolled patient population is representative of either the US patient population or a global multiregional cohort of patients with advanced BTC in terms of race and ethnic background.

Majority of the patients from Cohort 1 were enrolled in Asia (South Korea [N=28], China [N=22]) with 17 enrolled patients from the US. While FDA acknowledges that the highest incidence of BTC is in Asia, the study did not enroll Black/African American patients and the

Latino/Hispanic population is underrepresented. See below Section 13 for requested trials to study the effects of zanidatamab in underrepresented minorities.

FDA agrees with the Applicant statement of GBC having both a higher incidence in women and proportionally higher rate of HER-2 positivity (Lee, Chon et al. 2023).

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

Data:

Table 18: Baseline Disease Characteristics and Disease History (Study 203 Safety Analysis Set)

	Characteristic	Study 203 Cohort 1 (N=80)
Disease subtype, n (%)	Gallbladder cancer	41 (51.3)
	Intrahepatic cholangiocarcinoma	23 (28.8)
	Extrahepatic cholangiocarcinoma	16 (20.0)
Stage at study entry[a], n (%)	IIIA	1 (1.3)
	IIIB	8 (10.0)
	IV	27 (33.8)
	IVB	44 (55.0)
Baseline hepatic impairment[b], n (%)	None	44 (55.0)
	Mild	35 (43.8)
	Moderate	1 (1.3)
	Severe	0
Baseline renal impairment[c], n (%)	Normal	27 (33.8)
	Mild to moderate	53 (66.3)
Outcome to most recent prior therapy, n (%)	Progressed	72 (90.0)
	Intolerant	8 (10.0)
Time from initial diagnosis to metastatic or locally advanced (months)	Mean (StD)	4.68 (9.764)
IHC result[d,e], n (%)	3+	62 (77.5)
	2+	18 (22.5)

Abbreviations: IHC = immunohistochemistry; ISH = in situ hybridization; Max = maximum; Min = minimum; RECIST = Response Evaluation Criteria in Solid Tumors; StD = standard deviation.
[a] Disease staging categories varied by disease subtype; categories IV and IVB are mutually exclusive.
[b] Per criteria of National Cancer Institute Organ Dysfunction Working Group.
[c] Per the Cockcroft-Gault formula for estimating creatinine clearance and FDA guidance titled: Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling.
[d] Based on a central laboratory companion diagnostic testing.
[e] All participants in the study were ISH+ at screening, based on a central laboratory companion diagnostic test.
Source: ZWI-ZW25-203 CSR Table 11.

All 80 participants received at least 1 prior gemcitabine-containing regimen for metastatic or locally advanced disease before enrollment. Participants received a median of 1 (range: 1 to 7) prior regimen for metastatic or locally advanced disease with 41.3% of participants being more

heavily pretreated (≥ 2 regimens). Prior radiotherapy and any prior surgery with curative intent were reported in 16.3% and 31.3% of participants, respectively.

The Applicant's Position:

Overall, the baseline disease characteristics of participants in Study 203 Cohort 1 were representative of the target indicated population.

The FDA's Assessment:

The FDA analysis of patients baseline clinical characteristics stratified by IHC 3+ versus 2+ (central testing) is outlined in Table 19.

Table 19: FDA Analysis - Patient Demographics in Cohort 1 Stratified by Central IHC Expression

Zanidatamab 20 mg/kg (Cohort 1)	**Central IHC 3+**	**Central IHC 2+**
	N=62	**N=18**
Primary Tumor Classification (%)		
Gallbladder Cancer	33 (53)	8 (44)
IHCC	17 (27)	6 (33)
EHCC	12 (19)	4 (22)
Local HER2 IHC results (%)		
IHC 1+	1 (2)	1 (6)
IHC 2+	9 (15)	4 (22)
IHC 3+	20 (32)	2 (11)
Unknown/Not reported	32 (52)	10 (56)
Prior Curative Surgery (%)	17 (27)	8 (44)
Prior Radiotherapy (%)	9 (15)	4 (22)
Stage at Study Enrollment (%)		
III	8 (13)	1 (6)
IV	21 (34)	6 (33)
IVB	33 (53)	11 (61)
Number of prior systemic treatment (median, range)	1 (1, 7)	1 (1, 4)
Gemcitabine based treatment		
Any Gemcitabine	62 (100)	18 (100)
Gemcitabine/cisplatin	47 (76)	14 (78)
Gemcitabine/oxaliplatin	19 (31)	2 (11)
Prior Anti PD(L)-1 treatment	16 (26)	5 (28)

Source: FDA Analysis ADSL Dataset
Abbreviations: IHC: Immunohistochemistry; IHCC: intrahepatic cholangiocarcinoma; EHCC: extrahepatic cholangiocarcinoma; PD(L)-1: programmed death receptor (ligand)-1

The clinical characteristics of patients enrolled into Cohort 1 with centrally confirmed IHC 3+ expression were generally similar to all patients in Cohort 1. The majority of patients with IHC 3+ have a primary diagnosis of gallbladder cancer (53%) and an initial diagnosis of Stage IV disease (53%). All patients with centrally confirmed IHC 3+ had received gemcitabine based prior therapy, with 76% receiving gemcitabine plus cisplatin, 26% had received prior anti-PD(L)-1 treatment, and 40% had received 2 or more lines of systemic treatment.

As during the latter phase of this study, the standard of care in the US for first line advanced BTC changed to include anti-PD(L)-1 treatment, the proportion of patients who receive first line anti-PD(L)-1 treatment in the US now would be expected to be higher.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

The most common concomitant medications administered were the protocol-required premedications for IRR prophylaxis including anilides (100%), glucocorticoids (100%), and antihistamines (substituted alkylamines [51.7%] such as chlorphenamine or dexchlorpheniramine or aminoalkyl ethers [25.3%] such as diphenhydramine or dimenhydrinate).

The Applicant's position:

Participants enrolled at various centers globally generally received supportive care similar to that of the US per protocol. Prior and subsequent cancer treatments were similar to treatments used to treat BTC in general and specifically HER2-positive BTC and are applicable to the global population. Supportive care across the study was nearly identical with the exceptions of choice of H1 blocker used as premedication in Korea and more naturopathic remedies used in China. Thus, even though Study 203 was heavily represented by Asian participants, the results should remain generally applicable to other racial groups.

The FDA's Assessment:

The protocol for Study 203 prespecified prophylactic treatment prior to each infusion of zanidatamab, including:

- Corticosteroids: either hydrocortisone 100 mg IV or dexamethasone 10 mg IV or equivalent or per institutional guidelines
- Antihistamines – diphenhydramine 50 mg PO or IV or per institutional guidelines
- Acetaminophen or paracetamol – 650 to 1000 mg PO or per institutional guidelines

The protocol did not require prophylactic treatment for diarrhea. In Study 203, 30 (38%) patients received anti-diarrheal treatment, most (N=24 [30%]) receiving loperamide.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

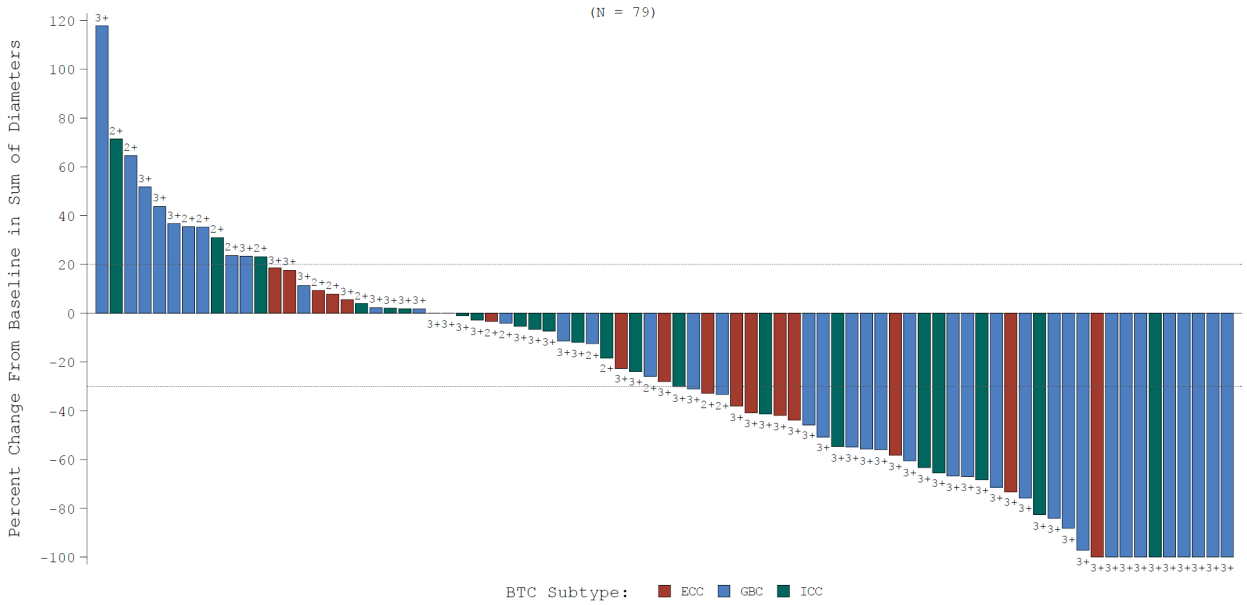
Data:

Table 20: Disease Response Assessed by ICR Using RECIST Version 1.1 (Study 203 Efficacy Analysis Set)

Endpoint		Study 203 Cohort 1 (N=80)
Confirmed objective response rate[a]	n (%)	33 (41.3)
	95% CI	(30.4, 52.8)
Confirmed best overall response, n (%)	Complete response	2 (2.5)
	Partial response	31 (38.8)
	Stable disease	22 (27.5)
	Progressive disease	24 (30.0)
	Not evaluable[b]	1 (1.3)
	Death	1 (1.3)[c]
Clinical benefit rate[d]	n (%)	38 (47.5)
	95% CI	(36.2, 59.0)
Disease control rate[e]	n (%)	55 (68.8)
	95% CI	(57.4, 78.7)

Abbreviations: CI = Clopper-Pearson binomial confidence interval; CR = complete response; ICR = independent central review; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
[a] Includes only confirmed CRs and PRs.
[b] No evaluable post-baseline response assessments.
[c] Participant died prior to first post-baseline tumor assessment.
[d] SD or non-CR/non-PD ≥ 24 weeks or confirmed best overall response of CR or PR.
[e] Best overall response of SD, non-CR/non-PD, or confirmed CR or PR.
Source: ZWI-ZW25-203 CSR Table 13.

Figure 4: Target Lesion Reduction by ICR (Study 203 Efficacy Analysis Set)



Abbreviations: BTC = biliary tract cancer; ECC = extrahepatic cholangiocarcinoma; GBC = gallbladder cancer; ICC = intrahepatic cholangiocarcinoma; ICR = independent central review; IHC = immunohistochemistry.
Notes: IHC status for each subject (2+ or 3+) is displayed above the individual bars.
Only subjects with measurable disease at baseline and at least 1 post-baseline assessment are included in the figure.
Source: ZWI-ZW25-203 CSR Figure 4.

Subgroup Analysis of cORR

The cORR for preplanned subgroups of disease subtype, intolerance to prior therapy, number of prior regimens, geographic region, sex, age, race, ECOG PS, and disease stage was similar to that for the overall population, with 95% CIs that overlapped. In the subgroup analysis by IHC expression status (2+ versus 3+), the cORR was 51.6% (95% CI: 38.6, 64.5) in participants with IHC 3+ (n=62) and 5.6% (95% CI: 0.1, 27.3) in participants with IHC 2+ (n=18).

The Applicant's Position:

The results from Study 203 show that zanidatamab monotherapy demonstrated clinically meaningful anticancer activity with durable responses in participants with HER2-amplified BTC who had received at least 1 prior gemcitabine-containing regimen. Although the cORR in participants with IHC 2+ (5.6%) was lower than the cORR in participants with IHC3+ (51.6%), the benefit in IHC2+ is comparable to the ORR of current later line treatment options for BTC including NCCN-recommended FOLFOX (5%).

The FDA's Assessment:

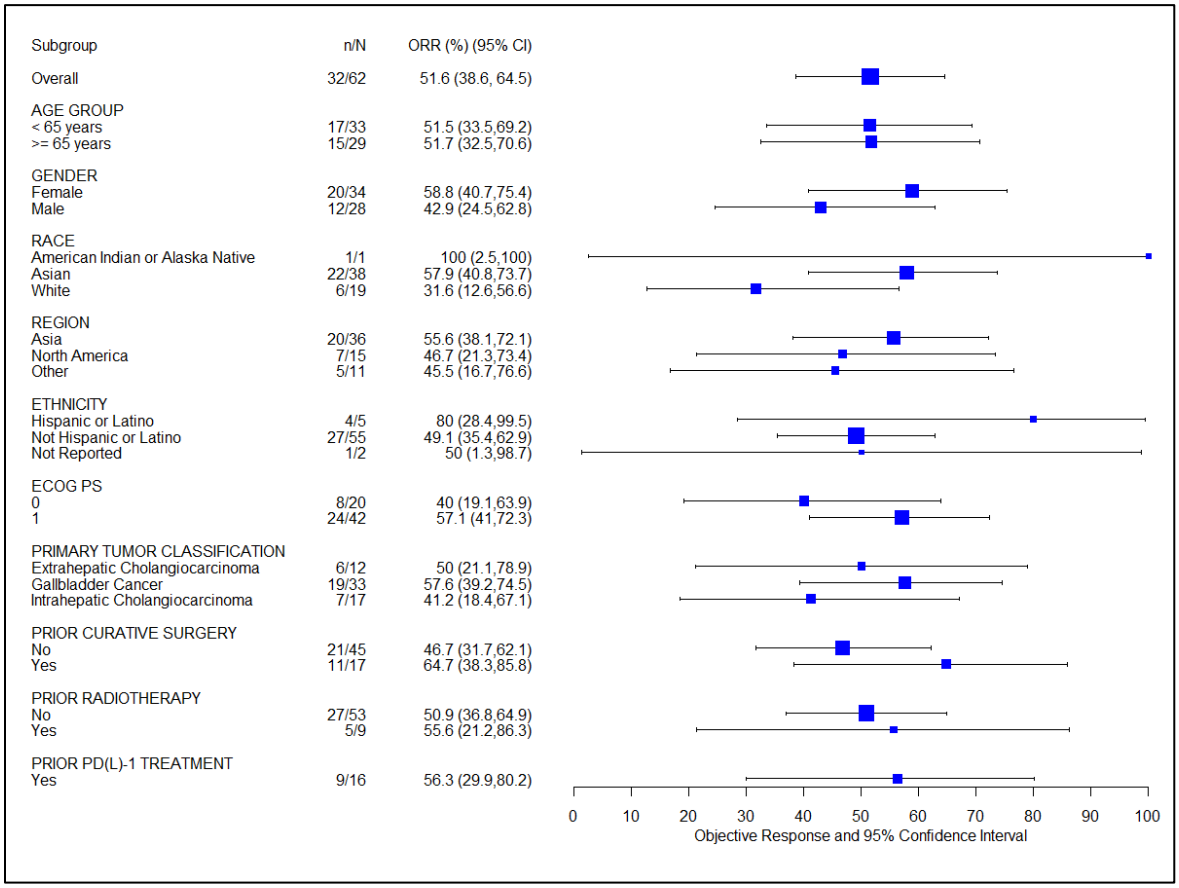
A summary of the overall efficacy stratified by IHC status in Cohort 1 of Study 203 is outlined in Table 21. FDA analyses of confirmed ORR by age, sex, geographical region, ECOG PS, and primary tumor site in patients with centrally determined ISH + IHC-3+ advanced BTC is outlined in Figure 5.

Table 21: FDA Analysis Efficacy Summary Stratified by IHC Status in Study 203

	IHC 3+ N=62	IHC 2+ N=18
ORR by ICR		
Responders, n	32	1
Response Rate, % (95% CI)	51.6 (38.6, 64.5)	5.6 (0.1, 27.3)
Complete Response, n (%)	2 (3.2)	0
Duration of Response		
Range, months	1.5+, 20.6	7.5*
Median (95% CI), months	14.9 (7.4, NE)	-
≥ 6 months, n (%)	19 (59)	1
≥ 12 months, n (%)	14 (44)	0
≥ 18 months, n (%)	4 (13)	0

Source: FDA Analysis, ADTTE, ADRS
Abbreviations: ORR: Objective Response Rate; ICR: Independent Central Review
*Observed DOR for the single responder.

Figure 5: Subgroup Analysis of ORR in IHC 3+



Source: FDA analysis; ADSL and ADRS datasets.

Data Quality and Integrity

Data and the Applicant's position:

The applicant does not anticipate data quality and integrity concerns.

The FDA's Assessment:

FDA acknowledges the Applicant's position. No specific concerns regarding data quality or integrity were identified during this review.

Efficacy Results – Secondary and other relevant endpoints

Data:

Duration of Response

For the 33 participants in Cohort 1 with a response (confirmed CR or confirmed PR), the median DOR was 14.92 months (95% CI: 7.39, NE). The Kaplan-Meier estimates for probability of

sustained response lasting for 16 weeks, 6 months, and 12 months were 93.10% (95% CI: 75.14%, 98.23%), 72.25% (95% CI: 52.08%, 85.05%), and 60.69% (95% CI: 40.11%, 76.11%), respectively.

Time to First Confirmed Objective Response

The median time to first confirmed objective response was approximately 8 weeks, corresponding to the first post-baseline disease assessment per protocol, and all responding participants responded by Week 25.

Progression-Free Survival, Including Sensitivity Analysis

The median PFS was 5.49 months (95% CI: 3.65, 7.29) and the maximum PFS time of 25.7 months was ongoing as of the DCO. The analysis of PFS was supported by similar results across sensitivity analyses.

Overall Survival

The median OS was 15.54 months (95% CI: 10.38, 18.46) and the maximum OS time of 31.8 months was ongoing as of the DCO. The probability of 6-month and 12-month survival, respectively, was 80.3% (95% CI: 69.4, 87.6) and 56.2% (95% CI: 44.3, 66.5).

The Applicant's Position:

Results of the secondary outcomes are supportive of the observed benefit in cORR. Zanidatamab monotherapy treatment in Study 203 Cohort 1 resulted in rapid, durable responses as displayed by the short median time to first confirmed response, the long DOR of participants who achieved a confirmed CR or PR, and a high probability of response lasting 16 weeks, 6 months, and 12 months. These data support the clinical benefit of zanidatamab monotherapy in the proposed indication.

The FDA's Assessment:

The FDA analyses and summary of clinical efficacy has been outlined in Table 21.

FDA considers the data presented by the Applicant for time to event efficacy endpoints (i.e., progression free survival and overall survival) as exploratory and not adequate as supportive measures of efficacy in single arm trials.

Dose/Dose Response

The Applicant's Position:

Results of PopPK and ER analyses are presented in Section 6.2. Overall, none of the PopPK covariates or the ER analysis results suggest any of the variables except for HER2 status (3+ versus 2+/1+/0) have a clinically relevant impact on the efficacy of zanidatamab in the indicated patient population.

The FDA's Assessment:

See FDA response in Section 6.2.

Durability of Response

The Applicant's Position:

For information on durability of response, refer to results for the secondary endpoint DOR. Zanidatamab monotherapy treatment in Study 203 Cohort 1 resulted in durable responses as displayed by the long DOR of participants who achieved a confirmed CR or PR, and there was a high probability of response lasting 16 weeks, 6 months, and 12 months.

The FDA's Assessment:

FDA analyses, including characterization of DOR, stratified by IHC status is outlined in Table 21. The median DOR in patients with centrally confirmed ISH + IHC 3+ was 14.9 months (range 1.5+, 20.9 months), with 59% of responses lasting greater than 6 months, and 44% lasting greater than 12 months.

Only 1 patient with ISH + IHC 2+ advanced BTC had a response, with the duration of response lasting 7.5 months.

Persistence of Effect

The Applicant's Position:

For information on persistence of effects, refer to results for the secondary endpoints of PFS and OS. The median PFS of 5.49 months indicated that zanidatamab provides a sustained clinical benefit for patients in the proposed indication population. This is in line with the reported historical data for the second-line or later setting (historical median PFS of 3 to 7 months). The median OS of 15.54 months displayed a trend of improvement in comparison with the historical median OS of 6 to 9 months for current treatments.

The FDA's Assessment:

In a single-arm trial, persistence of effect is generally assessed through duration of response; however, this endpoint is not able to clearly isolate the effect of a drug from underlying progression of disease following initial treatment response. FDA considers the data presented by the Applicant for time to event efficacy endpoints i.e., progression free survival and overall survival as exploratory and not adequate as measures of efficacy in single arm trials.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data and the Applicant's Position:

Quality of life outcomes as assessed by EQ-5D-5L visual analogue score tended to show modest improvements after zanidatamab treatment in participants with a BOR of confirmed PR, compared to those with a BOR of PD. Disease-related pain as assessed by the BPI was generally lower in participants with a BOR of confirmed PR than in participants with a BOR of PD. Based

on these assessments, quality of life appears to be maintained during treatment with zanidatamab and supports the efficacy findings of Study 203.

The FDA's Assessment:

The EQ-5D-5L is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit. Therefore, FDA did not review the EQ-5D-5L data in this application and cannot verify Applicant's statements provided above.

The baseline median VAS score of patients in Cohort 1 was 80 (range 30, 100), with a modest decline in VAS score at the end of treatment (median VAS 77.5 [range 0, 100]). FDA considers these findings exploratory and not adequate measures to support efficacy claims (e.g., due to lack of evaluation in a randomized trial).

8.1.3. Supportive Study ZWI-ZW25-101

Trial Design

The Applicant's Description:

Supportive Study 101 was a first-in-human, 3-part study that investigated the safety, tolerability, PK, and preliminary antitumor activity of zanidatamab as monotherapy (Parts 1 and 2) and in combination with selected chemotherapy regimens (Part 3) in participants with HER2-expressing locally advanced (unresectable) and/or metastatic cancers. Parts 1 and 2 are complete and included in this application. Part 3 is ongoing and does not include any participants with BTC. See Table 14 for details about the study design.

The FDA's Assessment:

FDA agrees with the Applicant's description of Study 101. Part 3 of Study 101 is evaluating zanidatamab as part of a combination regimen and the findings are not applicable to this submission.

Eligibility Criteria

The Applicant's Description:

In Part 2, eligible participants were diagnosed with locally advanced (unresectable) and/or metastatic HER2 expressing cancers that progressed after having received all therapies known to confer clinical benefit for which they were eligible and therefore had limited treatment options other than investigational therapies. Participants were ≥ 18 years of age with an ECOG PS of 0 or 1 and a life expectancy of at least 3 months. This part of the study included 5 cohorts investigating patient populations with different tumor types. Cohorts 1 and 2 included participants with breast cancer, Cohorts 3 and 4 included participants with GEA, and Cohort 5

included participants with several other types of HER2-expressing tumors, including BTC, which were defined as HER2 IHC 3+ or IHC 2+/FISH+.

The FDA's Assessment:

FDA agrees.

Study Endpoints

The Applicant's Description:

As this was a Phase 1 safety study, the primary endpoints were safety-related. Efficacy endpoints included ORR (confirmed ORR was reported), DCR, CBR, DOR, and PFS which were determined by RECIST version 1.1 assessed by the investigator. Overall survival was not an endpoint for this study and participants were not followed beyond the end of the safety follow-up period.

The FDA's Assessment:

FDA agrees.

Statistical Analysis Plan and Amendments

The Applicant's Description:

This was a single-arm, open-label study that included dose escalation and expansion. No statistical hypotheses were tested. Descriptive analyses were performed on the following data sets:

- Safety: all participants who received at least 1 dose of zanidatamab.
- Measurable disease: all participants in the safety analysis set who had at least 1 measurable target lesion (per RECIST version 1.1) at baseline.
- Response evaluable: all participants in the measurable disease analysis set with at least 1 evaluable post-baseline disease assessment (per RECIST version 1.1) or who discontinued study treatment due to death or unequivocal clinical progression.

The endpoints for Study 101 were analyzed using statistical methods similar to those described for the pivotal Study 203. There were no differences between the planned analyses and analyses actually performed. Data as of the DCO date of 14 January 2022 are presented.

The FDA's Assessment:

FDA agrees.

8.1.4. Study Results – Supportive Study ZWI-ZW25-101

Patient Disposition

Data and the Applicant's Position:

A total of 46 participants were enrolled in Part 1 and a total of 146 participants were enrolled in Part 2. In the BTC Cohort of Part 2, a total of 22 participants were enrolled.

As of the DCO, all 22 participants in the BTC Cohort had discontinued treatment and the study. The most common reason for treatment discontinuation was radiographic progression (18 [82%] participants), with clinical progression, death, withdrawal of consent, and physician decision being other reasons for discontinuation (1 [5%] participant each reason). All participants in the BTC Cohort received zanidatamab at 20 mg/kg Q2W. The median duration of follow-up for participants with BTC was 3.75 months (range, 0.2 to 28.2 months). The duration of follow-up and disposition of participants in the BTC Cohort is adequate to provide supportive information for this application.

The FDA's Assessment:

FDA agrees.

Demographic and Baseline Disease Characteristics

Data and the Applicant's Position:

Participants in the BTC Cohort were predominantly Asian (68%), 64% were female, and the median age was 62.5 years (range: 42 to 78 years). All participants had locally advanced unresectable or metastatic HER2-positive BTC (defined as IHC 3+ or HER2 IHC 2+ and FISH+). Participants in the BTC Cohort were more heavily treated than participants in the pivotal Study 203, based on a higher median number of prior regimens (2 versus 1). All participants in the BTC Cohort received all appropriate therapies known to confer a benefit, including 6 participants (27%) who had received prior HER-2 targeted therapy; participants with this prior therapy were excluded from Study 203. Overall, baseline demographics and disease characteristics of participants in the BTC Cohort were representative of the target indicated population and provide a similar population to Study 203 for supportive evaluation of zanidatamab therapy.

The FDA's Assessment:

The baseline demographic and disease characteristics of patients enrolled into Study 101 are outlined in Table 22.

Table 22: FDA Analysis Demographic and Disease Characteristics of BTC Patients in Study 101

Zanidatamab 20 mg/kg	Study 101

	BTC
	N=22
Age	
Median (min, max) years	62.5 (42, 78)
≥ 65 years (%)	8 (36)
Male (%)	14 (64)
Female (%)	8 (36)
Country (%)	
Korea	12 (55)
USA	10 (45)
Race (%)	
Asian	15 (68)
White	5 (23)
Black	1 (5)
Not reportable/Unknown	1 (5)
Primary Diagnosis	
Gallbladder	13 (59)
Intrahepatic Cholangiocarcinoma	5 (23)
Extrahepatic Cholangiocarcinoma	4 (18)
HER- 2 Status	
IHC 2+/ FISH +	8 (36)
IHC 3+/ FISH +	14 (64)
Received Prior Gemcitabine Therapy (%)	20 (91)
Received Prior HER2 targeted Therapy (%)	6 (27)

Source: FDA Analysis; ADSL

Abbreviations: BTC: Biliary Tract Cancer; IHC: Immunohistochemistry; FISH: Fluorescent in situ hybridization

Efficacy Results

Data:

In the Part 2 BTC Cohort, the cORR was 36.4% (95% CI: 17.2% to 59.3%). The confirmed BOR was PR in 8 (36.4%) participants, SD in 5 (22.7%) participants, and PD in 8 (36.4%) participants. The DCR was 59.1% (95% CI: 36.4, 79.3) and CBR was 36.4% (95% CI: 17.2, 59.3). The median DOR was 8.5 months (95% CI: 3.2, NE), with the longest DOR being 22.1 months. The median PFS was 3.5 months (95% CI: 1.8, 6.7).

The Applicant's Position:

Results from the supportive Study 101 Part 2 BTC Cohort were consistent with the results from the pivotal Study 203 and support reproducibility of results across the studies.

The FDA's Assessment:

The eligibility and study follow up differed for Study 101 and 203 respectively, FDA considers the efficacy findings from Study 101 to be exploratory. The cORR and DOR by IHC status are outlined in Table 23.

Table 23: FDA Analysis Efficacy Summary Stratified by IHC Status in Study 101

	IHC 3+ N=14	IHC 2+ N=8
ORR by ICR		
Responders, n	7	1
Response Rate, % (95% CI)	50 (23, 77)	12.5 (0.3, 52.7)
Complete Response, n (%)	0	0
Duration of Response		
Range, months	3.2, 22.1	9.5*
Median (95% CI), months	7.4 (3.2, NE)	-
≥ 6 months, n (%)	4 (57)	-
≥ 12 months, n (%)	3 (43)	-
≥ 18 months, n (%)	1 (14)	-

Source: FDA Analysis, ADTTE, ADRS
Abbreviations: ORR: Objective Response Rate; ICR: Independent Central Review
* Observed DOR for the single responder.

In this exploratory analysis, one patient with HER 2 IHC 2+/FISH + had a partial response, which is consistent with the variable responses by HER 2 IHC status seen in Study 203.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

See integrated assessment of effectiveness Section 8.1.7.

8.1.6. Assessment of Efficacy Across Trials

The Applicant's Position:

A pooled efficacy analysis was not performed due to differences in eligibility criteria and other features of the studies' designs and analyses. The efficacy data from Study 203 and BTC Cohort

of Study 101 are consistent in demonstrating clinical benefit with a durable response in the proposed indication of [redacted] (b) (4)

The FDA's Assessment:

FDA agrees. Study 203 and 101 had differing eligibility criteria and study design and pooled efficacy analyses were not performed.

FDA notes that in the exploratory analyses of efficacy in patients with advanced BTC in Study 101, patients with IHC 3+/ fluorescent in situ hybridization (FISH) + tumors had higher response rates [redacted] (b) (4) .

Additional Efficacy Considerations

The FDA's Assessment:

See Section 8.1.7.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

Efficacy analyses from 2 studies (Studies 203 Cohort 1 and 101 BTC Cohort), which in total enrolled 102 previously treated, HER2-positive BTC participants, demonstrated that zanidatamab monotherapy addresses the need for a treatment option with clinically relevant and durable efficacy responses. The consistency of efficacy results across studies supports assessment of the efficacy of zanidatamab monotherapy in the proposed indication.

The population of participants in Study 203 was representative of the proposed indication population. The results from the pivotal Study 203 and the totality of the supporting clinical data demonstrate that zanidatamab monotherapy in the intended population provides a benefit to patients as evidenced by clinically relevant improvements in cORR, DOR, PFS, and OS. Specifically, the cORR as assessed by ICR per RECIST version 1.1 in Cohort 1 was 41.3%, more than double the historical response rate of 3% to 15% for second-line therapies (Ayasun, 2023; Brieau, 2015; Fornaro, 2015; Lamarca, 2014; Lamarca, 2021; Valle, 2017; Yoo, 2021). The DOR with a median of 14.92 months demonstrated a durable response to treatment. Zanidatamab also showed persistence of effect with a favorable median PFS of 5.49 months and median OS of 15.54 months at the DCO date. Finally, improvements in HRQoL were observed in participants who had BORs of PR compared to participants who demonstrated progressive disease.

In subgroup analysis, the cORR, PFS, DCR and CBR were higher in participants with IHC 3+ than participants with IHC 2+ in both Study 203 and Study 101; however, it is unclear whether this trend is due to limited sample size, intrinsic differences between IHC 2+ and IHC 3+ tumors,

or the heterogeneity of HER2 expression in the tumors. Although the cORR in participants from Study 203 with IHC 2+ (5.6%) was lower than the cORR in participants with IHC3+, the benefit in IHC2+ is comparable to the ORR of current later line treatment options for BTC including ESMO and NCCN-recommended FOLFOX (5%) (Section 2.2). The subgroup analysis of DOR in participants with IHC 2+ from Study 203 Cohort 1 included only 1 participant, who was censored after 7.5 months for initiating subsequent anticancer therapy.

Overall, these results represent a substantial improvement over current standard of care for adults with previously treated, unresectable locally advanced or metastatic HER2-positive BTC and fulfills an unmet medical need for the intended patient population.

The FDA's Assessment:

The review of efficacy in this Application is supported by the results in Cohort 1 of Study 203, which was a non-randomized, single arm cohort evaluating zanidatamab 20 mg/kg administered every 2 weeks in patients with advanced BTC who are HER2 positive (IHC 2 or 3+ and ISH +) and who have received first line gemcitabine containing combination regimen.

The ORR in the subgroup of patients with IHC 3+ was 51.6% (95% CI 38.6, 64.5) compared to an ORR of 5.6% (95% CI 0.1, 27.3) in the subgroup of patients with IHC 2+. In the IHC 3+ patient population (N=62) there were 2 (3.2%) complete responses, and the median duration of response was 14.9 months (95% CI: 7.4, NE). These findings represent clinically meaningful improvement compared to current standard of care available in the second line setting for patients with HER2 IHC 3+ advanced BTC. FDA does not agree that an ORR of 5.6% in patients who are ISH+ and IHC 2+ (i.e., one response in 18 treated patients) is clinically meaningful or likely to predict benefit in progression-free or overall survival nor it represents meaningful improvement over available therapy. The study design and small sample size does not adequately characterize the efficacy in this patient population.

The difference in magnitude of treatment effect of zanidatamab in patients with IHC 3+ and IHC 2+ advanced BTC is consistent with the findings of Study 101, where there was an isolated partial response in patients with IHC 2+.

Although all patients in Study 203 were required to be ISH positive, data from the corresponding companion diagnostic submission (P990081/S054) demonstrates a HER2 amplification rate of 94% by ISH in patients with IHC 3+ expression. FDA subgroup analyses support the assessment of HER2 expression using IHC as a predictive biomarker in patients with advanced BTC, with patients expressing IHC3+ deriving the greatest ORR benefit. In clinical practice, generally IHC testing precedes ISH testing, and ISH is requested for IHC2+ or when IHC results are equivocal. Given the low prevalence of ISH negativity in patients with tumors that are IHC3+ and consistently with standard of care practice, further ISH testing was not required as a companion diagnostic to identify the patient population likely to benefit. A requirement for ISH testing may unnecessarily delay treatment, and in some cases, tissue may not be available to perform such testing.

Overall, results of Study 203 show, in patients with HER2+, IHC3+ relapsed/refractory BTC treated with zanidatamab as a clinically meaningful ORR accompanied by a long duration of response that is likely to predict clinical benefit.

8.2. Review of Safety

Data and the Applicant's Position:

The overall safety review for zanidatamab monotherapy is primarily based on the following populations:

- Primary Safety Population (N = 80): All participants with BTC treated with zanidatamab in Cohort 1 of Study 203, to match the primary efficacy population.
- The 20 mg/kg Q2W Population (N = 233): All participants treated with zanidatamab at 20 mg/kg Q2W in Cohort 1 or Cohort 2 of Study 203 or in Part 1 or Part 2 of Study 101, regardless of tumor type, to provide a broader assessment of safety among study participants who were treated with the proposed zanidatamab dosage regimen, regardless of tumor type.

The size of the safety database provides sufficient data for a comprehensive safety profile of zanidatamab monotherapy and is appropriate to identify safety signals in this rare population of patients with HER2-positive BTC.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The pooled safety database, comprising 233 patients who received zanidatamab 20 mg/kg every 2 weeks (ZWI-ZW205-203 N = 87 [N= 80 Cohort 1, N = 7 Cohort 2], ZWI-ZW25-101 (N=146), consisted predominantly of patients with advanced BTC (47%). Table 24 outlines the primary tumor location of the patients included in the pooled safety database.

Table 24: FDA Analysis - Primary Tumor Location

Primary Tumor Location	Zanidatamab 20 mg/kg Pooled
	N = 233
	N (%)
Biliary Tract Cancer	109 (47)
Other[#]	37 (15)
Breast	30 (13)
Gastric/Esophageal	30 (13)
Colorectal	27 (12)

[#] - Other includes (salivary gland [N=7], non-small cell lung cancer [N=5], ampullary [N=4], bladder, endometrial [N=3 each], duodenum, ovarian, pancreatic, small bowel [N=2 each], cancer of unknown origin, cervical, fallopian, hepatocellular lacrimal, parotid, skin, and vulva [N=1 each])

8.2.1. Safety Review Approach

The Applicant's Position:

The main AEs reported with HER2 receptor antagonists are heart failure and LVEF decreased, noninfectious pulmonary toxicity, and embryo-fetal harm. Diarrhea and IRRs are also known to be common AEs associated with the use of anti-HER2 antibodies. Clinical studies of zanidatamab included specific assessments to monitor and mitigate these and other potentially unidentified toxicities. Methods for evaluating safety were similar across studies and included all participants who received at least 1 dose of study treatment.

The FDA's Assessment:

The primary safety analysis was conducted on patients that were enrolled to Cohort 1 of Study 203 and the pooled safety population who had received at least 1 dose of zanidatamab 20 mg/kg every 2 weeks in Study 101 and Study 203, as outlined above. The data cutoff date for patients enrolled to Study 203 was July 28, 2023. The data cutoff date for patients enrolled to Study 101 was January 14, 2022. A safety update was provided on June 27, 2024, with a data cutoff date of March 1, 2024. The safety update data included additional safety information on 30 patients (N=20 in the primary safety population) who were either receiving treatment or undergoing follow up at the original data cutoff date, no new patients were enrolled. The safety update was reviewed for consistency with the primary safety analysis.

The FDA safety review focuses on the incidence of treatment emergent adverse events (TEAEs), regardless of causality assessment. An adverse event (AE) was considered a TEAE, if reported either for the first time or worsening of a pre-existing AE after the first dose of zanidatamab until 30 days after the last dose. The safety analysis including fatal and non-fatal SAEs, AEs leading to permanent treatment discontinuation, and treatment delay or interruption.

Adverse events of special interest (AESI) specified within the protocol included infusion related reactions (IRR), non-infectious pulmonary toxicities, cardiac events (absolute decrease in left ventricular ejection fraction [LVEF] of $\geq$ 10% from pretreatment baseline and absolute value below 50%, and/or Grade 2 or higher heart failure). Additional toxicities associated with HER2 directed therapy includes the risk for diarrhea and embryo-fetal toxicity, the risks of which have been summarized separately.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 25: Summary of Zanidatamab Exposure in the Safety Populations

	Statistic	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Duration of treatment (months)	Mean (StD)	7.79 (6.922)	6.99 (7.142)
	Median (min, max)	5.55 (0.5, 27.2)	4.70 (0.2, 44.6)
Relative dose intensity [a] (%)	Mean (StD)	97.420 (6.3902)	96.798 (10.4428)
	Median (min, max)	100.000 (67.23, 100.01)	100.000 (4.67, 109.00)

Abbreviations: max = maximum; min = minimum; Q2W = once every 2 weeks; StD = standard deviation.
[a] Relative dose intensity (%) = 100%*Actual dose intensity(mg/kg/week)/Intended dose intensity (mg/kg/week).
Source: Module 2.7.4 Table 2.

The Applicant's Position:

Zanidatamab exposure was generally similar across both safety analysis populations; although, the median duration of zanidatamab treatment in the pooled population was shorter (4.7 months in the 20 mg/kg Q2W Population) when compared with those observed in participants with BTC (5.55 months in the Primary Safety Population). This may be due to the inclusion of participants with other tumor types in Study 101, compared with Study 203. This also may be due to the line of therapy as a function of disease indications in Study 101.

The FDA's Assessment:

FDA agrees with the Applicant's summary of zanidatamab exposure. The median duration of treatment was longer in patients included in the primary safety population compared to the pooled safety population. The differences in exposure is likely multifactorial, with the primary safety population including patients with advanced BTC with either HER2 IHC 3+ ISH + (N=62 [78%]) or HER2 IHC 2+ ISH+ (N=18 [22%]), whereas the pooled safety data consisted of multiple primary tumor locations (Table 24) and HER2 protein expression among the participants were IHC 3+ (70%), IHC 2+ (24%), IHC 1+ (3%), and IHC 0 (1.7%). Among 233 patients in the pooled safety analyses, 39% were exposed to zanidatamab for 6 months or longer, and 17% were exposed for greater than 12 months.

Relevant characteristics of the safety population:

Data:

Overall, the demographic and baseline characteristics were similar across the safety analysis populations, with the exception that more participants with BTC were Asian in the Primary Safety Population (65.0%) when compared with the pooled population (51.5% in the 20 mg/kg Q2W Population). Notably, the majority of participants in Study 203 were enrolled in Asia (62.5%); whereas the majority of participants in the pooled population were enrolled from regions in the Rest of World (53.6% in the 20 mg/kg Q2W Population).

The Applicant's Position:

The demographic and baseline characteristics of the safety analysis populations were clinically relevant for the target patient population who would receive zanidatamab monotherapy following regulatory approval in the proposed indication.

The FDA's Assessment:
The baseline demographics and clinical characteristics of the primary safety population has been outlined in Section 8.1.2, the demographics and country of enrollment of patients in the pooled safety populations are outlined in Table 26.

Table 26: FDA Analysis: Baseline Demographics the Pooled Safety Population

Zanidatamab 20 mg/kg	Pooled Safety Population
	N=233
Age	
Median (min, max) years	62 (24, 86)
Male (%)	108 (46)
Female (%)	125 (54)
Country (%)	
Canada	19 (8)
China	24 (10)
Korea	84 (36)
Other[#]	14 (6)
USA	92 (40)
Race (%)	
Asian	119 (51)
White	96 (41)
Black	5 (2)
American Indian or Alaskan Native	1 (0.4)
Not reportable/Unknown/Other/Multiple	12 (5)
Ethnicity (%)	
Hispanic or Latino	12 (5)

Not Hispanic or Latino	215 (92)
Not Reported/ Unknown	6 (3)

#Other includes: Chile (N=1), France (N=4); Great Britain (N=2), Italy (N=3), and Spain (N=4)

Source: FDA Analyses ADSL datasets

Majority of patients included in the pooled safety data were enrolled in the US and were predominantly either Asian (51%) or White (41%), with patients from racial and ethnic minorities being underrepresented.

Adequacy of the safety database:

The Applicant's Position:

The size of the safety database and durations of treatment and follow-up are considered adequate to characterize the risks of zanidatamab treatment in the indicated population, which will be managed via labelling recommendations and monitored with postmarketing surveillance.

The FDA's Assessment:

The size of the safety database and the reported frequency of TEAEs is adequate to characterize the safety of zanidatamab monotherapy. Further characterization of the safety profile of zanidatamab may potentially be available upon review of the ongoing randomized controlled trial JZP598-302.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives. These were sufficiently complete for a thorough review of safety.

The FDA's Assessment:

FDA conducted an audit of the coding of the terms in the safety dataset. Verbatim terms for safety events were accurately coded using the MedDRA dictionary. No data integrity issues were uncovered in the review.

Categorization of Adverse Event

The Applicant's Position:

Adverse events were coded using MedDRA, version 25.0. The severity of AEs was graded using the NCI-CTCAE version 4.03 for Study 101 and version 5.0 for Study 203.

The FDA's Assessment:

FDA agrees.

Routine Clinical Tests

The Applicant's Position:

Clinical safety tests included clinical laboratory values, physical examination findings (including vital signs, body weight, and lung auscultation), cardiac function (12-lead ECG, ECHO/MUGA scan), ECOG performance status, and ADAs and NAbs.

The FDA's Assessment:

All patients received a baseline echocardiogram/MUGA prior to starting treatment with zanidatamab in Study 203 and Study 101. In Study 203, repeat assessment of LVEF occurred at 6 weeks and then every 12 weeks. Patients had hematology and serum chemistry assessment prior to each infusion (i.e., Day 1 and 15 of each cycle).

8.2.4. Safety Results

Deaths

Data:

Table 27: Summary of All Deaths in BTC Clinical Studies with Zanidatamab

	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Any, n (%)	52 (65.0)	66 (28.3)
Within 30 days after last dose, n (%)	4 (5.0)	14 (6.0)
Disease progression	2 (2.5)	8 (3.4)
Adverse event	2 (2.5)	5 (2.1)
Other	0	1 (0.4)
More than 30 days after last dose, n (%)	48 (60.0)	52 (22.3)
Disease progression	32 (40.0)	35 (15.0)
Adverse event	0	1 (0.4)
Other [a]	3 (3.8)	3 (1.3)
Unknown [b]	13 (16.3)	13 (5.6)

Abbreviations: BTC = biliary tract cancer; Q2W = once every 2 weeks.
[a] All "other" cases of death were reported as gallbladder carcinoma.
[b] Cause of death was not available at the study center
Source: Module 2.7.4 Table 11.

Six (2.6%) participants in the 20 mg/kg Q2W Safety Population had AEs leading to death with no trend observed by cancer type. None of the AEs leading to death were considered to be related to treatment with zanidatamab.

The Applicant's Position:

A higher incidence of death was observed in the Primary Safety Population compared with the 20 mg/kg Q2W Population, which could be attributed to the difference in the protocol-specified follow-up period and the study discontinuation criteria between studies. Notably, participants in Study 203, which comprised the Primary Safety Population, were followed long-term for survival status; whereas participants in Study 101, which comprised the majority of participants in the 20 mg/kg Q2W Safety Population, were followed until 30 days of the last dose of zanidatamab.

The FDA's Assessment:

FDA agrees with the cited proportions of deaths within and beyond 30 days after the last dose of zanidatamab for both the primary safety and pooled safety population (Table 27).

A summary of the narratives of deaths within 30 days of zanidatamab is outlined in Table 52. The preferred term "hepatic failure" has been included in Section 6 of the USPI, based on the review of the case narratives.

The cause of death for 13 patients who died 30 days after the last dose of zanidatamab is unknown; however, at the time of death all patients had discontinued treatment due to radiographic disease progression. The median time from last dose of zanidatamab to death was 130 days (range: 68 to 440 days).

Serious Adverse Events

Data:

Table 28: Serious TEAEs ≥ 2%, by SOC and PT (Safety Analysis Set)

System Organ Class, n (%) Preferred Term	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Any Serious TEAE	42 (52.5)	78 (33.5)
Hepatobiliary disorders	17 (21.3)	24 (10.3)
Jaundice cholestatic	5 (6.3)	5 (2.1)
Biliary obstruction	4 (5.0)	4 (1.7)
Cholangitis	3 (3.8)	6 (2.6)
Jaundice	2 (2.5)	2 (0.9)
Gastrointestinal disorders	15 (18.8)	25 (10.7)
Obstruction gastric	3 (3.8)	4 (1.7)
Diarrhea	2 (2.5)	4 (1.7)
Infections and infestations	14 (17.5)	29 (12.4)
Pneumonia	4 (5.0)	11 (4.7)
Sepsis	4 (5.0)	6 (2.6)
Bacteremia	2 (2.5)	2 (0.9)
General disorders and administration site conditions	3 (3.8)	7 (3.0)
Asthenia	2 (2.5)	2 (0.9)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; Q2W = once every 2 weeks; SOC = system organ class.; TEAE = treatment-emergent adverse event.
Notes: Events presented by decreasing frequency of SOC then PT based on the Primary Safety Population. Multiple occurrences of an event in a participant are counted once. AEs coded using MedDRA version 25.0.
Source: Module 2.7.4 Table 13.

The Applicant's Position:

The SAEs in participants with BTC were typically associated with the underlying disease (such as cholangitis, jaundice cholestatic, biliary obstruction, and gastric obstruction) or concurrent illnesses or conditions (such as pneumonia, sepsis, and hypertension).

The FDA's Assessment:
FDA replicated the analysis in Table 28. The most common (>2%) SAEs (preferred terms were grouped where clinically indicated) included within the USPI were biliary obstruction (15%), biliary tract infection (8%), sepsis (8%), pneumonia (5%), diarrhea (3.8%), gastric obstruction (3.8%), and fatigue (2.5%).

FDA agrees that several listed SAEs may be associated with the underlying disease or intercurrent illnesses. However, the safety data for zanidatamab was generated from single arm studies, where attribution is confounded by design, hence the incidence of SAEs cited and used in the USPI are irrespective of attribution.

Dropouts and/or Discontinuations Due to Adverse Effects

Data and the Applicant's Position:

Permanent discontinuation of zanidatamab due to an adverse reaction occurred in 2.5% of participants in the 20 mg/kg Q2W population. Adverse reactions that resulted in permanent treatment discontinued included ejection fraction decreased (1.3%) and pneumonitis (1.3%). Overall, zanidatamab treatment was tolerable and resulted in few treatment discontinuations.

The FDA's Assessment:
FDA analyses of adverse event leading to treatment discontinuation is outlined in Table 29.

Table 29: FDA Analysis - Adverse Events Leading to Treatment Discontinuation.

	Zanidatamab 20 mg/kg Cohort 1 Study 203	**Zanidatamab 20 mg/kg Pooled**
	N = 80	**N = 233**
Treatment Discontinued	**2 (2.5)**	**7 (3.2)**
LVEF decreased	1 (1.3)	2 (0.8)
Pneumonitis	1 (1.3)	1 (0.4)

IRR	0	1 (0.4)
Pulmonary Embolism	0	1 (0.4)
Sudden Death	0	1 (0.4)
Weight Decreased	0	1 (0.4)

Source: FDA Analysis; ADAE dataset

The patient who discontinued treatment in the primary safety population due to Grade 3 pneumonitis received last treatment on Cycle 8 Day 15 (Study Day 211) and developed the adverse event on Day 223. Treatment was discontinued on Day 253 and the pneumonitis improved a severity of Grade 1 at the time of treatment discontinuation.

Two patients discontinued treatment due to LVEF decrease in the pooled safety population. In Study 203, a participant with advanced BTC had a baseline LVEF of 56% and had a further decline to 44% that led to study discontinuation on Study Day 337. The patient had a past medical history of atrial fibrillation and hypertension which confounded the assessment. In Study 101, a participant with ovarian cystadenocarcinoma was noted to have an asymptomatic decline LVEF of 50% which was 10% lower than baseline assessed approximately 12 months earlier. The patient had further clinical assessment, while continuing treatment, with further decline in LVEF to 44% and discontinuation of treatment after Cycle 19 Day 15.

The reported case of sudden death occurred in a patient with a diagnosis of breast cancer with chest wall disease, who was found unresponsive at home, and had received Cycle 2 Day 15 twelve days earlier. No autopsy was performed, and the cause of death was unknown.

FDA agrees that the incidence of TEAEs leading to treatment discontinuation in the primary and pooled safety population was low. Section 2 of the USPI contains specific instructions for dose modifications and discontinuations in the event of left ventricular dysfunction, diarrhea, infusion related reactions, and pneumonitis.

Dose Interruption/Reduction Due to Adverse Effects

Data and the Applicant's Position:

In the 20 mg/kg Q2W population, 26% of participants had a dose interruption and 4% of participants had a dose reduction. Adverse reactions that led to dose interruption were infusion-relation reaction (26%) and extravasation (1.3%). Adverse reactions that led to dose reduction were diarrhea (3%), nausea (1%), and weight decreased (1%). Treatment with zanidatamab resulted in few dose reductions.

The FDA's Assessment:
FDA analyses of dose delay in the primary safety and pooled safety populations are outlined in Table 30.

Table 30: FDA Analysis - TEAEs Leading to Treatment Delay of Zanidatamab (Incidence ≥ 3%)

	Zanidatamab 20 mg/kg Cohort 1 Study 203	Zanidatamab 20 mg/kg Pooled
	N = 80	N = 233
Any Treatment Delay	**33 (41)**	**57 (24)**
Diarrhea (GT)	5 (6)	7 (3.0)
ALT Increased	4 (5)	6 (2.6)
AST Increased	4 (5)	5 (2.1)
Ejection Fraction Decreased	4 (5)	6 (2.6)
Pneumonia (GT)	4 (5)	5 (2.1)
Cholangitis	3 (3.8)	4 (1.7)
Fatigue (GT)	3 (3.8)	7 (3.0)
Jaundice Cholestatic	3 (3.8)	3 (1.3)

Source: FDA Analyses ADAE dataset
Grouped Terms: Diarrhea (GT): diarrhea, colitis, enteritis; enterocolitis; Pneumonia (GT): pneumonia, lower respiratory tract infection; pneumocystis jirovecii pneumonia; Fatigue (GT): asthenia, fatigue.

Diarrhea was the most common reason for treatment delay in the primary and pooled safety populations and was also the most common reason for patients requiring a dose reduction (N=2 Cohort 1 Study 203, N=3 pooled safety). Five patients (2.1%) required dose reduction in the pooled safety population in total, all patients receiving 15 mg/kg zanidatamab (N=1 nausea and decreased weight [Cohort 1 Study 203], N=1 ejection fraction decreased [pooled safety population]).

Temporary interruption of zanidatamab infusion due to an IRR was required in 21 (26%) patients in the primary safety population, and 59 (25%) patients in the pooled safety population.

FDA agrees with the Applicant on the low incidence of dose reductions in patients receiving zanidatamab 20 mg/kg every 2 weeks. Three (3.8%) patients in the primary safety population,

and 5 (2.1%) patients in the pooled safety population had TEAEs leading to dose reduction. The 5 patients had 6 TEAEs leading to dose reduction including diarrhea (N=3), ejection fraction decreased (N=1), nausea (N=1), and decreased weight (N=1). Following protocol Amendment 2 (details outlined above), the Applicant had revised the prespecified provisions for a dose reduction of zanidatamab 15 mg/kg to dose reductions to be considered following discussions with medical monitor. The USPI contains guidance for dose reduction to 15 mg/kg in patients who require dose modification.

Significant Adverse Events

Data:

Table 31: Grade ≥ 3 TEAEs ≥ 5%, by SOC and PT (Safety Analysis Set)

System Organ Class, n (%) Preferred Term	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Any TEAE	49 (61.3)	116 (49.8)
Gastrointestinal disorders	19 (23.8)	39 (16.7)
Diarrhea	7 (8.8)	12 (5.2)
Hepatobiliary disorders	17 (21.3)	24 (10.3)
Jaundice cholestatic	5 (6.3)	5 (2.1)
Biliary obstruction	4 (5.0)	4 (1.7)
Infections and infestations	14 (17.5)	28 (12.0)
Pneumonia	4 (5.0)	10 (4.3)
Sepsis	4 (5.0)	6 (2.6)
Investigations	14 (17.5)	31 (13.3)
Alanine aminotransferase increased	4 (5.0)	4 (1.7)
Aspartate aminotransferase increased	4 (5.0)	5 (2.1)
Blood and lymphatic system disorders	12 (15.0)	27 (11.6)
Anemia	10 (12.5)	24 (10.3)
Vascular disorders	8 (10.0)	15 (6.4)
Hypertension	6 (7.5)	12 (5.2)
Metabolism and nutrition disorders	7 (8.8)	16 (6.9)
Hypokalemia	4 (5.0)	5 (2.1)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; Q2W = once every 2 weeks; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes: Events presented by decreasing frequency of SOC and then PT based on the Primary Safety Population. Multiple occurrences of an event in a participant are counted once. AEs coded using MedDRA version 25.0.
Source: Module 2.7.4 Table 10.

In the Primary Safety Population, Grade 3 or higher AEs assessed to be zanidatamab-related by the investigator were reported in 21.3% of participants, with diarrhea (5.0%), and anemia and ejection fraction decreased (each in 3.8%) as the most frequently reported events; none of these events were Grade 4 or Grade 5.

The Applicant's Position:

Several of the Grade 3 or higher AEs in participants with BTC (such as cholangitis, jaundice cholestatic, and biliary obstruction) are typical symptoms or complications associated with the underlying disease. High-grade AEs assessed to be related to zanidatamab were infrequent.

The FDA's Assessment:

FDA replicated the analysis summarized in Table 31. The most common Grade ≥3 AE was diarrhea; further details have been outlined in the "Diarrhea" section below. When grouping preferred terms diarrhea, enteritis, and colitis, the incidence was 6% in the pooled safety population and 10% in the primary safety population.

In the primary safety population, there were 7 Grade 4 TEAEs in 5 patients, including hepatic failure, hypokalemia, ALT and AST (N=2) elevation, pleural effusion, and biliary obstruction. The case narrative of the patient experiencing hepatic failure has been outlined in Table 52, in the other two patients with Grade 4 ALT and AST elevations, the abnormal LFTs were transient and improved with treating the biliary obstruction. FDA generally agrees with the Applicant that the majority of the Grade 3 or higher TEAEs are likely reflective of the symptom burden from the underlying disease.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 32: Overall Summary of AEs (Safety Analysis)

Adverse Events, n (%)	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Treatment-emergent [a]	78 (97.5)	228 (97.9)
Grade 3 or higher	49 (61.3)	116 (49.8)
Zanidatamab-related [b]	61 (76.3)	172 (73.8)
Grade 3 or higher	17 (21.3)	26 (11.2)
Serious	42 (52.5)	85 (36.5)
Treatment emergent [a]	42 (52.5)	78 (33.5)
Zanidatamab-related [b]	8 (10.0)	10 (4.3)

Abbreviations: AE = adverse event; Q2W = once every 2 weeks.
[a] AE with onset on or after first dose of study treatment through 30 days after final dose of study treatment inclusive.
[b] Relatedness to zanidatamab treatment assessed by the investigator.
Note: The worst toxicity grade per participant is summarized.
Source: Module 2.7.4 Table 8.

Table 33: Zanidatamab-Related TEAEs ≥ 5%, by SOC and PT (Safety Analysis Set)

System Organ Class, n (%) Preferred Term	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Any TEAE	61 (76.3)	172 (73.8)
Gastrointestinal disorders	36 (45.0)	108 (46.4)
Diarrhoea	32 (40.0)	95 (40.8)

System Organ Class, n (%) Preferred Term	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Nausea	8 (10.0)	24 (10.3)
Vomiting	6 (7.5)	15 (6.4)
Injury, poisoning and procedural complications	28 (35.0)	71 (30.5)
Infusion related reaction	28 (35.0)	71 (30.5)
Investigations	18 (22.5)	29 (12.4)
Ejection fraction decreased	9 (11.3)	14 (6.0)
Alanine aminotransferase increased	6 (7.5)	6 (2.6)
Aspartate aminotransferase increased	6 (7.5)	6 (2.6)
Skin and subcutaneous tissue disorders	14 (17.5)	52 (22.3)
Pruritus	4 (5.0)	14 (6.0)
General disorders and administration site conditions	10 (12.5)	35 (15.0)
Fatigue	5 (6.3)	24 (10.3)
Nervous system disorders	10 (12.5)	19 (8.2)
Peripheral sensory neuropathy	4 (5.0)	4 (1.7)
Metabolism and nutrition disorders	9 (11.3)	19 (8.2)
Decreased appetite	4 (5.0)	10 (4.3)
Blood and lymphatic system disorders	5 (6.3)	7 (3.0)
Anaemia	4 (5.0)	6 (2.6)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; Q2W = once every 2 weeks; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes: Events presented by decreasing frequency of SOC and then PT based on the Primary Safety Population. Multiple occurrences of an event in a participant are counted once. Relatedness to zanidatamab assessed by the investigator. AEs coded using MedDRA version 25.0.
Source: Module 2.7.4 Table 9.

The Applicant's Position:

In a heavily pre-treated population of participants with locally advanced and/or unresectable tumors, zanidatamab demonstrated a favorable safety profile. The most commonly reported AEs of IRR and diarrhea were manageable in the outpatient setting with premedication or symptomatic treatment. Serious or high-grade toxicities assessed to be related to zanidatamab were infrequent. The clinical benefit of zanidatamab was supported by a well-tolerated safety profile in the 20 mg/kg Q2W Safety Population, which included all participants treated with the proposed zanidatamab dose, regardless of tumor type, in Study 203 and Study 101 (Part 1 or Part 2). No unknown or unexpected safety signals were observed. Safety data were consistent across studies, disease indications, and different dose regimens.

The FDA's Assessment:

FDA analyses included grouping of clinically relevant preferred terms to provide the incidence of common TEAEs (Table 34). As stated above, as the data are from single-arm studies, attribution cannot be ascertained and therefore FDA does not consider relatedness in the safety analysis. The product USPI reflects the AEs as reported, irrespective of investigator attribution.

Table 34: FDA Analyses: Common (≥ 10%) TEAEs in the Primary and Pooled Safety Populations

	Zanidatamab 20 mg/kg Cohort 1		Zanidatamab 20 mg/kg Pooled	
	N = 80		N = 233	
	All grades	Grades 3-4	All grades	Grades 3-4
	(%)	(%)	(%)	(%)
Patients with TEAEs	98	59	98	47
Gastrointestinal Disorders				
Diarrhea (GT)	50	10	48	6
Abdominal Pain (GT)	29	1.3	1	0.4
Nausea	18	1.3	19	0.4
Vomiting	15	1.3	14	0.4
Injury, Poisoning and Procedural Complications				
IRR	35	1.3	30	0.4
Investigations				
Anemia	24	13	22	10
ALT Increased	20	5	12	1.7
AST Increased	20	5	12	2.1
LVEF Decreased	14	3.8	7	1.3
Weight Decreased	14	0	11	0.4
Blood Bilirubin Increased	11	2.5	7	3
Hypokalemia	14	5	13	2.1
General Disorders and Administration Site Conditions				
Fatigue (GT)	24	3.8	25	3.9
Pyrexia	16	0	11	0.4
Decreased Appetite	16	0	16	1.3

Skin and Subcutaneous Tissue Disorders				
Rash (GT)	19	0	24	0
Pruritus	14	0	9	0
Other				
Hypertension	13	8	11	5
Musculoskeletal Pain (GT)	13	0	20	0.9
Neuropathy (GT)	11	0	8	0

Source: FDA Analysis ADAE dataset

Abbreviations: IRR: Infusion Related Reactions

Diarrhea includes diarrhea and enteritis; Abdominal pain includes abdominal pain and abdominal pain upper; Fatigue includes asthenia and fatigue; Rash includes dermatitis, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, rash, rash maculo-papular, and rash pustular; Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, musculoskeletal chest pain, non-cardiac chest pain, neck pain; Peripheral Neuropathy includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, polyneuropathy, peripheral sensory neuropathy, peripheral motor neuropathy.

The incidence and management of specific toxicities including diarrhea, decreased LVEF, and IRR have been outlined in the relevant sections below. Details on abnormalities in investigations including assessment for drug induced liver injury (DILI) are outlined in the "Laboratory Findings" section below.

The incidence of common adverse reactions cited in the USPI are reflective of the clinically relevant groupings of preferred terms used in the FDA analyses.

Laboratory Findings

Data:

Table 35: Grade ≥ 3 Treatment-Emergent Laboratory Abnormalities ≥ 5% (Safety Analysis Set)

Laboratory Parameter, n (%)	Directionality	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
All tests, any		35 (43.8)	104 (44.6)
Hematology, any		16 (20.0)	44 (18.9)
Hemoglobin	Low	11 (13.8)	26 (11.2)
Lymphocytes	Low	6 (7.5)	20 (8.6)
Chemistry, any		28 (35.0)	82 (35.2)
Aspartate aminotransferase	High	8 (10.0)	16 (6.9)

Laboratory Parameter, n (%)	Directionality	Primary Safety Population (N = 80)	20 mg/kg Q2W (N = 233)
Sodium	Low	8 (10.0)	18 (7.7)
Alanine aminotransferase	High	6 (7.5)	7 (3.0)
Alkaline phosphatase	High	4 (5.0)	15 (6.4)
Potassium	Low	4 (5.0)	8 (3.4)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; Q2W = once every 2 weeks.
Notes: Multiple occurrences in a participant are counted once, using the highest toxicity grade. CTCAE version 5.0 grading criteria for Study 203 and CTCAE version 4.03 for Study 101.
Source: Module 2.7.4 Table 25.

The Applicant's Position:

Overall, laboratory abnormalities were consistent with the AE profile and no additional safety signals were shown from the laboratory abnormalities. There were no notable differences in hematology or clinical chemistry level across the Safety Analysis Populations.

The FDA's Assessment:

FDA analyses of common lab abnormalities are outlined in Table 36.

Table 36: FDA Analyses – Common Lab Abnormalities in the Primary and Pooled Safety Populations

	Zanidatamab 20 mg/kg Cohort 1		Zanidatamab 20 mg/kg Pooled	
	N = 80		N = 233	
	All Grades	Grade 3 + 4	All Grades	Grade 3 + 4
	%	%	%	%
Hematologic (Incidence > 25%)				
Hemoglobin low	88	14	83	11
Lymphocyte low	44	8	43	9
Platelets low	29	0	22	0
Chemistry (Incidence > 15%)				
LDH High	55	0	20	0

Albumin Low	53	0	51	3
AST High	47	10	42	7
ALT High	46	8	34	3
ALP High	41	5	52	6
Sodium Low	35	10	27	8
Potassium Low	34	5	26	3
Bilirubin High	24	9	18	4
Calcium Low (reported)	23	0	14	0
Urate High	20	0	19	2
Magnesium Low	19	3	6	1
Creatinine High	18	1	19	1

Source: FDA Analyses ADLB dataset

Seven patients in the primary safety population met the laboratory criteria for potential Hy's Law; no patients in Study 101 experienced simultaneous Grade ≥2 bilirubin and Grade ≥3 transaminase increases. A description of the case of hepatic failure has been outlined in Table 50. Five patients had elevated liver function tests within 30 days of end of treatment, with evidence of disease progression, and one patient met the lab criteria for Hy's law concurrently with a diagnosis of bile duct stenosis. The incidence of LFT abnormalities including elevation in AST, ALT and total bilirubin were greater in the primary safety population than in the pooled safety population, which is anticipated given the primary safety population comprises of patients with advanced BTC. There were no cases of pathology confirmed drug induced liver injury.

All patients in the primary safety population had received prior therapy with gemcitabine-based chemotherapy, with the majority (75%) receiving gemcitabine with cisplatin. The incidence of low grade cytopenia would be anticipated for patients with previous exposure to myelosuppressive chemotherapy. Twenty-four (30%) patients required concomitant electrolyte solutions during the study, the most common (> 5%) were potassium chloride (N=14 [18%]), magnesium sulfate (N=6 [7.5%]), and potassium phosphate (N=5 [6.3%]).

The laboratory abnormalities are primarily consistent with observations seen in patients with advanced BTC who have received prior cytotoxic chemotherapy. Patients with electrolyte abnormalities were managed with replacement therapy.

Vital Signs

Data and the Applicant's Position:

An integrated analysis of vital signs was not performed. Any clinically relevant changes in vital signs and physical examination findings associated with zanidatamab use and those that led to substantial interventions were reported and discussed as AEs.

The FDA's Assessment:

FDA evaluated the maximum and minimum changes from baseline in treatment emergent vital signs in the primary safety population. There were no additional trends in vital signs that was not captured in the analyses of adverse events.

Left Ventricular Ejection Fraction

Data:

In Study 203, all participants had baseline LVEF ≥ 50% for study eligibility. In Study 101, adequate left ventricular function (LVEF ≥ institutional standard of normal) was required for study eligibility. In the pooled 20 mg/kg Q2W Population, 9 (3.9%) participants had a postbaseline LVEF result that was < 50% and a decrease ≥ 10% from baseline.

The Applicant's Position:

The rate of LVEF decreased was in line with reported data from other anti-HER2 antibodies.

The FDA's Assessment:

In the pooled safety population, there were 10 (4.3%) patients who had a post baseline LVEF < 50%, and all had a decline in LVEF of ≥ 10% (range: 10% - 36%). Further details of LVEF dysfunction are outlined in the "Cardiac Events" section below.

ECGs and QT Interval Corrected by Fridericia's Formula

Data:

Of the 233 participants in the pooled 20 mg/kg Q2W Population, 24 (10.3%) participants had a maximum QTcF increase from baseline of 30 to 60 milliseconds and 5 (2.1%) participants had a maximum QTcF increase from baseline of > 60 milliseconds. Postbaseline, 24 (10.3%) participants had maximum QTcF of 450 to 480 milliseconds and 7 (3.0%) participants had maximum QTcF > 480 but not more than 500 milliseconds; 1 (0.4%) participant had a maximum QTcF > 500 milliseconds. Five (2.1%) participants from Study 101 that received zanidatamab at the 20 mg/kg Q2W dose regimen had Grade 1 or Grade 2 AEs of ECG QT prolonged.

The Applicant's Position:

As a large, targeted antibody, zanidatamab is considered to have a low likelihood of direct ion channel interactions. QTc prolongation (> 500 ms) was uncommon. Furthermore, the concentration-QT analysis suggests that zanidatamab is not expected to cause a clinically relevant prolongation of the QT interval at 20 mg/kg Q2W.

The FDA's Assessment:
As monoclonal antibodies are generally above 50 kDa and do not cross the cell membrane, FDA considers that this pharmacological class is unlikely to directly block hERG channels, and therefore are generally not required to undergo hERG testing or be evaluated in Thorough QT studies (unless there are nonclinical or clinical data suggesting that a specific mAb has the potential to cause arrhythmia) (Wu, Choe et al. 2023). The Applicant summarized their findings in Section 6.2.1 of this review. No events of arrhythmia were reported in the safety database.

Immunogenicity

Data:

The overall treatment-emergent incidence of ADAs to zanidatamab was 1.6 % (3 of 183 evaluable participants) and 1.2 % (1 of 85 evaluable participants) in Studies 101 and 203, respectively. The participant with ADA-positivity in Study 203 also tested positive for NAbs to zanidatamab. The incidence of ADA was low and there was no apparent impact of anti-zanidatamab antibodies on the safety of zanidatamab.

The Applicant's Position:

Zanidatamab is categorized as a low-risk molecule to elicit an immune response on the basis of assessment of the immunogenicity risk factors and the low incidence of ADA observed to date across the clinical studies, with no apparent impact of ADAs on PK or safety from a limited dataset during zanidatamab treatment.

The FDA's Assessment:
See FDA assessment in Section 6.2.1 for further details. Although the Applicant reported a low incidence (1.5%) of ADA in patients who received zanidatamab, FDA considers that the incidence of ADA should be reevaluated following the development of a new immunogenicity assay.

8.2.5. Analysis of Submission-Specific Safety Issues

Infusion-Related Reactions

The Applicant's Position:

In the 20 mg/kg Q2W Population, 71 (30.5%) participants experienced 75 events of IRR, all of which were assessed by the investigator as related to zanidatamab treatment. Most IRR events occurred in Cycle 1, and incidence decreased with subsequent infusions. All IRR events were Grade 1 or Grade 2 in severity and not serious, except for 1 participant with a serious Grade 3 event. All events of IRR resolved. The proposed prescribing information requires premedication with corticosteroid hormones, histamine receptor antagonists, and acetaminophen for each zanidatamab infusion to prevent or reduce severity of IRRs. Additional management and dose modification on IRRs will be described in the dose adjustments section.

The FDA's Assessment:

The clinical protocol for Study 203 required the use of prophylactic agents for infusion related reactions from initiation.

Following an information request sent by FDA, the Applicant provided a rationale for instituting mandatory prophylaxis over the course of Study 101. Following zanidatamab 10 mg/kg dosing in the initial 4 patients who did not receive prophylaxis, 3 patients developed a Grade 2 IRR. Prophylaxis with acetaminophen as a single agent resulted in 1 of 4 patients developing an IRR. A subsequent amendment to Study 101 (submitted March 2017) instituted IRR prophylaxis with acetaminophen and diphenhydramine. The rate of IRR was 47% (9 out of 19 patients [no Grade 3 IRR]) with acetaminophen and diphenhydramine, resulting in the addition of corticosteroids (amendment submitted February 2018). The incidence of IRR (all Grade 1-2 events) reduced to 30% (7 out of 23 patients) after instituting prophylaxis with acetaminophen, diphenhydramine, and corticosteroids.

In Study 203, one patient experienced a Grade 3 IRR on Cycle 1 Day 1 (the only reported case of a Grade 3 IRR in patients receiving zanidatamab monotherapy). The patient was managed with interruption of the infusion and required paracetamol, diphenhydramine, hydrocortisone, oxygen, and ondansetron. The IRR resolved on Day 3. Overall, 28 (35%) patients had a treatment emergent IRR in the primary safety population, 21 (26%) required interruption of the infusion, with no discontinuation. In the pooled safety population, 71 (30%) had an IRR, 59 (25%) requiring interruption of the infusion, with 1 patient discontinuing treatment.

The proposed USPI contains details for IRR prophylaxis and the dose modifications required based on severity.

Cardiac Events

The Applicant's Position:

In the 20 mg/kg Q2W Safety Population, 10 (4.3%) participants had 12 confirmed cardiac events; all were events of ejection fraction decreased. There were no participants with heart failure reported. The median time to first onset of cardiac events was 170.5 days (range: 50 to 570 days). Nine of the 12 events resolved; median time to resolution was 27.0 days (range: 3 to 168 days). All 10 participants were clinically asymptomatic and had pre-existing and concurrent medical conditions that were confounding.

Cardiotoxicity is a well-recognized adverse effect of HER2-targeted therapies and left ventricular dysfunction associated with HER2 receptor antibodies is typically considered reversible (Guarneri, 2006). Late occurrence of cardiotoxicity is uncommon (Cameron, 2017). Zanidatamab has not been studied in patients with a pretreatment LVEF value of < 50%, a history of MI or unstable angina within 6 months prior to zanidatamab treatment, troponin levels consistent with MI, clinically significant cardiac disease (such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic congestive heart failure). Therefore, a baseline cardiac assessment should be performed before the first dose of zanidatamab. LVEF should be monitored and evaluated periodically during treatment. The risk and management of LVEF decreased will be communicated in the appropriate sections of the product prescribing information.

The FDA's Assessment:

In the primary safety population, 16 (20%) patients had events within any of the broad MedDRA query terms "Cardiac Failure", Ejection Fraction Decreased", "Edema", "Pulmonary Edema" "Peripheral Swelling" and "Edema Peripheral". Of these, 5 (6%) patients had a decrease in LVEF < 50% with a ≥ 10% decline from baseline as assessed by Echo/MUGA. Four (5%) patients required dose delay of zanidatamab and 1 patient required treatment discontinuation. In the pooled safety population, the broad MedDRA query terms above identified 26 (11%) patients; of these, 10 (4.3%) patients had a decrease in LVEF < 50% with a ≥ 10% decline from baseline. One (0.4%) patient required dose reduction, 5 (2.1%) patients required dose delay, and 2 (0.9%) patients discontinued treatment. The median time of the onset of a decline in LVEF in the primary safety population was 58 days (range: 50, 305 days) and 170 days (range: 50, 570 days) in the pooled safety population.

From review of the case narratives of ejection fraction decreased, most patients reported no corresponding symptoms to the noted LVEF decline. Participant (b) (6), a 70-year-old male patient with a pre-existing diagnosis of atrial fibrillation enrolled into Study 203, had a worsening LVEF from 56% to 44%, leading to treatment discontinuation on Day 337. The patient's symptoms were cough and rhinitis, and he required the initiation of diuretic therapy with furosemide and spironolactone.

The proposed USPI provides details on the need for baseline and regular LVEF assessments while receiving treatment with zanidatamab. In addition, Sections 2, 5, and 6 of the USPI provide details of the observed toxicity in the pooled and primary safety datasets, and dose modification guidance.

Non-Infectious Pulmonary Toxicity

The Applicant's Position:

In the 20 mg/kg Q2W Safety Population, there was 1 event (0.4%) of non-infectious pulmonary toxicity, identified as a Grade 3 pneumonitis. Interpretation of the pneumonitis event was confounded by other factors, including a recent history of gemcitabine therapy (within 2 months of starting zanidatamab treatment) and ground glass opacities present on baseline CT scan. In

addition, a serious event of Grade 2 pneumonia required hospitalization 6 weeks prior to the diagnosis of pneumonitis. Noninfectious pulmonary toxicity can be detected by clinical symptoms and signs and generally be managed according to therapeutic principles for drug-induced interstitial lung disease. Therefore, no specific monitoring or management for noninfectious pulmonary toxicity is proposed in the product prescribing information.

The FDA's Assessment:

FDA agrees that there was a single reported case of pneumonitis in the pooled safety population. This event occurred in a 58-year-old male with a diagnosis of advanced intrahepatic cholangiocarcinoma enrolled in Study 203. The patient required treatment delay for the management of Grade 3 diarrhea (Day 69), and Grade 2 pneumonia (Day 181). After treatment with zanidatamab on Day 211 (Cycle 8 Day 15), he experienced Grade 3 pneumonitis on Day 223. Zanidatamab was discontinued on Day 259, with Grade 1 pneumonitis ongoing on Day 279. The patient died from disease progression on Day 715.

Although the incidence of pneumonitis was low in the pooled dataset, the proposed USPI contains guidance on treatment discontinuation upon the occurrence of Grade 2 or higher pneumonitis, consistent with the class labeling for antibodies targeting HER2.

Diarrhea

The Applicant's Position:

Diarrhea is known to be a common AE associated with the use of anti-HER2 antibodies. Diarrhea (48.5% incidence in the 20 mg/kg Q2W Safety Population) was the most common AEs with zanidatamab monotherapy and higher zanidatamab exposure was associated with increased probability of diarrhea. The majority of diarrhea events were Grade 1-2 and manageable with appropriate standard supportive care.

The FDA's Assessment:

FDA agrees that the diarrhea has been identified as an adverse reaction with HER2 targeted therapies. FDA analyses included groupings of clinically relevant preferred terms and the incidence of diarrhea in the primary safety population and the pooled safety population by maximum CTCAE severity grading, in addition to the rates of dose modifications, and dose reductions for diarrhea are outlined in Table 37.

Table 37: FDA Analysis: Incidence of Diarrhea and dose Modifications

	Zanidatamab 20 mg/kg Cohort 1	Zanidatamab 20 mg/kg Pooled
	N = 80	N = 233

	All Grades	Grade 3 + 4	All Grades	Grade 3 + 4
	N (%)	N (%)	N (%)	N (%)
Diarrhea (GT)	40 (50)	8 (10)	113 (48)	15 (6)
Diarrhea	40 (50)	7 (9)	113 (48)	12 (5)
Enteritis	1 (1.3)	1 (1.3)	1 (0.4)	1 (0.4)
Colitis	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.9)
Enterocolitis	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Treatment Delay/Hold				
Diarrhea	5 (6)		7 (3)	
Dose Reduction				
Diarrhea	2 (2.5)		3 (1.3)	

Source: FDA Analysis, ADAE dataset

The table contains the incidence of diarrhea (grouped term) and the constituent preferred terms (PTs) that were used. For the incidence of the grouped term the maximal toxicity for an individual patient of any of the related preferred terms for an individual patient was used.

FDA agrees that there were no Grade 4 or 5 TEAE for any of the listed preferred terms used for diarrhea. Twenty-five (31%) patients in the primary safety population were managed with anti-diarrheal agents (loperamide and/or atropine sulfate; diphenoxylate hydrochloride). In Study 203, the median time to onset for the initial diarrheal event was 16 days (range: 2, 518 days), with the median time to resolution 3 days (range: 1 to 313 days).

The proposed USPI cites the risks for diarrhea in the Warnings and Precautions section, with the incidences reflecting the composite groupings of clinically relevant preferred terms.

Embryo-fetal toxicity

The Applicant's Position:

Based on the mechanism of action, zanidatamab may cause embryo-fetal harm when administered to a pregnant woman. In postmarketing reports of other HER2 receptor antagonists, use during pregnancy resulted in reports of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. There are no animal data in pregnancy and no occurrence of pregnancy in clinical studies on the use of zanidatamab. The proposed prescribing information recommends patient and family caregivers should receive timely and up-to-date education about the use in pregnancy, and providers should

verify the pregnancy status prior to treatment with zanidatamab as well as suggest effective contraception use during and after treatment.

The FDA's Assessment:

FDA agrees with class-based concerns for embryo-fetal toxicity for HER2 targeted therapies. The proposed USPI containing warning for Embryo-Fetal toxicity, the need to verify pregnancy status prior to initiating treatment, and the use of effective contraception while receiving zanidatamab, and for 4 months following the last dose.

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

The Applicant's Position:

There were no patient-reported assessments for safety or tolerability outcomes included in the zanidatamab program.

The FDA's Assessment:

Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Data and the Applicant's Position:

There was no evidence that age, sex, or race affected the safety profile of zanidatamab. There was no clear pattern for an impact of renal or hepatic impairment on the safety of zanidatamab treatment.

The FDA's Assessment:

FDA analyses of safety by demographics demonstrated no clear difference in toxicity profile according to reported race, region of enrollment, and sex. There were small sample sizes within certain strata by demographic subgroups, limiting the inferences that can be drawn. There was an increase in the incidence of Grade 3 or 4 TEAEs in patients aged $\geq$ 65 years versus < 65 years in both the primary safety population (62% versus 56%) and pooled safety populations (50% versus 45%). There were no notable differences by age in terms of drug discontinuations and TEAEs leading to death, with event rates being low (<5%) across age strata.

8.2.8. Specific Safety Studies/Clinical Trials

Data and the Applicant's Position:

No specific safety clinical trials have been conducted.

The FDA's Assessment:

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Studies have not been conducted to evaluate the carcinogenic or mutagenic potential of zanidatamab. Zanidatamab is a bispecific antibody that binds to the extracellular domain of HER2 and is not expected to interact directly with DNA or other chromosomal material. Based on the mechanisms of action, zanidatamab is not expected to be carcinogenic.

The FDA's Assessment:

Carcinogenicity studies were not warranted (refer to Section 5.5.3). On the basis of a weight-of-evidence analysis supported by published literature indicating that embryo-fetal toxicity is a likely class effect of HER2 binding antibodies, the conduct of de novo developmental and reproductive toxicity studies were not warranted (refer to Section 5.5.4).

Human Reproduction and Pregnancy

Data and the Applicant's Position:

Based on mechanism of action, zanidatamab may cause fetal harm when administered to a pregnant woman. There are no human or animal data on the use of zanidatamab in pregnancy. Use of zanidatamab is not recommended during pregnancy. It is not known whether zanidatamab is secreted in human milk or what effect zanidatamab has on a breastfed child or milk production.

The FDA's Assessment:

FDA agrees.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Pediatric participants under age 18 years have not been enrolled in zanidatamab clinical trials.

The FDA's Assessment:

FDA agrees.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data and the Applicant's Position:

No overdoses have occurred. There is no nonclinical or clinical evidence that zanidatamab has potential for drug abuse, and specific clinical studies evaluating the potential for abuse have not been conducted. There is also no evidence of withdrawal or rebound phenomena associated with the discontinuation of zanidatamab in any clinical study.

The FDA's Assessment:

FDA agrees.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data and the Applicant's position:

Zanidatamab is not yet marketed; therefore, there is no postmarket experience.

The FDA's Assessment:

FDA agrees.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Toxicities have been adequately characterized in Study 203, supported with safety data in Study 101. Potential safety concerns beyond the risks identified in the proposed labelling with associated management recommendations are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected AEs.

The FDA's Assessment:

The characterization of zanidatamab monotherapy administered at 20 mg/kg every 2 weeks has been adequately characterized in the pooled safety dataset. The randomized controlled trial being conducted to verify clinical benefit will provide additional safety data of zanidatamab as part of a combination regimen in first line advance biliary tract cancer.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The integrated pooled safety analysis for this application is based on the pivotal Study 203 and supporting Study 101 (Parts 1 and 2) which include a total of 279 participants with different disease indications and different zanidatamab monotherapy doses. The totality of the safety package sufficiently supports the use of zanidatamab 20 mg/kg IV Q2W as monotherapy for patients with previously treated, unresectable locally advanced or metastatic HER2-positive BTC. The favorable benefit-risk of zanidatamab was supported by a well-tolerated safety profile in the 20 mg/kg Q2W Safety Population, which included all participants treated with zanidatamab monotherapy at 20 mg/kg Q2W, regardless of tumor type, in Study 203 and Study 101. In general, zanidatamab was well tolerated in participants with HER2-positive BTC. The safety profile was comparable to that of known HER2 drug-class effects, with adverse effects that were manageable during treatment. Zanidatamab was associated with a lower incidence of severe toxicities commonly reported with the current 2L BTC standard of care, FOLFOX.

Treatment with zanidatamab resulted in few treatment discontinuations or dose reductions. In the 20 mg/kg Q2W Population, the median duration of exposure was 4.7 months (range: 0.2 to 44.6 months). Diarrhea (40.8%) and IRR (30.5%) were the most frequently reported zanidatamab-related AEs and were manageable in the outpatient setting with premedication or symptomatic treatment. All other zanidatamab-related AEs were reported in < 15% of participants in the 20 mg/kg Q2W Population. Serious or high-grade toxicities assessed to be related to zanidatamab were infrequent. Safety data were consistent across studies in participants with BTC, across disease indications, and across different dose regimens. The safety profile in terms of overall AEs, Grade 3 or higher AEs, SAEs, or AESI was consistent with the established safety profile of zanidatamab.

The FDA's Assessment:

The adverse reaction profile is consistent with known profiles of HER2 targeted agents, and the comorbidities associated with the advanced solid tumors. The proposed USPI contains details of the risks for left ventricular dysfunction, infusion related reactions, and diarrhea, which are commonly associated with other HER2 targeted therapies.

The most common adverse reaction in the primary safety population was diarrhea (50%), which were predominantly Grade 1 or 2 severity. Onset of diarrhea was early in treatment (mostly in Cycle 1), and generally managed with a combination of treatment delay and anti-diarrheal agents. There were no Grade 4 or fatal events of diarrhea.

Based on the observed safety data from Study 101, Study 203 instituted mandatory prophylaxis for IRR at initiation of the study. With the use of prophylaxis, the incidence of IRR in the primary safety population was 35%, most were Grade 1 or 2 in severity, improved with infusion interruption, and 97% of IRRs resolved within one day.

The eligibility criteria for Study 203 required a baseline LVEF ≥50%, and LVEF was assessed at regular intervals while patients were receiving treatment. In the primary safety population, a decline in LVEF by greater than 10% and for LVEF <50% occurred in 5 (6%) patients, four patients requiring treatment delay and 1 patient treatment discontinuation. FDA agrees with the

Applicant that the rate of dose reductions or treatment discontinuations in the monotherapy development plan was low, and most patients were adequately managed with treatment delay and the use of supportive treatments.

FDA agrees that single agent zanidatamab 20 mg/kg administered intravenously every 2 weeks has an acceptable safety profile for the second line treatment of patients with advanced biliary tract cancer.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no statistical issues encountered when reviewing this application. Time-to-event endpoints are not interpretable in single-arm studies and therefore considered exploratory. The review team has conducted additional analyses to evaluate the benefit in HER2 subgroups (IHC 3+ vs IHC 2+).

8.4. Conclusions and Recommendations

The FDA's Assessment:

The review team considers the ORR and DOR results in Study 203 in patients with HER2 ISH-amplified IHC 3+ are reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, and representative of a meaningful advantage over existing treatments for the proposed indication. The submitted data satisfies the requirements for accelerated approval.

Due to the limited sample size, and the objective response being limited to a single patient with HER2 IHC 2+, the efficacy in the IHC 2+ was poorly characterized and the indication will be limited to patients with IHC3+ tumors.

The safety profile of zanidatamab is consistent with the class of HER2 targeted therapies. The risks of diarrhea, left ventricular dysfunction, and infusion related reactions are outlined in the Warnings and Precautions section of the USPI. Diarrhea was the most common adverse reaction. Most events of diarrhea were either Grade 1 or 2 and managed with a combination of dose delay and anti-diarrheal treatments. There were no Grade 4 or 5 diarrhea events. The overall rates of treatment discontinuations and dose reductions due to adverse reactions were low both in the primary and pooled safety population.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9. ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

This Application was not referred to an Advisory Committee meeting or external consultants. The clinical effect on ORR and duration of response and the risk-benefit profile of zanidatamab as compared to existing standard of care is considered to be favorable for the proposed patient population.

10. PEDIATRICS

The Applicant's Position:

As per the agreed iPSP, (b) (4)

The FDA's Assessment:

(b) (4) issued an Initial Pediatric Study Plan (iPSP) agreement on September 1, 2022.

The BLA contains a request for a waiver of pediatric studies with zanidatamab, which will be granted.

11. LABELING RECOMMENDATIONS

Data:

This is an original application. See annotated label in Module 1.14.1.2 for the Applicant's proposed labeling.

The Applicant's Position: N/A

Summary of Significant Labeling Changes (High-level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's Proposed Labeling**
1 Indications and Usage	ZIIHERA is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer, as detected by an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of benefit in a confirmatory trial(s).	ZIIHERA is indicated for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).
2 Dosage and Administration	2.1 Patient Selection (b) (4) 2.2 Premedications and 2.3 Recommended Dosage	Select patients for treatment of unresectable or metastatic biliary tract cancer based on HER2-positive (IHC 3+) tumor specimens, as detected by an FDA-approved test(s). FDA generally agreed; minor revisions

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.

	2.4 Dose modifications [redacted] (b) (4) Separate dosage modification tables for left ventricular dysfunction and infusion-related reactions 2.4 Preparation and Administration 2.5 Storage of Reconstituted or Diluted Product	Dosage reduction to 15mg/kg for adverse reactions Dosage modification tables combined into one table with additions for diarrhea, pneumonitis, and other adverse reactions FDA generally agreed; storage of reconstituted and diluted product moved to 2.4, and 2.5 was deleted
5 Warnings and Precautions	5.1 Embryo-fetal Toxicity 5.2 Left Ventricular Dysfunction 5.3 Infusion-related reactions	FDA generally agreed; removed [redacted] (b) (4) Revised to include incidence and degree of decreases of left ventricular dysfunction from trial population; additional edits to align with labeling practices Revised to include complete information on incidence and grades from trial population; additional edits to align with labeling practices Addition of 5.4 Diarrhea Warning and Precaution added for diarrhea.
6 Adverse Reactions	6.1 Biliary Tract Cancer, HERIZON-BTC-01 safety results	FDA generally agreed; edited to align with labeling practices
8 Use in Specific Populations	8.1, 8.2, 8.3, 8.4 and 8.5 included	FDA generally agreed; edited to align with labeling practices
12 Clinical Pharmacology	12.1 Mechanism of Action [redacted] (b) (4)	12.1 Mechanism of Action Zanidatamab-hrii is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. Binding of zanidatamab-hriii with HER2 results in internalization leading to a reduction of the receptor on the tumor cell surface. Zanidatamab-hrii induces complement-dependent cytotoxicity (CDC),

	(b) (4)	antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumor growth inhibition and cell death in vitro and in vivo.
	12.2 Pharmacodynamics – included statement on cardiac electrophysiology	FDA generally agreed; added statement that exposure-response relationships and time course of pharmacodynamic responses is unknown.
	12.3 Pharmacokinetics	Edited to align with labeling practice; inclusion of PK data from steady-state phase; and inclusion of distribution, elimination, and metabolism; deleted (b) (4)
	12.6 Immunogenicity	FDA deleted proposed language due to questionable status of ADA data. Included statement that insufficient data to characterize anti-drug antibody response.
14 Clinical Studies	HERIZON-BTC-01 description and efficacy results from Cohort 1 HER2-positive ICH3+/ (b) (4)	Study description and efficacy results limited to HER2-positive IHC3+ population

12. RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA's Assessment:

No REMS have been requested. The pharmacological class has been extensively used in cancer patients and the review did not uncover new safety signals. The risks of zanidatamab can be managed with standard of care monitoring and labeling recommendations.

.

13. POSTMARKETING REQUIREMENTS AND COMMITMENTS

The FDA's Assessment:

Although a randomized controlled study in the first-line setting of treatment for patients with HER2+ biliary tract cancer that would serve as the trial to confirm benefit in the event of an accelerated approval of zanidatamab based on data from Study 203 (refer to Section 3.1, Table 4) was discussed on a Type B meeting held on September 8, 2021, the study was not submitted to the IND until July 31, 2023. Submission of the study protocol followed meetings held on May 10, 2023, and June 26, 2023, where FDA advised Jazz on the need to have a confirmatory trial well underway and expressed concerns regarding the preliminary stage of planning for the proposed confirmatory study, given the intended timeline for BLA submission.

The Applicant and FDA further discussed the progress and enrollment of the randomized study intended to verify benefit, Study JZP598-302 "An open-label randomized trial of the efficacy and safety of zanidatamab with standard-of-care therapy against standard-of-care therapy alone for advanced HER2-positive biliary tract cancer" (Study 302) on several meetings and correspondence. As discussed on the late cycle meeting held on October 9, 2024, the study was (b) (4) .

Breakthrough designation for zanidatamab for the treatment of patients with HER2+ BTC was granted on 2020, and the data submitted to the BLA supports an accelerated approval in patients with HER2+ IHC3+ tumors. Given the rarity of this disease, the unique mechanism of action of zanidatamab, the magnitude of benefit observed in these patients, and the high unmet medical need, the target completion date and ability to meet that date were considered acceptable despite the confirmatory study being in the early stages of accrual. Thus, the confirmatory trial is considered to be underway in this circumstance, and the review team recommends granting the accelerated approval.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:	Is a PMC/PMR needed?

□	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.	_X_ Yes __ 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?	_X_ Yes __ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

Study 302 will also serve to fulfill a PMC to explore the effects of zanidatamab in the diverse US population.

The following PMR and PMCs have been agreed with Jazz and incorporated into the Approval letter:

PMR 4732-1: Complete the ongoing randomized clinical trial, Study JZP598-302, entitled, "An Open-Label Randomized Trial of the Efficacy and Safety of Zanidatamab with Standard-of-Care Therapy Against Standard-of-Care Therapy Alone for Advanced HER2-Positive Biliary Tract Cancer", intended to verify and describe the clinical benefit of zanidatamab for patients with HER2-positive (IHC3+), unresectable or metastatic biliary tract cancer. The trial should compare zanidatamab in combination with the standard of care in patients with HER2-positive (IHC3+), unresectable or metastatic biliary tract cancer.

Trial Completion: 03/2029
Final Report Submission: 09/2029

PMC 4732-2: Conduct an assessment of binding and neutralizing anti-zanidatamab antibody responses to evaluate the incidence of anti-drug antibodies (ADAs). Reanalyze the biliary tract cancer (BTC) samples from Study ZWI-ZW25-101 and all samples from Study ZWI-ZW25-203 using a validated assay capable of sensitively detecting ADA responses in the presence of zanidatamab levels that are expected to be present in the serum at the time of patient sampling. Reevaluate the immunogenicity of zanidatamab and the effect of ADAs on efficacy, pharmacokinetics (PKs), and safety of zanidatamab. Include the level of zanidatamab in each patient's test sample at each sampling point in the final report.

Draft Protocol Submission: 06/2025
Final Protocol Submission: 09/2025
Study Completion: 03/2026
Final Report Submission: 09/2026

PMC 4732-3: Conduct an integrated analysis of clinical trial data to allow for further characterization of the clinical effects of zanidatamab, including pharmacokinetics (PK), efficacy, and safety in the underrepresented racial and ethnic minority populations. These

clinical data, which may come from other ongoing trials with zanidatamab, should support an evaluation of comparative efficacy and safety between the aforementioned population and the population primarily represented in your trial.

Trial Completion:	03/2029
Final Report Submission:	09/2029

14. DIVISION DIRECTOR (DHOT) (NME ONLY)

X

15. DIVISION DIRECTOR (OCP)

X

16. DIVISION DIRECTOR (OB)

X

17. DIVISION DIRECTOR (CLINICAL)

I agree with the approval recommendations by the review teams. In the US, HER2 3+ BTC represents a subset of a rare disease (BTC) and the response rate of ~50% represents an effect that is reasonably likely to predict benefit in the intended patient population, considering the adverse event profile of zanidatamab, the underlying prognosis of the patient population, and the lack of effective available therapies. Although trastuzumab-deruxtecan (Enhertu) is approved (given the tissue agnostic use), the approval is an accelerated approval allowing consideration of zanidatamab's approval. Furthermore, the adverse event profile differs between zanidatamab and Enhertu (as the latter is an antibody-drug conjugate) allowing for an alternative option for patients.

X

18. OFFICE DIRECTOR (OR DESIGNATED SIGNATORY AUTHORITY)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19. APPENDICES

19.1. References

The Applicant's References:

Oh DY, Ruth A, Qin S, et al. NEJM Evid. 2022;1(8).

Ayasun R, Ozer M, Sahin I. Cancers. 2023;15(9):2628.

Brieau B, Dahan L, De Rycke Y, et al. Cancer. 2015;121(18):3290-7.

Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. Lancet. 2017;389(10075):1195-205.

Caparica R, Lengele A, Bekolo W, Hendlisz Aet al. Autops Case Rep. 2019;9:e2019087

Chan R, Hardy WR, Laing MA, et al. Mol Cell Biol. 2002;22(4):1073-8.

Erickson SL, O'Shea KS, Ghaboosi N, et al. Development. 1997;124(24):4999-5011.

Fock V, Plessl K, Draxler P, et al. J Cell Sci. 2015;128:4306-16.

Fornaro L, Vivaldi C, Cereda S, et al. J Exp Clin Cancer Res. 2015;34:156.

Guarneri V, Lenihan DJ, Valero V, et al. J Clin Oncol. 2006 Sep 1;24(25):4107-15.

Hyung J, Kim I, Kim KP, et al. JAMA Oncol. 2023:e230016.

ICH Tripartite Guideline (2009). Nonclinical Evaluation for Anticancer Pharmaceuticals S9. [cited 05 Mar 2024]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s9-nonclinical-evaluation-anticancer-pharmaceuticals.

ICH Tripartite Guideline (2011) S6(R1). [cited 05 Mar 2024]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals.

ICH Tripartite Guideline (2012) S10. [cited 05 Mar 2024]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s10-photosafety-evaluation-pharmaceuticals.

ICH Tripartite Guideline (2020) S5 (R3). [cited 05 Mar 2024]. Available from: https://www.ema.europa.eu/en/documents/scientific- guideline/ich-s5-r3-guideline-detection-reproductive-developmental-toxicity-human-pharmaceuticals-step-5_en.pdf.

Jansen H, Pape UF, Utku N. J Gastrointest Oncol. 2020;11(4):770-789.

Javle M, Borad MJ, Azad NS, et al. Lancet Oncol. 2021;22(9):1290-300.

Kim RD, Chung V, Alese OB, et al. JAMA Oncol. 2020;6:888-894.

Lamarca A, Hubner RA, David Ryder W, et al. Ann Oncol. 2014;25(12):2328- 38.

Lamarca A, Palmer DH, Wasan HS, et al. Lancet Oncol. 2021;22:690-701.

Lee CK, Chon HJ, Cheon J, et al. Lancet Gastroenterol Hepatol. 2023; 8: 56–65.

Lee KF, Simon H, Chen H, et al. Nature. 1995;378(6555):394-8.

Liu Z, Carvajal M, Carraway K, et al. Cornea. 2001;20(1):81-5.

Lowery MA, Ptashkin R, Jordan E, et al. Clin Cancer Res. 2018;24:4154–61.

Lwin, Z, Gomez-Roca, C, Saada-Bouzid E, et al. Ann Oncol. 2020;31:S1142-S1215.

Nakamura H, Arai Y, Totoki Y, et al. Nat Genet. 2015;47(9):1003-10.

National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: biliary tract cancers. Version 3.2023. 08 November 2023. Plymouth Meeting, PA: NCCN; 2023. 93 p.

Ohba A, Morizane C, Kawamoto Y, et al. J Clin Oncol. 2022; 40: 4006.

Press MF, Cordon-Cardo C, Slamon DJ. Oncogene. 1990;5(7);953- 62.

Quirke P, Pickles A, Tuzi NL, et al. Br J Cancer. 1989;60(1):64-9.

Rossi F, Perale G, Papa S, et al. Expert Opin Drug Del. 2013;10(3):385-96.

Sun W, Patel A, Normolle D, et al. Cancer. 2019 Mar 15;125(6):902-9.

Valle JW, Lamarca A, Goyal L, et al. Cancer Discov. 2017;7(9):943- 62.

Vogel A, Bridgewater J, Edeline J, et al. Ann Oncol. 2023;34(2):127-40.

Xia LY, Hu QL, Zhou Q. BMC Womens Health. 2021;21:169.

Yildirim N, Bahceci A. Anticancer Drugs. 2018;29:810- 13.

Yoo C, Kim K, Jeong JH, et al. Lancet Oncol. 2021;22(11):1560-72.

FDA References

Banales, J. M., J. J. G. Marin, A. Lamarca, P. M. Rodrigues, S. A. Khan, L. R. Roberts, V. Cardinale, G. Carpino, J. B. Andersen, C. Braconi, D. F. Calvisi, M. J. Perugorria, L. Fabris, L. Boulter, R. I. R. Macias, E. Gaudio, D. Alvaro, S. A. Gradilone, M. Strazzabosco, M. Marzioni, C. Coulouarn, L. Fouassier, C. Raggi, P. Invernizzi, J. C. Mertens, A. Moncsek, S. I. Ilyas, J. Heimbach, B. G. Koerkamp, J. Bruix, A. Forner, J. Bridgewater, J. W. Valle and G. J. Gores (2020). "Cholangiocarcinoma 2020: the next horizon in mechanisms and management." Nature Reviews Gastroenterology & Hepatology **17**(9): 557-588.

Bridgewater, J. A., K. A. Goodman, A. Kalyan and M. F. Mulcahy (2016). "Biliary Tract Cancer: Epidemiology, Radiotherapy, and Molecular Profiling." Am Soc Clin Oncol Educ Book **35**: e194-203.

Casak, S. J., V. Kumar, C. Song, M. Yuan, A. K. Amatya, J. Cheng, P. S. Mishra-Kalyani, S. Tang, S. J. Lemery, D. Auth, G. Davis, P. G. Kluetz, R. Pazdur and L. A. Fashoyin-Aje (2024). "FDA Approval Summary: Durvalumab and Pembrolizumab, Immune Checkpoint inhibitors for the Treatment of Biliary Tract Cancer." Clin Cancer Res.

Duffy, A., M. Capanu, G. K. Abou-Alfa, D. Huitzil, W. Jarnagin, Y. Fong, M. D'Angelica, R. P. Dematteo, L. H. Blumgart and E. M. O'Reilly (2008). "Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC)." J Surg Oncol **98**(7): 485-489.

Hundal, R. and E. A. Shaffer (2014). "Gallbladder cancer: epidemiology and outcome." Clin Epidemiol **6**: 99-109.

IMFINZI. (2024). "Durvalumab USPI." from https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761069s043lbledt.pdf.
Kelley, R. K., M. Ueno, C. Yoo, R. S. Finn, J. Furuse, Z. Ren, T. Yau, H. J. Klümpen, S. L. Chan, M. Ozaka, C. Verslype, M. Bouattour, J. O. Park, O. Barajas, U. Pelzer, J. W. Valle, L. Yu, U. Malhotra, A. B. Siegel, J. Edeline and A. Vogel (2023). "Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial." Lancet **401**(10391): 1853-1865.
KEYTRUDA. (2024). "Pembrolizumab USPI." from https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s161lbl.pdf.
Lamarca, A., D. H. Palmer, H. S. Wasan, P. J. Ross, Y. T. Ma, A. Arora, S. Falk, R. Gillmore, J. Wadsley, K. Patel, A. Anthoney, A. Maraveyas, T. Iveson, J. S. Waters, C. Hobbs, S. Barber, W. D. Ryder, J. Ramage, L. M. Davies, J. A. Bridgewater and J. W. Valle (2021). "Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial." The Lancet Oncology **22**(5): 690-701.
Lee, C. K., H. J. Chon, J. Cheon, M. A. Lee, H. S. Im, J. S. Jang, M. H. Kim, S. Park, B. Kang, M. Hong, J. W. Kim, H. S. Park, M. J. Kang, Y. N. Park and H. J. Choi (2023). "Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG-HB19-14)." Lancet Gastroenterol Hepatol **8**(1): 56-65.
Lowery, M. A., R. Ptashkin, E. Jordan, M. F. Berger, A. Zehir, M. Capanu, N. E. Kemeny, E. M. O'Reilly, I. El-Dika, W. R. Jarnagin, J. J. Harding, M. I. D'Angelica, A. Cercek, J. F. Hechtman, D. B. Solit, N. Schultz, D. M. Hyman, D. S. Klimstra, L. B. Saltz and G. K. Abou-Alfa (2018). "Comprehensive Molecular Profiling of Intrahepatic and Extrahepatic Cholangiocarcinomas: Potential Targets for Intervention." Clin Cancer Res **24**(17): 4154-4161.
Oh, D. Y., A. Ruth He, S. Qin, L. T. Chen, T. Okusaka, A. Vogel, J. W. Kim, T. Suksomboon charoen, M. Ah Lee, M. Kitano, H. Burris, M. Bouattour, S. Tanasanvimon, M. G. McNamara, R. Zaucha, A. Avallone, B. Tan, J. Cundom, C. K. Lee, H. Takahashi, M. Ikeda, J. S. Chen, J. Wang, M. Makowsky, N. Rokutanda, P. He, J. F. Kurland, G. Cohen and J. W. Valle (2022). "Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer." NEJM Evid **1**(8): EVIDoa2200015.
Patel, N. and B. Benipal (2019). "Incidence of Cholangiocarcinoma in the USA from 2001 to 2015: A US Cancer Statistics Analysis of 50 States." Cureus **11**(1): e3962.
Valle, J. W., R. K. Kelley, B. Nervi, D. Y. Oh and A. X. Zhu (2021). "Biliary tract cancer." Lancet **397**(10272): 428-444.
Valle, J. W., S. Qin, L. Antonuzzo, D. Tougeron, C. K. Lee, B. J. Tan, M. Ikeda, V. Guthrie, P. McCoon, Y. S. Lee, N. Rokutanda, M. Żotkiewicz, G. Cohen and D. Y. Oh (2022). "68O Impact of mutation status on efficacy outcomes in TOPAZ-1: A phase III study of durvalumab (D) or placebo (PBO) plus gemcitabine and cisplatin (+GC) in advanced biliary tract cancer (BTC)." Annals of Oncology **33**: S1457.
Wu, W. W., M. Choe, L. Johannesen, J. Vicente, G. Bende, N. L. Stockbridge, D. G. Strauss and C. Garnett (2023). "ICH S7B In Vitro Assays Do Not Address Mechanisms of QT(C) Prolongation for Peptides and Proteins - Data in Support of Not Needing Dedicated QT(C) Studies." Clin Pharmacol Ther **114**(6): 1332-1341.

Gougis P, Grandal B, Jochum F, et al. Treatments During Pregnancy Targeting ERBB2 and Outcomes of Pregnant Individuals and Newborns. JAMA Netw Open. 2023;6(10):e2339934. Published 2023 Oct 2. doi:10.1001/jamanetworkopen.2023.39934

19.2. Financial Disclosure

The Applicant's Position:

Covered Clinical Study (Name and/or Number): ZWI-ZW25-203

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 518		
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: not applicable Significant payments of other sorts: not applicable Proprietary interest in the product tested held by investigator: not applicable Significant equity interest held by investigator in study: not applicable Sponsor of covered study: not applicable		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Not applicable)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Not applicable)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Not applicable)

Covered Clinical Study (Name and/or Number): ZWI-ZW25-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 265		
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: not applicable Significant payments of other sorts: not applicable Proprietary interest in the product tested held by investigator: not applicable Significant equity interest held by investigator in study: not applicable Sponsor of covered study: not applicable		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ (Not applicable)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ (Not applicable)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Not applicable)

The FDA's Assessment:

FDA acknowledges the Applicant's position. Following an information request sent by FDA, the Applicant provided a list of all investigators that participated in either Study 203 or Study 101 and provided a statement that no investigators had reportable financial interests.

19.3. Nonclinical Pharmacology/Toxicology

Data and the Applicant's Position:

All data are presented in Section 5, Nonclinical Pharmacology/ Toxicology.

The FDA's Assessment:

See Section 5.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical

The FDA's Assessment:

FDA finds the Applicant's bioanalytical method validation and performance acceptable to determine the serum concentration of zanidatamab in studies 101 and 203.

Zanidatamab was measured using a validated enzyme linked immunosorbent assay (ELISA). The method was developed and validated at (b) (4). (Method HCL-442; Report SC-14/343-001 and addendeum-1) to support the PK assay for study 101. The method was then transferred and validated at (b) (4) Method ELISA-0968; Report 8425-100) and (b) (4) Method ICSH-20-014; Report 8414-357) to support the PK assay for study 203.

Summary of Validation Report 343-001 and Addendum-1

4. METHOD VALIDATION SUMMARY RESULTS

Method Validation Summary	
Method Validation Report ID	SC-14/343-001
Test Method ID	GCL-442 (Appendix A)
Compound Name	ZW25
Methodology	Enzyme-linked Immunosorbent Assay
Biological Matrix	Human serum
Anticoagulant	N/A
Calibration Curve Range	26.01 to 1500 ng/mL (includes anchor points)
LLOQ	58.53 ng/mL
ULOQ	1000 ng/mL
Regression Model	5-PL (Marquardt) with weighting factor $1/Y^2$
Minimum Required Dilution	1:100
Interference	No Hemolysis or Lipemia interference was observed at 2mg/mL
Stability	Short-term: 24 hours at 15-30 °C 24 hours at 2-8 °C Freeze/Thaw: 6 cycles Long-term: ongoing

4.2. Validation Samples and Dilutional Linearity

		Target Acceptance Criteria				
		Intra-assay	**> LLOQ**		**At LLOQ**	
		Accuracy (%RE)	Within ± 20%		Within ± 25%	
Accuracy and Precision		**Intra-assay and Inter-assay**	**> LLOQ**		**At LLOQ**	
		Precision (%CV)	≤ 20%		≤ 25%	
		Total Error	≤ 30%		≤ 40%	
Method Validation Performance						
Validation Principle	**Hyperlink**	Intra-assay (Pooled)		Inter-assay (ANOVA)		
Quality Control Samples All Runs		(%CV)	(%RE)	(%CV)	(%RE)	(%TE)
ULOQ (1000.00 ng/mL)	Table 3	7.2	-3.1	9.2	-2.9	12.1
HQC (750.00 ng/mL)	Table 5	6.8	-0.7	9.6	-0.7	10.3
MQC (300.00 ng/mL)	Table 7	9.3	-3.5	11.0	-3.5	14.5
LQC (150.00 ng/mL)	Table 9	9.0	-9.1	12.2	-9.1	21.3
LLOQ (58.53 ng/mL)	Table 11	19.9	-14.9	22.2	-14.9	37.1
Quality Control Samples Excluding Runs 5 and 6						
ULOQ (1000.00 ng/mL)	Table 4	7.2	-1.5	8.0	-1.5	9.5
HQC (750.00 ng/mL)	Table 6	6.2	-2.2	7.5	-2.2	9.7
MQC (300.00 ng/mL)	Table 8	4.4	-2.7	6.1	-2.7	8.8
LQC (150.00 ng/mL)	Table 10	3.0	-5.4	3.5	-5.4	8.9
LLOQ (58.53 ng/mL)	Table 12	3.6	-11.7	7.2	-11.7	18.9

Stability Assessments

Validation Principle	Hyperlink	Target Acceptance Criteria
		Mean calculated concentrations of the stability samples are within ± 20% RE of nominal concentration
Method Validation Performance		
Long-term Stability	Table 4	1463 Days at -60°C to -85°C
Sub stock stability	Table 5	370 days at -60°C to -85°C

Summary of Validation Report 8414-357

5 SUMMARY

Analyte Name(s)	ZW25
Species	Human
Analytical Matrix	Serum
Validated Method	ICSH 20-014
Validated Range	50.0 to 3200 ng/mL (anchor point:25.0 and 4000 ng/mL)
Quality Control (QC) Levels	50.0 ng/mL 150 ng/mL 600 ng/mL 2560 ng/mL 3200 ng/mL
Type of Assay	Enzyme-Linked Immunosorbent Assay (ELISA)
Minimum Required Dilution (MRD)	1 in 100
MRD Solution	Assay buffer
Calibration Model	5 Parametric
Weighting Factor	1/Y^2
Accuracy and Precision	Intra-assay and inter-assay accuracy and precision at ULOQ, HQC, MQC, LQC and LLOQ met the acceptance criteria
Selectivity (Normal/Haemolysed/Lipaemic)	1.No matrix effect was observed in normal human serum 2.No matrix effect was observed in Haemolysed/Lipaemic human serum
Dilution Linearity/Hook Effect	Maximum dilution factor 1:10000 No hook effect was observed when ZW25 concentration up to 500 µg/mL
Specificity/Interference	No Specificity effect was observed in blank matrix, LLOQ and ULOQ when concentration of BGB-A317 up to 500 µg/mL
Freeze/Thaw (F/T) Stability	6 F/T at -60 to -80°C and -10 to -30°C
Bench Top Stability	72 hours 10 mins
Refrigerator Stability	72 hours 42 mins
Freezer Stability	442 days at -10 to -30°C; 588 days at -60 to -80°C Long term stability is still on-going.

Summary of Validation Report 8425-100 and Addendum-1

5. SUMMARY

Validation Study Number:	8425-100
Method Type:	ELISA
Curve Fit; Weighting Factor	5PL; $1/y^2$ weighting
Analyte Name(s):	ZW25
Species Matrix:	Human Serum
Sample Volume:	1.0 mL requested (0.5 mL minimum)
Minimum Required Dilution (MRD):	1/100
Calibrator:	ZW25
Plate type:	Microtiter Plate Nunc No. 439454
Capture Reagent:	Anti-ZW25 Antibody
Detection Reagents:	Human Anti-Trastuzumab Antibody:HRP
Substrate:	Tetramethylbenzidine (TMB)
Lower Limit of Quantitation (LLOQ):	75.0 ng/mL
Upper Limit of Quantitation (ULOQ):	3200 ng/mL
Sample Storage Temperature:	-60 to -80°C
Freeze/Thaw Stability:	Up to 6 cycles
Room Temperature Stability:	Up to 27 hours 40 min
Refrigerated Temperature (2 to 8°C) Stability:	Up to 71 hours 43 min
Long Term Stability:	Up to 357 days at -60 to -80°C Up to 219 days at -15 to -30°C
Working Stock Stability:	Up to 387 days at -60 to -80°C
Dilutional Linearity:	1/15,000
Method Developed By:	(b) (4)

Validation Item	Result	Reference Table*
Accuracy and Precision	Intra-assay, inter-assay bias, precision (%CV) and total error for the LLOQ, LQC, MQC, HQC and ULOQ were within the target specifications.	Table 4
Selectivity	Normal human serum selectivity evaluated in 10 lots met the acceptance criteria at LLOQ (75.0 ng/mL) and HQC (2560 ng/mL).	Table 6
	Lipemic matrix selectivity evaluated in 5 lots met target specifications criteria at LLOQ and HQC.	Table 7
	Hemolyzed selectivity evaluated in 5 lots met target specifications criteria at LLOQ and HQC.	Table 8

Validation Item	Result	Reference Table*
Dilutional Linearity/Hook Effect	Linearity with serial dilutions up to 1:15,000 met target specifications. No hook effect was observed.	Table 9
Cross validation between (b) (4)	A total of 30 samples prepared in pooled normal human serum met the cross validation specifications.	Addendum-1 Table 6
Cross validation between (b) (4)	The comparison of spiked samples analyzed at (b) (4) met acceptance criteria.	Addendum-1 Table 7

* Table source: Module 5.3.1.4, 8425-100 Validation Report and Addendum-1

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment:

Zanidatamab PK data obtained from 279 patients (192 from Study ZWI-ZW25-101 and 87 from Study ZWI-ZW25-203) were used for the development of the PopPK model.

The final zanidatamab PopPK model was a 2-compartment model with zero-order drug input and parallel linear and nonlinear CL pathways to describe elimination kinetics. The model was parameterized based on the duration of the zero-order infusion, linear CL, maximum rate of nonlinear elimination (Vmax), the drug amount at 50% of the maximum nonlinear elimination (Km), Vc, Vp, and intercompartmental CL. Interindividual variability was estimated for CL, Vc, and Vp and was described using exponential error models. Residual variability was estimated using a proportional error model.

Although the covariate analysis identified baseline body weight, albumin (ALB), baseline number of lesions, and cancer type as significant predictors of CL, as well as body weight and cancer type as significant predictors of Vc and cancer type as predictor of Vp, these covariates are unlikely to cause clinically relevant differences in steady state zanidatamab exposures at the proposed dosing regimen of 20 mg/kg Q2W. Therefore, no dosage adjustments are recommended for the intrinsic and extrinsic covariates evaluated.

19.4.2.2. PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		• *Develop a PopPK model to describe the zanidatamab concentration-time course in patients with HER2-expressing cancers by pooling data from 2 clinical studies* • *Assess and quantify the impact of intrinsic and extrinsic patient factors on zanidatamab PK variability, including an evaluation to determine whether the magnitude of any covariate effects had a clinically meaningful impact on zanidatamab exposures that may warrant dose adjustments* • *Perform model-based simulations to explore the expected exposures for specific zanidatamab treatment regimens* • *Using the final PopPK model, generate individual zanidatamab exposure measures for use in ER efficacy and safety analysis*
Study Included		*ZWI-ZW25-101, ZWI-ZW25-203*
Dose(s) Included		*5, 10, 15 mg/kg QW, 20, 25, 30 mg/kg Q2W, and 30 mg/kg Q3W (Study 101) and 20 mg/kg Q2W (Study 203)*
Population Included		*Locally advanced (unresectable) and/or metastatic HER2-expressing cancers (Study 101) and advanced or metastatic HER2-amplified biliary tract cancers (Study 203)*
Population Characteristics	General	*Table 38 (continuous) and Table 39 (categorical) present age, weight, sex, and race among other parameters.*
	Organ Impairment	• *Hepatic (NCI): 172 (61.6%) normal, 104 (37.3%) mild impairment, 3 (1.1%) moderate impairment* • *Renal (CL_{CR}, etc): 138 (49.5%) normal, 114 (40.9%) mild impairment, 27 (9.7%) moderate impairment*
	Pediatrics (if any)	*Not applicable*
No. of Patients, PK Samples, and BLQ		*A total of 3711 serum concentrations from 279 participants were included in the PopPK analysis:* • *2728 concentrations from n=192 in Study 101* • *983 concentrations from n=87 in Study 203* *BLQ records were excluded, as follows:* • *Pre-first-dose BLQ: 188 records in Study 101, 87 records in Study 203* • *Post-dose BLQ: 7 records in Study 101, 1 record in Study 203*
Sampling Schedule	Rich Sampling	*Sampling time points are:* *Study 101 QW: Cycle 1 Day 1 (predose, 0, 2, 4, and 8 hours postdose), Day 3 (48 hours postdose), Day 5 (96 hours post dose), Day 8 and 15 (predose), and Day 22 (0 hours postdose). Cycle 2 Days 1 and 8 (predose) and Days 15 and 22 (0 hours postdose). Additional Cycles (predose and postdose), End of Treatment and End of Study.* *Study 101 Q2W: Cycle 1 Day 1 (predose, 0, 2, 4, 8 hours post dose), Day 3 (48 hours postdose), Day 5 (96 hours postdose), and Day 15 (predose and 0 hours postdose). Cycle 2 Days 1 and 15 (predose and 0 hours postdose). Additional Cycles (Day 1 of even cycles predose and 0 hours postdose), End of Treatment, and End of Study.* *Study 101 Q3W: Cycle 1 Day 1 (predose, 0, 2, 4, 8 hours postdose), Day 3 (48 hours postdose), and Day 5 (96 hours postdose). Cycles 2, 3, and 4 Day 1 (predose and 0 hours postdose). Additional Cycles (every 6 weeks predose and 0 hours postdose), End of Treatment, and End of Study.* *Study 101 Steady State: Cycle 4 Day 1 (predose, 0, 2, 4, 8 hours post dose), Day 7 (168 hours postdose), and Day 14 (336 hours postdose).* *Study 203: Cycle 1 Day 1 (predose, end of infusion, 2, 4, 8 hours postdose), Day 2 (24 hours postdose), Day 5 (96 hours postdose), and Day 15 (predose*

		and end of infusion). Cycle 2 Days 1 and 15 (predose and end of infusion). Additional Cycles (Day 1 predose and end of infusion) and End of Treatment. Study 203 Steady State Cycle 4 (or subsequent): Day 1 (predose, end of infusion, 2, 4, 8 hours postdose), Day 3 (48 hours postdose), Day 5 (96 hours postdose), and Day 15 (336 hours postdose).
	In ITT Population	*Not applicable*
Covariates Evaluated	Static	*Details of covariates evaluated in Section 6.3.2.3*
	Time-varying	*Not evaluated*

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	*NONMEM (Version 7, Level 3.0)* *SAS (Version 9.4)* *KIWI (Version 4 2022R1)* *R (Version 4.1.3)*	Acceptable
Model Structure	*Nonlinear mixed-effects modeling approach using a first-order conditional estimation with interaction method. The final PK model was a 2-compartment model with zero-order drug input (using actual IV infusion duration times) and with parallel linear and nonlinear CL pathways to describe elimination kinetics.*	Acceptable
Model Parameter Estimates	*Predicted CL, V_c, V_p, K_m, and V_{max} appear in Section 6.2.1 and Table 40.*	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*All fixed effect parameters (representing PK parameters and covariate effects) and random effect parameters (describing IIV and RV) were estimated with ≤ 39.4 %RSE and ≤ 28.7 %RSE, respectively. The magnitudes of estimated IIV in CL and V_c were relatively modest (27.9 %CV and 21.9 %CV, respectively); the magnitude of estimated IIV was larger for V_p (66.1 %CV). Bayesian shrinkage in the estimates of the IIV for CL, V_c, and V_p was 8.8%, 10.0%, and 22.0% respectively. Residual variability was estimated to be 21.1 %CV, with low Bayesian shrinkage (7.97%) in the estimate of the RV term. The final model condition number was 34.4.*	Acceptable
BLQ for Parameter Accuracy	*Eight postdose PK records were BLQ (0.215%). The BLQ samples were excluded from the analyses, according to M1 method, ie, when BLQ samples represented <5% of the total samples in the dataset, and if the occurrence of BLQ samples did not appear to be treatment-group dependent.*	Acceptable
GOF, VPC	*Final model GOF: Figure 4* *Final model VPC: Figure 7*	Acceptable
Significant Covariates and Clinical Relevance	*The final PopPK model covariates appear in Section 6.2.2.2. The influences of body weight, ALB, and number of lesions are not likely to have a clinically relevant impact on zanidatamab AUC_{ss}, $C_{avg,ss}$, and $C_{max,ss}$ exposures, as the GMR values for all covariate groups were maintained within the bounds of 0.8 to 1.25, with only the 90% CI overlapping these bounds for certain covariate subgroups (Figure 5). Gastroesophageal adenocarcinoma was the only cancer type that exhibited considerably lower zanidatamab exposures relative to BTC.*	Acceptable

Analysis Based on Simulation (optional)	*Model-based simulations suggest the target-mediated elimination pathway was likely saturated at the dose level of 20 mg/kg Q2W, since it was comparable to that of the higher dose of 30 mg/kg Q2W (Figure 6).*	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	(b) (4)	The applicant's proposed original drug labeling has undergone extensive revisions. Following recommendations from the Office of Clinical Pharmacology labeling team, only essential steady-state PK parameters have been retained in the labeling. This ensures that section 12 provides clinically relevant PK information essential for the safe and effective use of the drug, specifically aimed at healthcare professionals who may not have extensive clinical pharmacology expertise.

Abbreviations: %CV = coefficient of variation expressed as a percent; %RSE = relative standard error expressed as a percent; ALB = albumin; AST = aspartate aminotransferase; AUC_{ss} = area under the concentration-time curve within a dosing interval at steady state; $AUC_{0-\infty}$ = area under the concentration-time curve between zero and infinity; BLQ = below the limit of quantification; BTC = biliary tract cancer; $C_{avg,ss}$ = average concentration at steady state; CKD-EPI = chronic kidney disease epidemiology collaboration; CI = confidence interval; CL = clearance; C_{max} = maximum concentration; $C_{max,ss}$ = maximum concentration at steady state; $C_{trough,ss}$ = trough concentration at steady state; eGFR = estimated glomerular filtration rate; ER = exposure-response; ECD = extracellular domain; FDA = Food and Drug Administration; GMR = geometric mean ratio; GOF = goodness of fit; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IIV = interindividual variability; ITT = intent-to-treat; IV = intravenous; K_m = amount of drug at 50% of maximum nonlinear elimination; NCI = National Cancer Institute; NONMEM = nonlinear mixed-effects modeling; PK = pharmacokinetic; PopPK = population pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; QW = every week; RV = relative variability; TBIL = total bilirubin; ULN = upper limit of normal; V_c = central volume of distribution; V_p = peripheral volume of distribution; V_{max} = maximum velocity.

Table 38: Summary Statistics of Continuous Demographic Characteristics and Laboratory Values, Overall and Stratified by Study, for the PK Analysis Population

Variable	Statistic	Study ZWI-ZW25-101 (N = 192)	Study ZWI-ZW25-203 (N = 87)	Overall (N = 279)
Age (y)	Mean (StD)	59.2 (11.8)	62.7 (9.48)	60.3 (11.2)
	Median	60	64	62
	Min, Max	24, 88	32, 79	24, 88
Serum Albumin (g/dL)	Mean (StD)	3.74 (0.51)	3.86 (0.539)	3.78 (0.521)
	Median	3.75	3.9	3.8
	Min, Max	1.9, 5	2.6, 5.09	1.9, 5.09
Alanine Aminotransferase (U/L)	Mean (StD)	28.3 (19.9)	29.5 (26.9)	28.7 (22.3)
	Median	24	22	24
	Min, Max	6, 153	5, 165	5, 165
Aspartate Aminotransferase (U/L)	Mean (StD)	41 (28.4)	39.3 (26.2)	40.5 (27.7)
	Median	31	33	32
	Min, Max	9, 178	11, 145	9, 178
Body Surface Area (m^2)	Mean (StD)	1.77 (0.236)	1.73 (0.222)	1.76 (0.232)
	Median	1.8	1.7	1.8
	Min, Max	1.2, 2.4	1.3, 2.3	1.2, 2.4
eGFR (mL/min/1.73 m^2)	Mean (StD)	90.6 (27.2)	89.5 (27.1)	90.2 (27.1)
	Median	90.2	85.5	88
	Min, Max	33, 190	32.2, 202	32.2, 202
sHER2 ECD Concentration (ng/mL)	Mean (StD)	104 (248)	76.7 (291)	95.7 (262)
	Median	29	11.9	21
	Min, Max	3.6, 2120	5, 1920	3.6, 2120
	N	182	83	265
	Missing	10	4	14
Number of Lesions	Mean (StD)	5.17 (2.73)	4.95 (2.41)	5.1 (2.63)
	Median	5	4	5
	Min, Max	1, 20	1, 13	1, 20
Bilirubin, Total (mg/dL)	Mean (StD)	0.621 (0.328)	0.714 (0.372)	0.65 (0.344)
	Median	0.5	0.6	0.6
	Min, Max	0.1, 2	0.2, 1.8	0.1, 2
Tumor Size (mm)	Mean (StD)	82.8 (54)	77.8 (45.5)	81.2 (51.5)
	Median	69.5	68	69
	Min, Max	12, 312	13, 183	12, 312
Weight (kg)	Mean (StD)	69.8 (17.3)	66.9 (15.7)	68.9 (16.8)
	Median	68.8	65.3	68.5
	Min, Max	35.4, 128	39.5, 113	35.4, 128

Abbreviations: ECD = extracellular domain; eGFR = estimated glomerular filtration rate; sHER2 = soluble human epidermal growth factor receptor 2; Max = maximum; Min = minimum; N = number of patients; PK = pharmacokinetic(s); StD = standard deviation.
Source: PPK Report Table 9.

Table 39: Summary Statistics of Categorical Demographic Characteristics and Laboratory Values, Overall and Stratified by Study, for the PK Analysis Population

Variable		Study ZWI-ZW25-101 (N = 192)	Study ZWI-ZW25-203 (N = 87)	Overall (N = 279)
Cohort, N (%)	Part 1, Cohort 1 (5 mg/kg QW)	3 (1.56)	0 (0)	3 (1.08)
	Part 1, Cohort 2 (10 mg/kg QW)	6 (3.12)	0 (0)	6 (2.15)
	Part 1, Cohort 3 (15 mg/kg QW)	7 (3.65)	0 (0)	7 (2.51)
	Part 1, Cohort 4 (20 mg/kg Q2W)	7 (3.65)	0 (0)	7 (2.51)
	Part 1, Cohort 5 (25 mg/kg Q2W)	6 (3.12)	0 (0)	6 (2.15)
	Part 1, Cohort 6 (30 mg/kg Q2W)	6 (3.12)	0 (0)	6 (2.15)
	Part 1, Cohort 7 (30 mg/kg Q3W)	11 (5.73)	0 (0)	11 (3.94)
	Part 2, Cohort 1 (20 mg/kg Q2W)	3 (1.56)	0 (0)	3 (1.08)
	Part 2, Cohort 2 (various regimens)	28 (14.6)	0 (0)	28 (10)
	Part 2, Cohort 3 (20 mg/kg Q2W)	1 (0.521)	0 (0)	1 (0.358)
	Part 2, Cohort 4 (various regimens)	28 (14.6)	0 (0)	28 (10)
	Part 2, Cohort 5a (various regimens)	61 (31.8)	0 (0)	61 (21.9)
	Part 2, Cohort 5b (20 mg/kg Q2W)	25 (13)	0 (0)	25 (8.96)
	Cohort 1 (20 mg/kg Q2W)	0 (0)	80 (92)	80 (28.7)
	Cohort 2 (20 mg/kg Q2W)	0 (0)	7 (8.05)	7 (2.51)
Dose Regimen, N (%)	QW	23 (12)	0 (0)	23 (8.24)
	Q2W	158 (82.3)	87 (100)	245 (87.8)
	Q3W	11 (5.73)	0 (0)	11 (3.94)
Cancer Type, N (%)	Breast	53 (27.6)	0 (0)	53 (19)
	Gastroesophageal	50 (26)	0 (0)	50 (17.9)
	Ovarian	2 (1.04)	0 (0)	2 (0.717)
	Colorectal	29 (15.1)	0 (0)	29 (10.4)
	Non-small cell lung	5 (2.6)	0 (0)	5 (1.79)
	Biliary tract	22 (11.5)	87 (100)	109 (39.1)
	Other	31 (16.1)	0 (0)	31 (11.1)
HER2 Expression, N (%)	0	2 (1.04)	4 (4.6)	6 (2.15)
	1+	12 (6.25)	3 (3.45)	15 (5.38)
	2+	44 (22.9)	18 (20.7)	62 (22.2)
	3+	132 (68.8)	62 (71.3)	194 (69.5)
	Missing	2 (1.04)	0 (0)	2 (0.717)
NCI Liver Function Group, N (%)	Normal	125 (65.1)	47 (54)	172 (61.6)
	Mild impairment (Group A)	57 (29.7)	30 (34.5)	87 (31.2)
	Mild impairment (Group B)	8 (4.17)	9 (10.3)	17 (6.09)
	Moderate impairment	2 (1.04)	1 (1.15)	3 (1.08)

Variable		Study ZWI-ZW25-101 (N = 192)	Study ZWI-ZW25-203 (N = 87)	Overall (N = 279)
Number of Lesions, N (%)	1	7 (3.65)	1 (1.15)	8 (2.87)
	2	18 (9.38)	7 (8.05)	25 (8.96)
	3	33 (17.2)	21 (24.1)	54 (19.4)
	4	28 (14.6)	18 (20.7)	46 (16.5)
	5	34 (17.7)	9 (10.3)	43 (15.4)
	6	23 (12)	12 (13.8)	35 (12.5)
	7	18 (9.38)	6 (6.9)	24 (8.6)
	8	9 (4.69)	5 (5.75)	14 (5.02)
	9	9 (4.69)	4 (4.6)	13 (4.66)
	10	8 (4.17)	1 (1.15)	9 (3.23)
	11	1 (0.521)	1 (1.15)	2 (0.717)
	12	1 (0.521)	1 (1.15)	2 (0.717)
	13	1 (0.521)	1 (1.15)	2 (0.717)
	15	1 (0.521)	0 (0)	1 (0.358)
	20	1 (0.521)	0 (0)	1 (0.358)
Race, N (%)	White	106 (55.2)	25 (28.7)	131 (47)
	Black/African American	7 (3.65)	0 (0)	7 (2.51)
	Asian	67 (34.9)	57 (65.5)	124 (44.4)
	Native Hawaiian/Pacific Islander	2 (1.04)	0 (0)	2 (0.717)
	Multiple/other	4 (2.08)	1 (1.15)	5 (1.79)
	Unknown	6 (3.12)	4 (4.6)	10 (3.58)
Renal Function Category, N (%)	Normal	100 (52.1)	38 (43.7)	138 (49.5)
	Mild renal impairment	75 (39.1)	39 (44.8)	114 (40.9)
	Moderate renal impairment	17 (8.85)	10 (11.5)	27 (9.68)
Sex, N (%)	Male	89 (46.4)	40 (46)	129 (46.2)
	Female	103 (53.6)	47 (54)	150 (53.8)

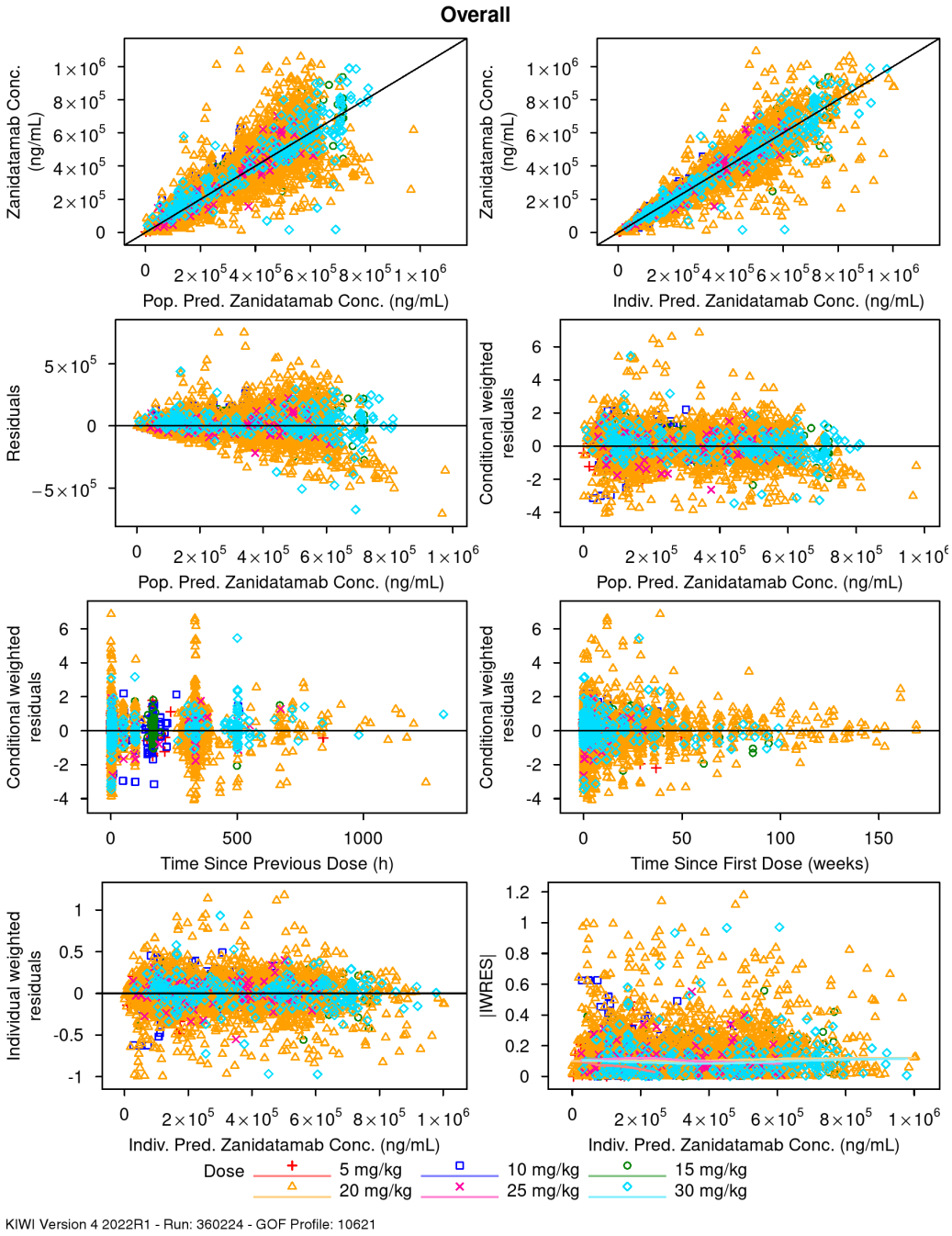
Abbreviations: HER2 = human epidermal growth factor receptor 2; N = number of patients; NCI = National Cancer Institute; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q3W = every 3 weeks; QW = every week.
Source: PPK Report Table 10.

Table 40: Parameter Estimates and Standard Errors for the Final Population PK Model of Zanidatamab

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL	Clearance (L/h)	0.0115	3.73	27.9 %CV	12.4
	Exponent of (WTKG/68.5) for CL	0.694	12.0		
	Exponent of (ALB/3.8) for CL	-0.883	18.1		
	Exponent of (NLESIONS/5) for CL	0.154	26.2		
	Additive Shift in CL for Breast Cancer	0.00140	39.4		
	Additive Shift in CL for GEA	0.00284	24.8		
	Additive Shift in CL for "Other" Cancer Types	0.00241	27.0		
V_c	Central Volume of Distribution (L)	3.51	2.02	21.9 %CV	13.8
	Exponent of (WTKG/68.5) for V_c	0.605	10.2		
	Additive Shift in V_c for GEA	1.15	16.3		
	Additive Shift in V_c for Colorectal Cancer	0.836	23.8		
	Additive Shift in V_c for "Other" Cancer Types	0.598	23.7		
Q	Intercompartmental Clearance (L/h)	0.0307	11.3	NE	NA
V_p	Peripheral Volume of Distribution (L)	3.95	6.67	66.1 %CV	15.9
	Additive Shift in V_p for Breast Cancer	-1.58	23.0		
	Additive Shift in V_p for "Other" Cancer Types	-1.21	31.6		
K_m	Amount of Drug at 50% of Maximum Nonlinear Elimination (µg/mL)	8.92	FIXED	NE	NA
V_{max}	Maximum Rate of Nonlinear Elimination (µg/mL/day)	4.37	9.83	NE	NA
cov(IIV in V_c, IIV in CL)		0.0180[a]	28.7	NA	NA
Proportional Residual Variability		0.0446	7.57	21.1 %CV	NA
Minimum Value of the Objective Function = 85755.007					

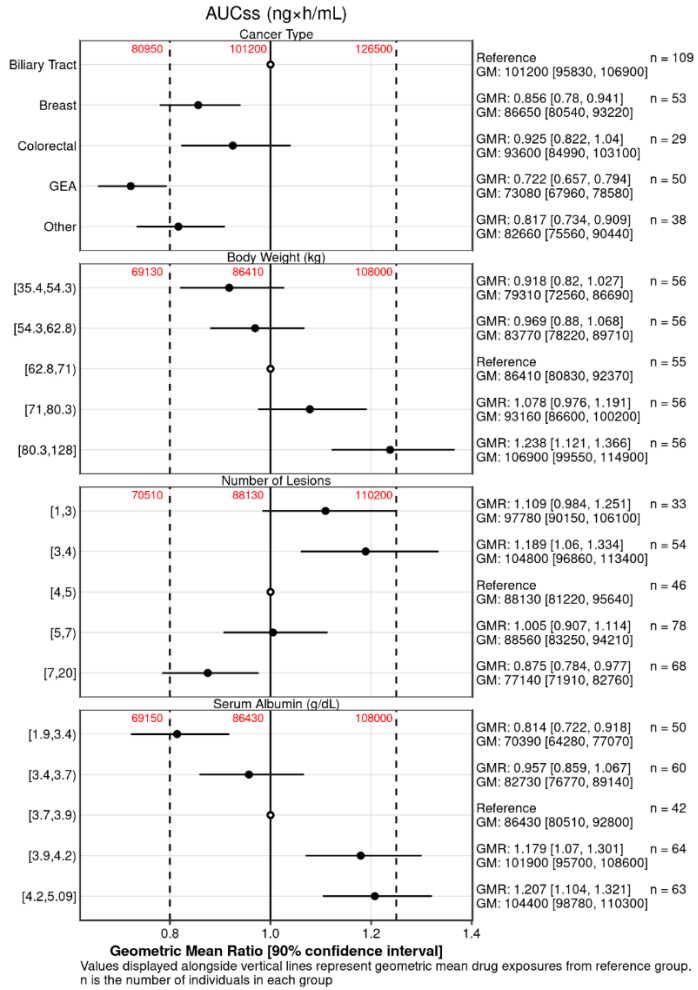
Abbreviations: %CV = coefficient of variation expressed as a percent; %RSE = relative standard error expressed as a percent; ALB = albumin; CL = clearance; GEA = gastroesophageal adenocarcinoma; IIV = interindividual variability; K_m = amount of drug at 50% of maximum nonlinear elimination; NA = not applicable; NE = not estimated; NLESIONS = number of lesions; PK = pharmacokinetic(s); V_c = central volume of distribution; V_p = peripheral volume of distribution; WTKG = body weight in kg.
[a] The calculated correlation coefficient (r) associated with cov (IIV in V_c, IIV in CL) was 0.304 with $r^2 = 0.0924$.
Shrinkage estimates: 8.8% for IIV in CL, 10.0% for IIV in V_c, and 22.0% for IIV in V_p.
Source: PopPK Report Table 16.

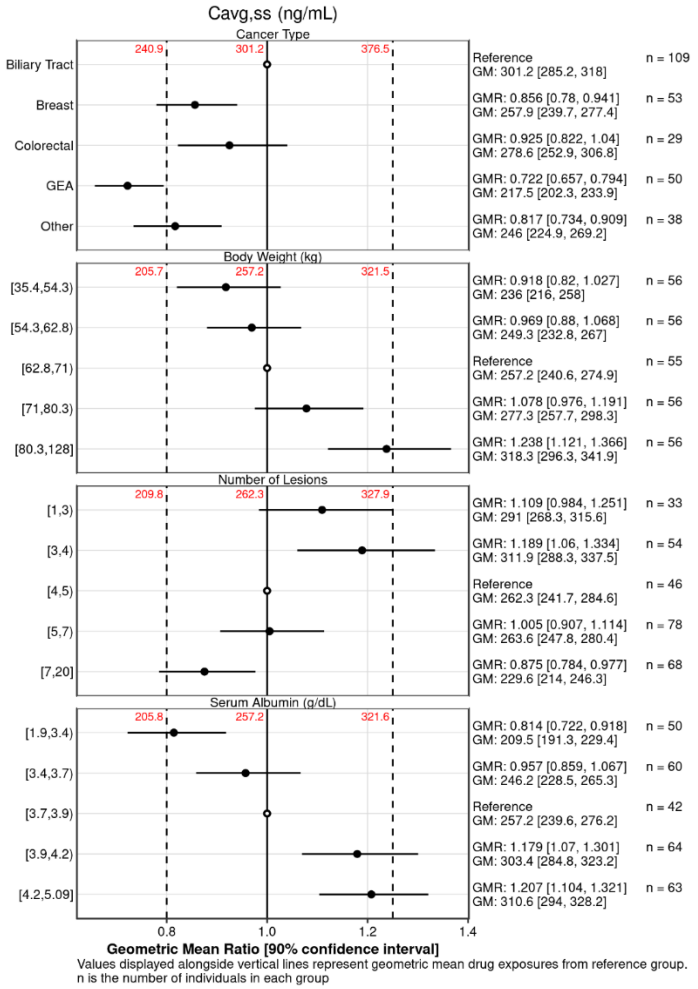
Figure 6: Goodness-of-Fit Plots for the Final PK Model of Zanidatamab for the Overall Analysis Population, Stratified by Dose

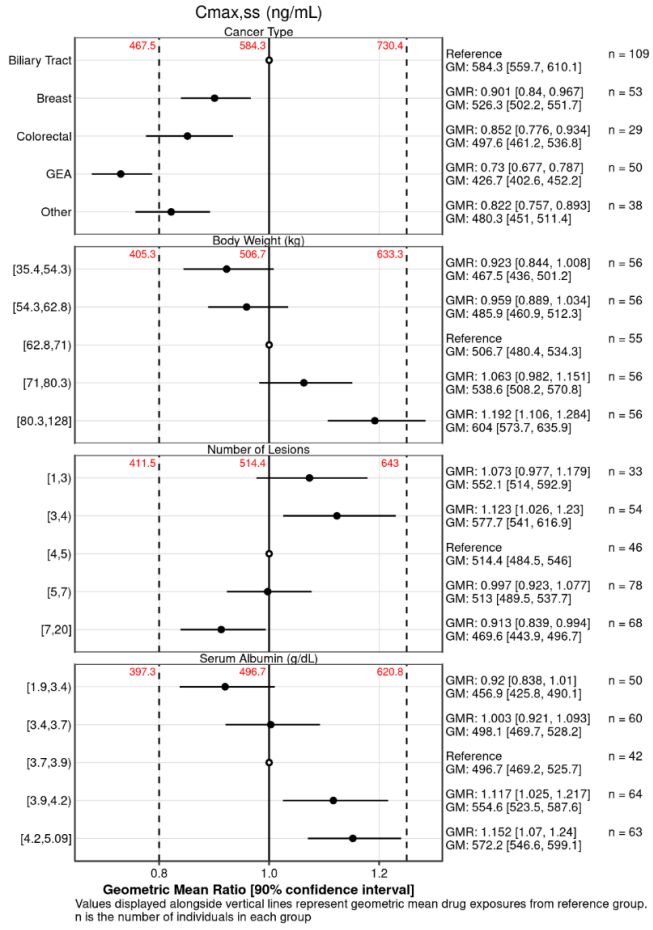


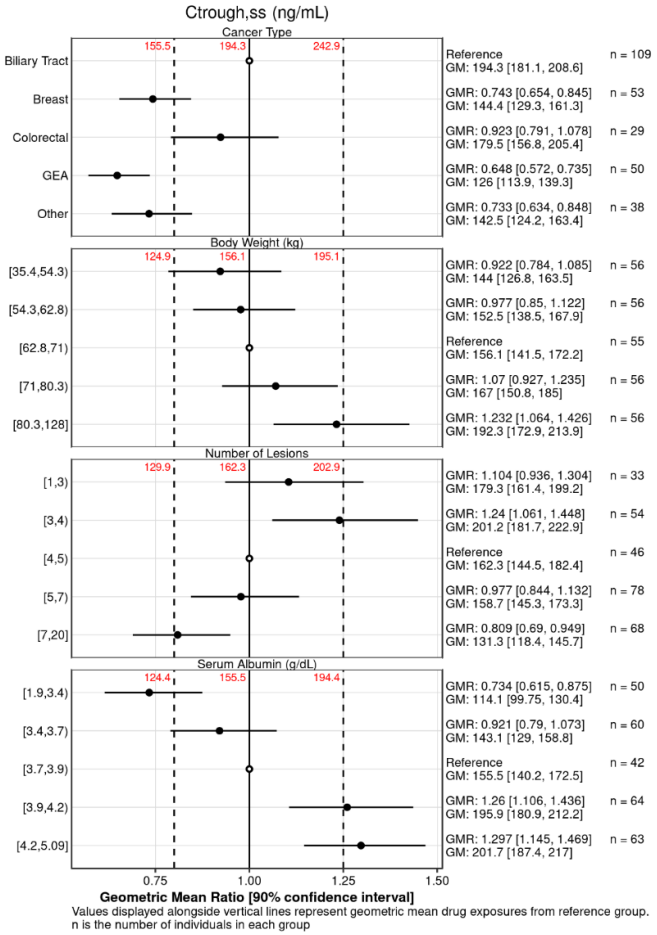
Abbreviations: Conc. = concentration; Indiv. = individual; |IWRES| = absolute value of the individual weighted residuals; PK = pharmacokinetic(s); Pop. = population; Pred. = predicted.
Source: PopPK Report Figure 25.

Figure 7: Forest Plots of GMR (90% CI) of Estimated Covariate Effects on Steady-State Zanidatamab Exposures Following Hypothetical 20 mg/kg Q2W Dosing



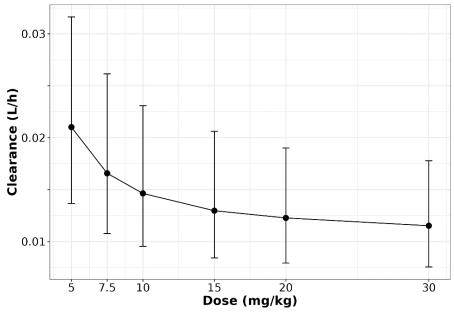






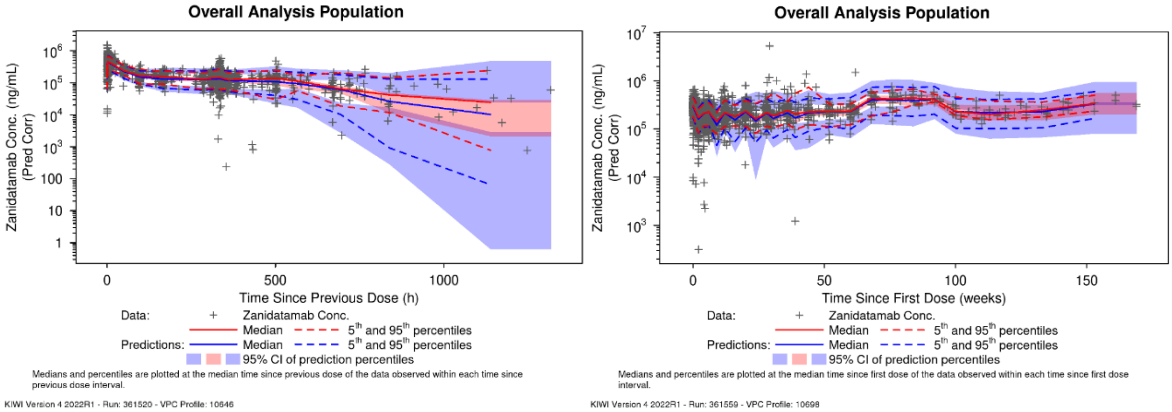
Abbreviations: AUC_{ss} = area under the concentration-time curve within a dosing interval at steady state; $C_{avg,ss}$ = average concentration at steady state; CI = confidence interval; $C_{max,ss}$ = maximum concentration at steady state; $C_{trough,ss}$ = trough concentration at steady state; GEA = gastroesophageal adenocarcinoma; GM = geometric mean; GMR = geometric mean ratio; Q2W = every 2 weeks.
Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.
Source: PopPK Report Figure 46.

Figure 8: Predicted Steady-State Zanidatamab Clearance versus Dose Following Different Zanidatamab Q2W Dose Regimens



Abbreviations: $AUC_{0\text{-}14days,ss}$ = area under the concentration time curve from zero to 14 days (steady state); Q2W = every 2 weeks.
Black circles and error bars represent the median, 10th to 90th percentiles steady-state clearance of 1000 simulated patients with biliary tract cancer administered 25 doses of 5, 7.5 10, 15, 20, and 30 mg/kg once every 2 weeks. Steady-state clearance was calculated as dose (mg) divided by the $AUC_{0\text{-}14days,ss}$ (µg·h/mL) at steady state.
Source: Clearance vs Dose Report Figure 1.

Figure 9: Prediction-Corrected Visual Predictive Check of the Final PK Model, Overall Analysis Population



Abbreviations: CI = confidence interval; Conc. = concentration; PK = pharmacokinetic(s); Pred Corr = prediction corrected.
Source: PopPK Report Figure 21.

The FDA's Assessment:

PopPK Analysis

A total of 3711 zanidatamab serum concentrations obtained from 279 patients (192 from Study ZWI-ZW25-101 and 87 from Study ZWI-ZW25-203) were used for the development of the PopPK model.

The analysis population was predominantly White (47%) or Asian (44%), comprised of 150 females and 129 males, with an overall median (range) body weight of 68 kg (35 to 128 kg) and a median (range) age of 62 years (24 to 88 years). Biliary tract cancer was the most prevalent

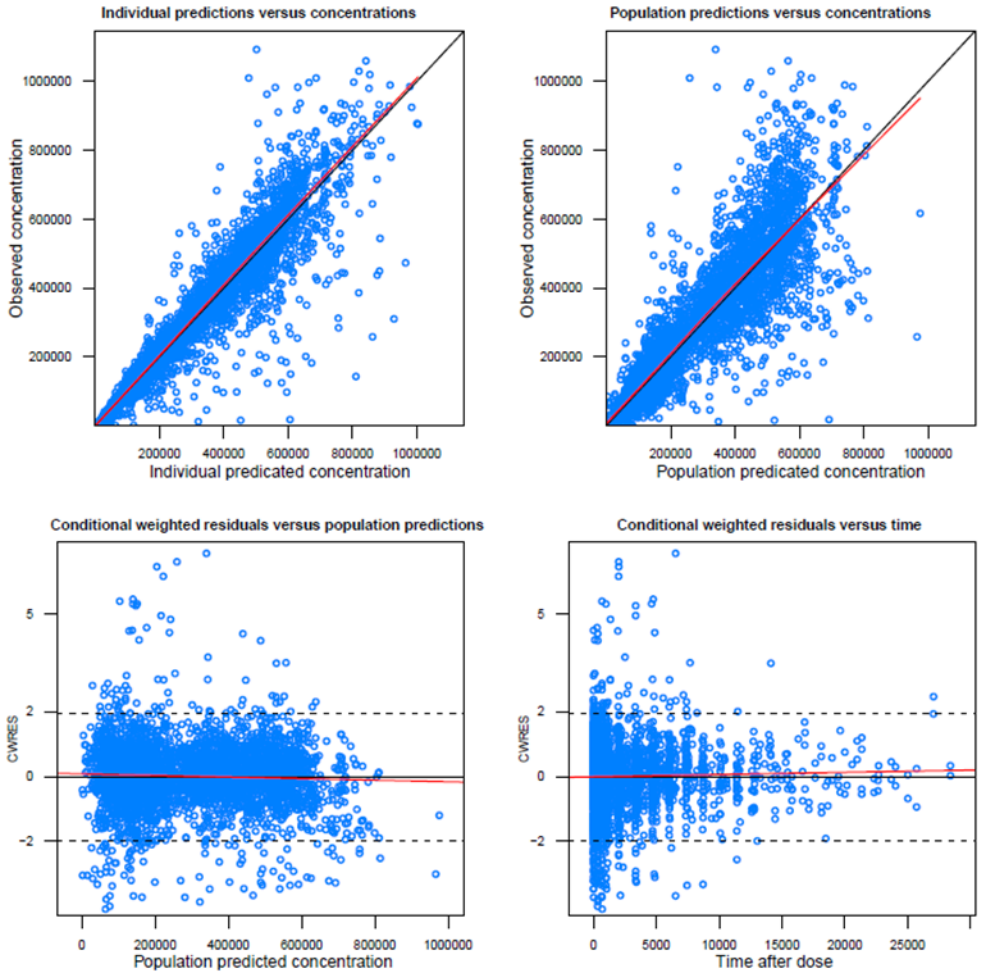
cancer type (39%), with breast cancer, GEA, and CRC comprising 19%, 18%, and 10% of the analysis population, respectively. The remainder of the cancer types included non-small cell lung (1.8%), ovarian (0.7%), and other cancer types (11%) (**Table 38, Table 39**).

The final PK model was a 2-compartment model with zero-order drug input (using observed IV infusion duration times) and with parallel linear and nonlinear clearance (CL) to describe elimination kinetics. The model was parameterized in terms of the duration of the zero-order infusion, linear CL, maximum rate of nonlinear elimination (Vmax), amount of drug at 50% of maximum nonlinear elimination (Km), central volume of distribution (Vc), peripheral volume of distribution (Vp), and intercompartmental clearance (Q). Interindividual variability was estimated for CL, Vc, and Vp, and was described using exponential error models. Residual variability was estimated using a proportional error model.

The parameter estimates of the final zanidatamab PopPK model are summarized in **Table 41**. Goodness-of-fit plots show that the final PK model provides reasonably accurate predictions of the zanidatamab PK data throughout the dose range and dose regimens studied (**Figure 10**).

Based on the population PK analysis, patients with BTC were predicted to have an estimated elimination half-life (t½) of approximately 21 days with an associated typical linear CL of 0.01 L/h, typical Vc of 3.5 L, typical Vp of 3.9 L. The model estimates and model diagnostics are consistent with applicant's results.

Figure 10: Goodness-of-Fit Plots for the Final PK Model of Zanidatamab



Source: Reviewer's Analysis

Table 41: PopPK Final Model Parameter Estimation

Parameter	Estimate	RSE %
Clearance (CL, L/h)	0.0115	3.7
Exponent of (WTKG/68.5) for CL	0.694	12.0
Exponent of (ALB/3.8) for CL	-0.883	18.1
Exponent of (NLESIONS/5) for CL	0.154	26.2
Additive Shift in CL for Breast Cancer	0.00140	39.4
Additive Shift in CL for GEA	0.00284	24.8
Additive Shift in CL for "Other" Cancer	0.00241	27.0
Central Volume of Distribution (Vc, L)	3.51	2.0
Exponent of (WTKG/68.5) for Vc	0.605	10.1

Additive Shift in Vc for GEA	1.15	16.2
Additive Shift in Vc for Colorectal Cancer	0.836	23.9
Additive Shift in Vc for "Other" Cancer	0.597	22.9
Intercompartmental Clearance (Q, L/h)	0.0307	8.7
Peripheral Volume of Distribution (Vp, L)	3.95	6.5
Additive Shift in Vp for Breast Cancer	-1.58	22.0
Additive Shift in Vp for "Other" Cancer	-1.21	29.2
Amount of Drug at 50% of Maximum Nonlinear Elimination (Km, μg/mL)	8.92 (FIXED)	
Maximum Rate of Nonlinear Elimination (Vmax, μg/mL/day)	4.37	9.6
IIV CL	27.9	
IIV Vc	21.9	
IIV Vp	66.1	
Residual variability (prop)	21.1	

Source: Reviewer's Analysis

The zanidatamab PopPK model incorporates a 2-compartmental structure with parallel linear and nonlinear (Michaelis-Menten) elimination pathways. This model was developed utilizing pooled data from Study ZWI-ZW25-101 and Study ZWI-ZW25-203.

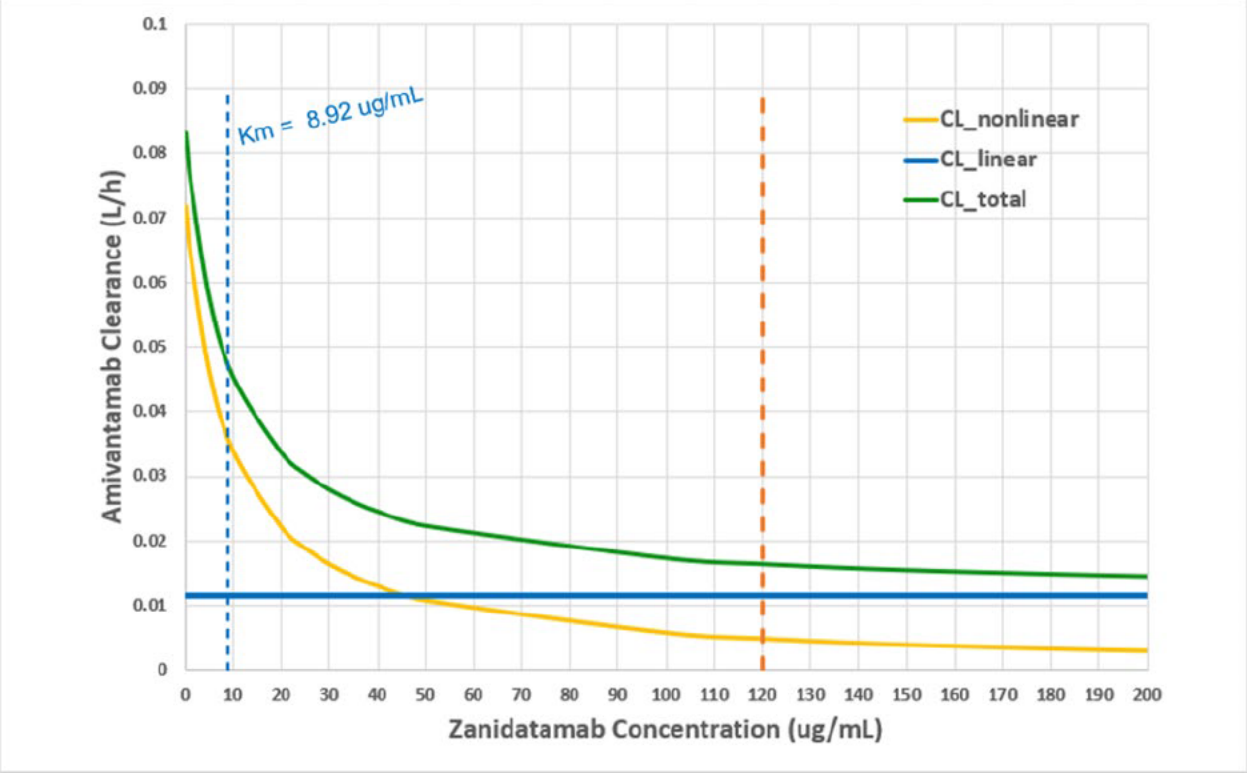
The typical parameter values for zanidatamab linear clearance (CL_linear), non-linear clearance (CL_nonlinear) and total clearance (CL_total) were plotted against the observed range of zanidatamab plasma concentrations following zanidatamab administration.

As shown in **Figure 11**, starting from approximately 120 μg/mL, linear clearance becomes the dominant elimination pathway, accounting for ≥ 70% after the first dose (Cavg = 128 ug/mL). At steady state (Cavg = 254 μg/mL), linear clearance contributes to ≥83% of the total clearance. **Table 42** provides a detailed breakdown of the nonlinear clearance contribution across the observed range of zanidatamab plasma concentrations.

In addition, simulations based on the final zanidatamab PopPK model were conducted to investigate the relationship between the predicted steady-state clearance and various dosing regimens, ranging from 5 to 30 mg/kg Q2W in adult patients with BTC. The simulation results (**Figure 6**) indicate that as dose increases, the contribution of nonlinear (Michaelis-Menten) clearance decreases. Consequently, at steady state, the TMDD process is close to saturation and total drug clearance is expected to decline and approach linear clearance at the proposed 20 mg/kg Q2W dose level.

These findings indicate that under the proposed dosing regimen, once zanidatamab systemic exposure reaches steady state, the pharmacokinetics are approximately linear, demonstrating dose proportionality.

Figure 11: Visualization of Typical Zanidatamab Clearance versus the Range of Zanidatamab Plasma Concentrations



Source: Reviewer's Analysis

Table 42: Percentage of Nonlinearity versus the Range of Zanidatamab Plasma Concentrations after Zanidatamab Administration.

Zanidatamab Concentration (ug/mL)	Percentage of Nonlinearity
0	86.2
5	80.0
10	74.6
15	69.9
20	65.8
25	62.1
30	58.8
35	55.9

Zanidatamab Concentration (ug/mL)	Percentage of Nonlinearity
40	53.2
50	48.5
100	33.8
120	30.1
150	25.9
200	21.0
250	17.7
300	15.2
400	12.0
500	9.8
600	8.4
700	7.3
800	6.4
900	5.8

Source: Reviewer's Analysis

Reviewer's comments:

The PK of zanidatamab, administered at the dosing regimens of 5 to 30 mg/kg Q2W, were reasonably well described using a 2-compartment PopPK model with zero-order drug input (based on observed IV infusion durations) and parallel linear and nonlinear clearance (CL) pathways to describe elimination kinetics.

With the proposed body weight-based dosing regimen at 20 mg/kg Q2W, the significant covariates identified, namely, baseline body weight, albumin (ALB), baseline number of lesions, and cancer type as significant predictors of CL, as well as body weight and cancer type as significant predictors of Vc and cancer type as predictor of Vp, are unlikely to lead to clinically relevant differences in steady state zanidatamab exposures. Therefore, no dosage adjustments were recommended for the intrinsic and extrinsic covariates evaluated.

Zanidatamab, a bispecific antibody, exhibits complex, time- and concentration-dependent PK, which may be associated with target-mediated drug disposition (TMDD). A Michaelis-Menten approximation was incorporated into the PopPK model, with parameters for the maximal rate of nonlinear elimination (Vmax) and the concentration at which half-maximal nonlinear elimination occurs (Km).

Simulation findings suggest that under the proposed 20 mg/kg Q2W dosing regimen, once zanidatamab reaches steady-state systemic exposure, the TMDD process is close to saturation and its pharmacokinetics become approximately linear, demonstrating dose proportionality.

19.4.3. Exposure-Response Analysis

19.4.3.1. Exposure-Response (ER) Executive Summary

The FDA's Assessment:

In this submission, the exposure-response (E-R) relationships for both efficacy and safety endpoints of zanidatamab were evaluated using data from Study 203 (efficacy and safety) and Study 101 (safety). Predicted zanidatamab pharmacokinetic (PK) exposures, along with efficacy and safety data, were explored using logistic regression models and survival models.

The E-R relationship for efficacy was assessed for confirmed OR and PFS from Study 203 (N = 87) in participants with HER2-amplified BTC.

The analysis showed a trend indicating that the probability of confirmed OR as assessed by independent central review (ICR), increased with higher zanidatamab exposures (steady-state Cavg or Cycle 1 Cmin), but approached a plateau at the second quartile and beyond. However, this positive exposure-efficacy trend should be interpreted with caution due to 1). the relatively lower percentage of participants with IHC 3+ in the first quartile may potentially confounding the E-R assessment, and 2). the analysis was conducted using only one dosing regimen with limited total participants. In addition, the exposure-efficacy relationship of zanidatamab for PFS investigation results are inconclusive due to inconsistencies across exposure quartiles based on daily Cavg.

The E-R relationship for safety was assessed for AEs including diarrhea, Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, IRRs, Grade ≥ 3 IRRs, and SAEs using data from 279 participants: Study 101 (N = 192) involving participants with HER2-expressing cancers, and Study 203 (N = 87) in participants with HER2-amplified BTC.

No statistically significant E-R relationship was identified for any of the safety endpoints examined (including Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, or IRR), except for the probability of diarrhea, where higher zanidatamab exposure was associated with an increased probability of diarrhea. Despite the apparent E-R relationship for the occurrence of diarrhea, there is no statistically significant E-R relationship for Grade ≥ 3 diarrhea.

Extrapolating the observed E-R relationships for efficacy and safety to untested dosing regimens is unwarranted due to the narrow exposure range from the single dose level included in the analysis and the potential confounding effects of time-dependent clearance.

19.4.3.2. ER (Efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		*Characterize the relationship between zanidatamab exposure and efficacy endpoints (cOR and PFS) in patients with HER2-expressing BTC*
Study Included		*ZWI-ZW25-203*
Endpoint		*Primary: cOR by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) assessed by ICR* *Secondary: PFS, by RECIST 1.1 assessed by ICR.*
No. of Patients (total, and with individual PK)		*A total of 87 participants (Study 203) were included in the efficacy dataset for these analyses.*
Population Characteristics	General	• *Age, weight, sex, and race info appears in Table 43*
	Pediatrics (if any)	*Not applicable*
Dose(s) Included		*20 mg/kg Q2W*
Exposure Metrics Explored (range)		*Based on the final PopPK model and individual empiric Bayesian PK parameter estimates, NONMEM was used to generate predicted zanidatamab exposures. The ER-OR analyses Cycle 1 C_{min} range was 2.29 to 263.75 µg/mL.*
Covariates Evaluated		*Age, baseline weight, baseline lactate dehydrogenase, sex, race, number of lesions, baseline tumor size, HER2 expression (as determined by IHC or FISH), and ECOG performance status.*

Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*The final model for the probability of confirmed OR was a logistic regression model on the logit scale including an intercept and a power function of Cycle 1 C_{min}.* *The final model for PFS was a Cox proportional hazard model including the effect of daily C_{avg} and the covariate effect of HER2 status (3+ versus 2+/1+/0).*	Acceptable
Model Parameter Estimates	*The final model parameters estimates for the probability of confirmed OR appear in Table 45: the intercept was -0.365 (54.8 %RSE); the exponent for Cycle 1 C_{min} was -1.66 (41.2 %RSE).* *The final model parameter estimates for PFS appear in Table 46: the coefficient for daily C_{avg} was -0.007794 (16.5 %RSE), and the coefficient for HER2 expression effect was -1.172 (23.6 %RSE).*	Acceptable
Model Evaluation	*Agreement between the observed and predicted proportion of OR across the range of exposure indicates no apparent bias in the overall model fit. All KM curves are within the 90% prediction intervals except there was an overprediction bias for the third quartile and HER2 status 2+/1+/0.*	Acceptable
Covariates and Clinical Relevance	*No tested covariates met the criteria (or model convergence) for inclusion in the ER model for OR.* *The final ER-PFS model was a Cox proportional hazards model that included the effect of zanidatamab daily C_{avg} and the covariate effect of HER2 status (3+ versus 2+/1+/0). Based on the available limited data, there may be an association between PFS and exposure (based on daily C_{avg}); however, due to inconsistencies*	Acceptable

	across exposure quartiles no definitive conclusion can be drawn. The ER results should be interpreted with caution especially since IHC status is identified as a covariate in the ER-PFS analysis	
Simulation for Specific Population	*Simulations using the final PK model were performed to predict Cycle 1 zanidatamab C_{min} for 1000 simulated BTC patients each administered doses of 15 and 20 mg/kg Q2W. These predicted exposure measures were used to calculate the predicted probability of OR using the final ER efficacy model (Figure 12, Table 47). As Cycle 1 zanidatamab C_{min} increased, the model-predicted probability of experiencing OR increased and approached a plateau at the second quartile and beyond (at the trough concentration of 125 µg/mL or higher). The 20 mg/kg Q2W is predicted to achieve higher probability of OR than 15 mg/kg Q2W regimen. Following the administration of 20 mg/kg Q2W at steady state, 85.8% of patients would have trough levels associated with confirmed OR of 41%.*	Acceptable
Visualization of ER relationships	*ER-OR relationships: Figure 8 (boxplots; exposure range for responders and non-responders overlap) and Figure 9 (quartile plots).* *The ER-OR final model: Figure 10.* *Table 44 provides the baseline demographics stratified by the Cycle 1 C_{min} quartiles. The KM plot of PFS versus time, by quartiles of zanidatamab daily C_{avg}: Figure 11.*	Acceptable
Overall Clinical Relevance for ER	*The exposure-efficacy relationship analysis showed a trend toward approaching a plateau for the probability of cOR assessed by ICR (as the zanidatamab exposure [ie, steady-state C_{avg} or Cycle 1 C_{min}] increased, the probability of OR increased and approached a plateau at the second quartile and beyond), suggesting that higher exposure is not expected to result in higher OR. Importantly, the relatively lower percentage of participants with IHC 3+ in quartile 1 may have contributed to the apparent low ORR in this quartile and confounding the assessment of ER.* *The exposure-efficacy relationship of zanidatamab for PFS was analyzed in participants with HER2-amplified BTC in the efficacy population from Study 203 (N = 87). The results are inconclusive due to inconsistencies across exposure quartiles based on daily C_{avg}; the ER analysis on the limited data from a single arm study should be interpreted with caution.*	Acceptable

Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	*Cardiac Electrophysiology* (b) (4) [redacted]	The following modified version has been conveyed to the Sponsor: *A mean increase in the QTc interval > 20 ms was not observed at the recommended approved dosage.*

Abbreviations: %RSE = relative standard error expressed as a percent; BTC = biliary tract cancer; C_{avg} = average concentration; C_{min} = minimum concentration; cOR = confirmed objective response ECOG = Eastern Cooperative Oncology Group; E-R = exposure-response; FDA = Food and Drug Administration; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; KM = Kaplan-Meier; NONMEM = nonlinear mixed-effects modeling; OR = objective response; PFS = progression free survival; PK = pharmacokinetic(s); PopPK = population pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; QTc = QT interval corrected for heart rate; QW = every week; RECIST = Response Evaluation Criteria in Solid Tumors; VPC = visual predictive check.

Table 43: Summary Statistics of Demographic Characteristics for the ER Efficacy Analysis of Confirmed Objective Response

Patient Characteristic	Statistic	Study ZWI-ZW25-203 (n = 87)
Age (y)	Mean (StD)	62.7 (9.5)
	Median	64.0
	Min, Max	32, 79
Weight at Baseline (kg)	Mean (StD)	66.88 (15.72)
	Median	65.30
	Min, Max	39.5, 112.9
Baseline LDH (U/L)	Mean (StD)	358.8 (397.0)
	Median	219.4
	Min, Max	125, 2500
Baseline Sum of Diameters per ICR (mm)	Mean (StD)	77.12 (45.42)
	Median	68.00
	Min, Max	13.0, 183.0
Baseline Soluble HER2 (ng/mL)	Mean (StD)	73.79 (284.78)
	Median	12.00
	Min, Max	5.0, 1924.8
Maximum Percent Decrease in Soluble HER2 From Baseline (ng/mL)	Mean (StD)	-57.02 (21.38)
	Median	-57.14
	Min, Max	-99.7, 22.9
Week of First Confirmed Response per ICR	Mean (StD)	10.18 (5.08)
	Median	7.71
	Min, Max	7.1, 24.1
Sex, n (%)	Male	40 (46.0)
	Female	47 (54.0)
Race, n (%)	White	25 (28.7)
	Asian	57 (65.5)
	Other	5 (5.7)
Baseline Number of Lesions per ICR, n (%)	1	1 (1.1)

Patient Characteristic	Statistic	Study ZWI-ZW25-203 (n = 87)
	2	7 (8.0)
	3	21 (24.1)
	4	18 (20.7)
	5	10 (11.5)
	6	11 (12.6)
	7	6 (6.9)
	8	5 (5.7)
	9	4 (4.6)
	10	1 (1.1)
	11	1 (1.1)
	12	1 (1.1)
	13	1 (1.1)
ECOG at Baseline, n (%)	Normal (Grade 0)	23 (26.4)
	Symptoms/ambulatory (Grade 1)	64 (73.6)
IHC HER2 Expression Central Results, n (%)	0	4 (4.6)
	1+	3 (3.4)
	2+	18 (20.7)
	3+	62 (71.3)
Stage at Initial Diagnosis, n (%)	STAGE I	2 (2.3)
	STAGE II	11 (12.6)
	STAGE III	26 (29.9)
	STAGE IV	46 (52.9)
	Unknown	2 (2.3)
Diagnosis Group, n (%)	Biliary tract	87 (100.0)
Primary Diagnosis - Original, n (%)	Extrahepatic cholangiocarcinoma	16 (18.4)
	Gallbladder cancer	45 (51.7)
	Intrahepatic cholangiocarcinoma	26 (29.9)
Cohort, n (%)	Cohort 1	80 (92.0)
	Cohort 2	7 (8.0)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; n = number of patients; StD = standard deviation.
Source: ER Report Table 6.

Table 44: Summary of Demographic Characteristics for the ER Efficacy Analysis, by Quartiles of Zanidatamab Cycle 1 C_{min}

Patient Characteristic	Statistic	Zanidatamab Cycle 1 C_{min}				
		[2.3, 92.2)	[92.2, 122.3)	[122.3, 150.3)	[150.3, 263.8]	Overall
Age	Mean (StD)	62.7 (10.7)	63.3 (7.3)	60.3 (10.8)	64.5 (8.8)	62.7 (9.5)
	Median	62.0	65.0	62.0	67.5	64.0
	Min, Max	32, 79	47, 73	42, 79	38, 74	32, 79
	n	21	22	22	22	87
Baseline LDH (U/L)	Mean (StD)	597.8 (668.6)	223.5 (77.9)	320.0 (226.3)	304.6 (285.4)	358.8 (397.0)
	Median	262.0	209.5	218.5	215.0	219.4
	Min, Max	157, 2500	125, 493	133, 1109	147, 1526	125, 2500
	n	21	22	22	22	87
Baseline Soluble HER2 (ng/mL)	Mean (StD)	148.39 (422.60)	16.48 (14.26)	35.80 (67.80)	97.87 (382.24)	73.79 (284.78)
	Median	15.00	11.20	13.43	12.45	12.00
	Min, Max	5.8, 1924.8	5.0, 54.3	7.7, 299.4	6.3, 1808.7	5.0, 1924.8
	n	21	22	22	22	87
Baseline Sum of Diameters ICR (mm)	Mean (StD)	78.05 (42.79)	65.27 (33.06)	92.18 (60.41)	73.02 (39.49)	77.12 (45.42)
	Median	69.00	69.50	75.50	59.75	68.00
	Min, Max	23.0, 182.0	15.0, 120.0	13.0, 183.0	28.0, 171.0	13.0, 183.0
	n	21	22	22	22	87
Maximum Percent Decrease in Soluble HER2 From Baseline (ng/mL)	Mean (StD)	-60.48 (27.22)	-54.54 (16.12)	-59.23 (20.37)	-53.98 (21.41)	-57.02 (21.38)
	Median	-62.07	-51.49	-62.77	-51.05	-57.14
	Min, Max	-99.2, 22.9	-91.1, -33.3	-95.5, 2.8	-99.7, -12.5	-99.7, 22.9
	n	21	22	22	22	87
Week of First Confirmed Response per ICR	Mean (StD)	7.95 (0.68)	10.56 (5.63)	10.97 (5.60)	9.75 (5.16)	10.18 (5.08)
	Median	7.71	8.00	8.07	7.71	7.71
	Min, Max	7.4, 8.7	7.1, 23.7	7.1, 24.1	7.1, 23.6	7.1, 24.1
	n	3	9	10	11	33
Weight at Baseline (kg)	Mean (StD)	64.99 (16.57)	62.16 (11.44)	71.89 (19.87)	68.37 (13.02)	66.88 (15.72)
	Median	61.50	63.50	68.75	69.80	65.30
	Min, Max	39.5, 108.8	44.0, 90.0	47.0, 112.9	49.8, 95.0	39.5, 112.9
	n	21	22	22	22	87

Patient Characteristic	Statistic	Zanidatamab Cycle 1 C_{min}				
		[2.3, 92.2)	[92.2, 122.3)	[122.3, 150.3)	[150.3, 263.8]	Overall
Baseline Number of Lesions per ICR, n (%)	1	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.1)
	2	1 (4.8)	3 (13.6)	2 (9.1)	1 (4.5)	7 (8.0)
	3	5 (23.8)	4 (18.2)	2 (9.1)	10 (45.5)	21 (24.1)
	4	4 (19.0)	7 (31.8)	4 (18.2)	3 (13.6)	18 (20.7)
	5	4 (19.0)	1 (4.5)	2 (9.1)	3 (13.6)	10 (11.5)
	6	2 (9.5)	1 (4.5)	4 (18.2)	4 (18.2)	11 (12.6)
	7	2 (9.5)	1 (4.5)	2 (9.1)	1 (4.5)	6 (6.9)
	8	0 (0.0)	1 (4.5)	4 (18.2)	0 (0.0)	5 (5.7)
	9	2 (9.5)	2 (9.1)	0 (0.0)	0 (0.0)	4 (4.6)
	10	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	1 (1.1)
	11	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	1 (1.1)
	12	0 (0.0)	0 (0.0)	1 (4.5)	0 (0.0)	1 (1.1)
	13	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Cohort, n (%)	Cohort 1	17 (81.0)	21 (95.5)	22 (100.0)	20 (90.9)	80 (92.0)
	Cohort 2	4 (19.0)	1 (4.5)	0 (0.0)	2 (9.1)	7 (8.0)
Diagnosis Group, n (%)	Biliary tract	21 (100.0)	22 (100.0)	22 (100.0)	22 (100.0)	87 (100.0)
ECOG at Baseline, n (%)	Normal	3 (14.3)	7 (31.8)	6 (27.3)	7 (31.8)	23 (26.4)
	Symptoms/ambulatory	18 (85.7)	15 (68.2)	16 (72.7)	15 (68.2)	64 (73.6)
IHC HER2 Central Results, n (%)	0	2 (9.5)	1 (4.5)	0 (0.0)	1 (4.5)	4 (4.6)
	1+	2 (9.5)	0 (0.0)	0 (0.0)	1 (4.5)	3 (3.4)
	2+	6 (28.6)	6 (27.3)	2 (9.1)	4 (18.2)	18 (20.7)
	3+	11 (52.4)	15 (68.2)	20 (90.9)	16 (72.7)	62 (71.3)
Primary Diagnosis - Original, n (%)	Extrahepatic cholangiocarcinoma	2 (9.5)	5 (22.7)	5 (22.7)	4 (18.2)	16 (18.4)
	Gallbladder cancer	12 (57.1)	10 (45.5)	9 (40.9)	14 (63.6)	45 (51.7)
	Intrahepatic cholangiocarcinoma	7 (33.3)	7 (31.8)	8 (36.4)	4 (18.2)	26 (29.9)
Race, n (%)	White	8 (38.1)	2 (9.1)	6 (27.3)	9 (40.9)	25 (28.7)
	Asian	13 (61.9)	18 (81.8)	14 (63.6)	12 (54.5)	57 (65.5)
	Other	0 (0.0)	2 (9.1)	2 (9.1)	1 (4.5)	5 (5.7)
Sex, n (%)	Male	9 (42.9)	11 (50.0)	11 (50.0)	9 (40.9)	40 (46.0)
	Female	12 (57.1)	11 (50.0)	11 (50.0)	13 (59.1)	47 (54.0)
Stage at Initial Diagnosis, n (%)	STAGE I	0 (0.0)	1 (4.5)	1 (4.5)	0 (0.0)	2 (2.3)

Patient Characteristic	Statistic	Zanidatamab Cycle 1 C_{min}				
		[2.3, 92.2)	[92.2, 122.3)	[122.3, 150.3)	[150.3, 263.8]	Overall
	STAGE II	1 (4.8)	2 (9.1)	4 (18.2)	4 (18.2)	11 (12.6)
	STAGE III	6 (28.6)	8 (36.4)	4 (18.2)	8 (36.4)	26 (29.9)
	STAGE IV	14 (66.7)	10 (45.5)	12 (54.5)	10 (45.5)	46 (52.9)
	Unknown	0 (0.0)	1 (4.5)	1 (4.5)	0 (0.0)	2 (2.3)

Abbreviations: C_{min} = minimum concentration; ECOG = Eastern Cooperative Oncology Group; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; n = number of patients; StD = standard deviation.
Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.
Source: ER Report Table 16.

Table 45: Parameter Estimates and Standard Errors From the ER Base (Final) Logistic Regression Model for the Probability of cOR

Parameter		Final Parameter Estimate	
		Population Mean	%RSE
INT	Response at Median CY1CMIN (logit) (-)	-0.365	54.8
SLP	Exponent for CY1CMIN	-1.66	41.2
Minimum Value of the Objective Function = 107.696			

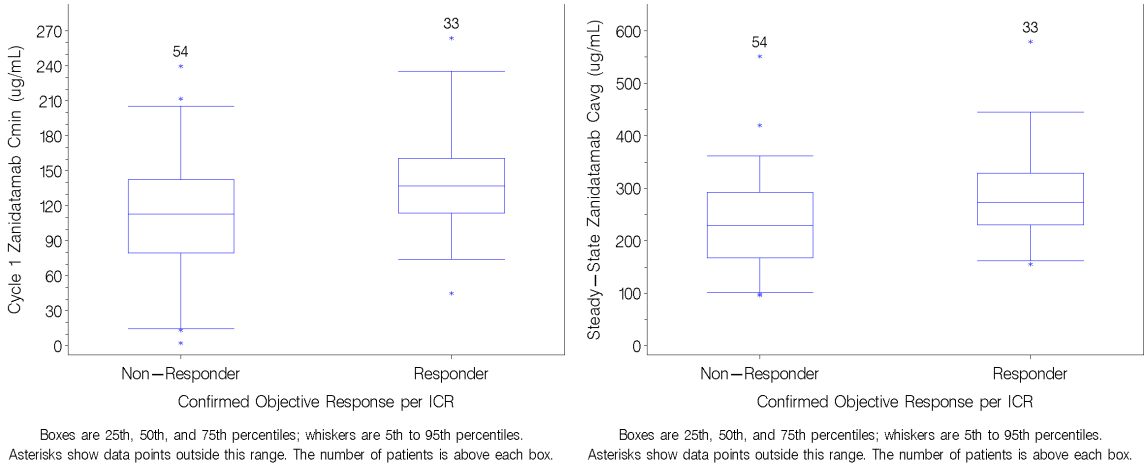
Abbreviations: %RSE = relative standard error expressed as a percent; C_{min} = minimum concentration; CY1CMIN = Cycle 1 zanidatamab C_{min}; cOR = confirmed objective response; ER = exposure-response.
Source: ER Report Table 14.

Table 46: Parameter Estimates and Standard Errors From the ER Final Model for Time to PFS

Variable	Coefficient	SE	%RSE	*P* value	Hazard Ratio (95% CI)
Zanidatamab Daily C_{avg} (µg/mL)	-0.007794	0.001285	16.49	1.319e-09	0.9922 (0.9897, 0.9947)
HER2 Expression (3+ versus 2+/1+/0)	-1.172	0.2767	23.6	2.257e-05	0.3096 (0.18, 0.5325)

Abbreviations: %RSE = relative standard error expressed as a percent; C_{avg} = average concentration; CI = confidence interval; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; *P* = probability; PFS = progression-free survival; SE = standard error.
Source: ER Report Table 25.

Figure 12: Boxplots of Zanidatamab Exposure Measures Versus the Occurrence of cOR

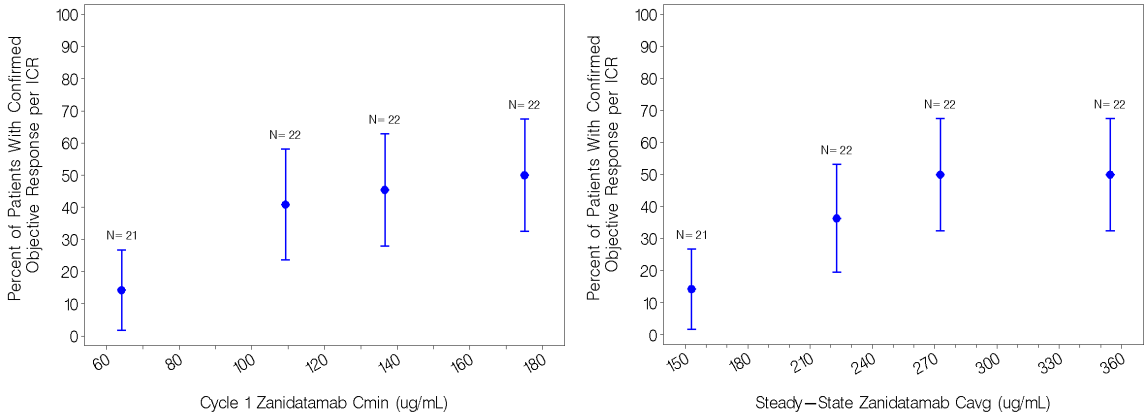


Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of patients is above each box.

Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of patients is above each box.

Abbreviations: AUC = area under the concentration-time curve; Avg = average; C_{avg} = average concentration; C_{max} = maximum concentration; C_{min} = minimum concentration; cOR = confirmed objective response; ICR = independent central review.
Note: Figures show comparable exposure between responders and nonresponders.
Source: ER Report Figure 9.

Figure 13: Observed Percentage of Patients With cOR Versus Zanidatamab Exposure Measures

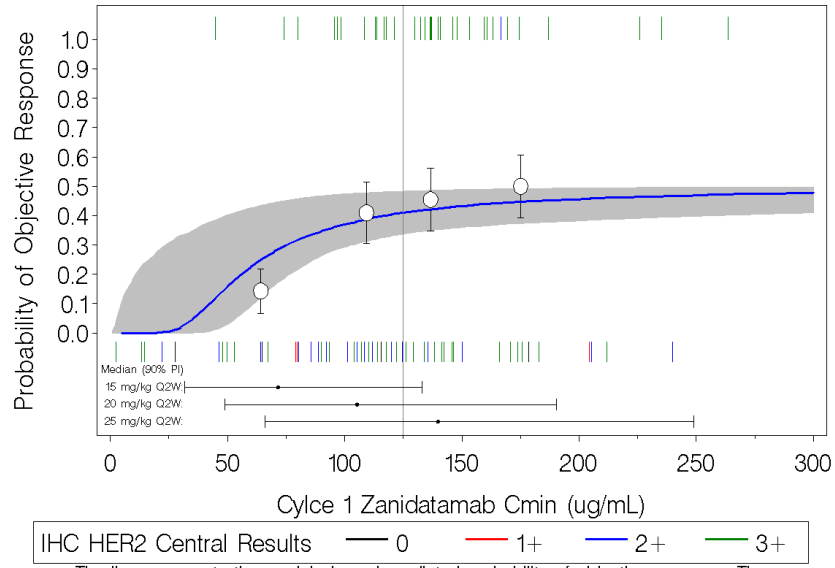


The circles and bars represent the associated observed probabilities and 90% CI, respectively, at the median exposure of each quartile.

The circles and bars represent the associated observed probabilities and 90% CI, respectively, at the median exposure of each quartile.

Abbreviations: Avg = average; C_{avg} = average concentration; CI = confidence interval; C_{min} = minimum concentration; cOR = confirmed objective response; ICR = independent central review; N = number of patients.
Source: ER Report Figure 10.

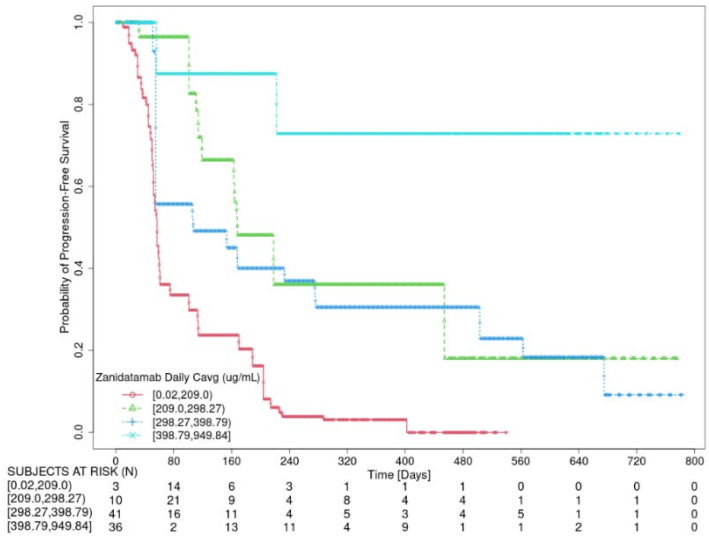
Figure 14: Observed and Model-Predicted Probability of cOR Versus Cycle 1 Zanidatamab C_{min} for the ER Base (Final) Logistic Regression Model



The line represents the model−based predicted probability of objective response. The shaded region represents the 90% prediction interval around the model predictions. The circles represent observed OR +/− 1 SD and are plotted at the median Cycle 1 Cmin for each quartile. The hash marks at the top and bottom of the figure represent the individual Cycle 1 Cmin for objective response yes and no, respectively. The vertical line represents the median Cmin.

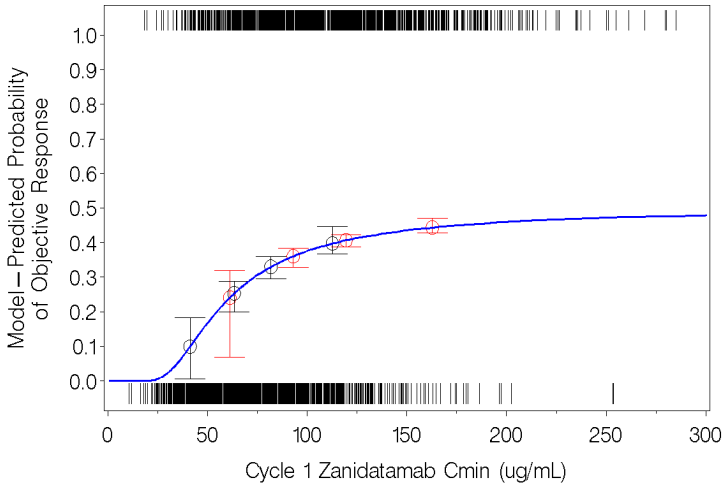
Abbreviations: C_{min} = minimum concentration; cOR = confirmed objective response; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; OR = objective response; PI = prediction interval; Q2W = every 2 weeks; SD = standard deviation.
Source: ER Report Figure 11.

Figure 15: Kaplan-Meier Plot of PFS Versus Time, by Quartiles of Exposure Measures



Abbreviations: C_{avg} = average concentration; PFS = progression-free surival.
Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.
Source: ER Report Figure 15.

Figure 16: Simulated Model-Predicted Probability of cOR Versus Zanidatamab Exposure for Virtual Patients, by Regimen



The line represents the model–based predicted probability of objective response. The black (15 mg/kg Q2W) and red (20 mg/kg Q2W) circles and bars represent the associated predicted median probabilities and 5th and 95th percentiles, respectively, at the median Cycle 1 Cmin values of each quartile. The hash marks at the top (20 mg/kg Q2W) and bottom (15 mg/kg Q2W) of the figure represent the individual Cycle 1 Cmin for 1000 virtual patients.

Abbreviations: C_{min} = minimum concentration; cOR = confirmed objective response; Q2W = every 2 weeks.
Source: ER Report Figure 39.

Table 47: Summary of Simulated Model-Predicted Probability of OR for Virtual Patients, by Quartiles of Cycle 1 Zanidatamab C_{min} for 15 and 20 mg/kg Q2W

15 mg/kg Q2W						
	Statistic	**[10.7, 53.4]**	**[53.4, 71.5]**	**[71.6, 93.9]**	**[93.9, 253.5]**	**Overall**
Probability of Objective Response	Mean (StD)	0.10 (0.06)	0.25 (0.03)	0.33 (0.02)	0.40 (0.02)	0.27 (0.12)
	Median	0.10	0.25	0.33	0.40	0.29
	Min, Max	0.0, 0.2	0.2, 0.3	0.3, 0.4	0.4, 0.5	0.0, 0.5
	n	250	250	250	250	1000
20 mg/kg Q2W						
	Statistic	**[18.5, 79.8]**	**[80, 105.3]**	**[105.3, 137.4]**	**[137.4, 356.5]**	**Overall**
Probability of Objective Response	Mean (StD)	0.23 (0.08)	0.36 (0.02)	0.41 (0.01)	0.45 (0.01)	0.36 (0.09)
	Median	0.24	0.36	0.41	0.44	0.39
	Min, Max	0.0, 0.3	0.3, 0.4	0.4, 0.4	0.4, 0.5	0.0, 0.5
	n	250	250	250	250	1000

Abbreviations: C_{min} = minimum observed concentration; Max = maximum; Min = minimum; n = number of patients; OR = objective response; Q2W = every 2 weeks; StD = standard deviation; Q2W = Once every 2 weeks.
Source: ER Report Table 59.

19.4.3.3. ER (Safety) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		*The goal of the ER analysis was to develop ER safety models to describe the relationships between the probability of incidence of diarrhea, Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, IRRs, Grade ≥ 3 IRRs, and SAEs, if feasible, in patients with HER2-expressing cancers and zanidatamab exposure.*
Study Included		*ZWI-ZW25-203 and ZWI-ZW25-101.*
Population Included		*Exposure-response analyses of safety AEs were performed on data collected from participants with available zanidatamab exposure estimates from Study 203 (N = 87) in participants with HER2 amplified BTC and Study 101 (N = 192) in participants with HER2-expressing cancers.*
Endpoint		*Diarrhea, Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, IRRs, Grade ≥ 3 IRRs, and SAEs related to zanidatamab.*
No. of Patients (total, and with individual PK)		*The ER safety analysis dataset for AEs included a total of 279 patients (all had available model-predicted exposure measures for ER analyses).*
Population Characteristics	General	• *Demographics information appears in Table 48*
	Organ impairment	• *See Section 19.4.1.2, Population characteristics, Organ impairment row.*
	Pediatrics (if any)	*Not applicable*
	Geriatrics (if any)	*Age 65 to < 75: 93 (33.3%)* *Age ≥ 75: 16 (5.7%)*
Dose(s) Included		*5, 10, 15 mg/kg QW, 20, 25, 30 mg/kg Q2W, and 30 mg/kg Q3W (Study 101) and 20 mg/kg Q2W (Study 203)*
Exposure Metrics Explored (range)		*Exposure metrics were summarized in ER Report Table 28 (eg, steady-state C_{avg} range: 69.61 to 701.80 µg/mL).*

Covariates Evaluated	*Age, baseline weight, baseline lactate dehydrogenase, sex, race, number of lesions, baseline tumor size, HER2 expression (as determined by IHC or FISH), and ECOG performance status*	
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*The final model for diarrhea is a logistic regression on the logit scale including an additive shift for HER2 status of 0/1+ plus a linear function of $C_{avg,ss}$ centered by its median.*	Acceptable
Model Parameter Estimates	*Parameter estimates for the final model of diarrhea show additive shift for HER2 0/1+ is -1.91 (34.5 %RSE) and slope for $C_{avg,ss}$ is 0.00429 (29.2 %RSE) (Table 50).*	Acceptable
Model Evaluation	*In Figure 12, the model-based predicted probability of diarrhea AEs (blue and red lines for HER2 status of 2+/3+ and 0/1+, respectively) was superimposed on the observed data points (circles and plusses) for both HER2 status groups across the range of zanidatamab $C_{avg,ss}$, indicating that the final model corresponded well with the observed data.*	Acceptable
Covariates and Clinical Relevance	*Although HER2 IHC status was a statistically significant covariate where participants with HER2 IHC 0 or 1+ had a lower probability of diarrhea relative to those with IHC 2+ or 3+, the clinical relevance of this observation is unknown. Despite the apparent ER trend for probability of diarrhea, there is no statistically significant ER relationship for Grade ≥ 3 diarrhea, which is considered more clinically relevant. No statistically significant relationships were observed between zanidatamab exposure and Grade ≥ 3 TEAE, IRRs (all grades), and Grade ≥ 3 IRRs. Limited participants had SAEs that were zanidatamab related (n = 10 out of 85 total patients with SAEs), hence no meaningful analyses were summarized.*	Acceptable
Simulation for Specific Population	*Simulations using the final PK model were performed to predict zanidatamab $C_{avg,ss}$ for 1000 simulated BTC patients each administered doses of 15 and 20 mg/kg Q2W. These predicted exposure measures were used to obtain model-predicted probabilities of diarrhea using the final model. A summary of the model-predicted probabilities of diarrhea in each quartile of zanidatamab $C_{avg,ss}$, by regimen (Table 51, and Figure 14). The risk of an AE of diarrhea is predicted to exceed 50% for the highest exposure quartile for 15 mg/kg Q2W and the 2 highest exposure quartiles of zanidatamab $C_{avg,ss}$ for 20 mg/kg Q2W.*	Acceptable
Visualization of ER relationships	• *Final model for diarrhea logistic regression vs $C_{avg,ss}$: Figure 13* • *Baseline demographics stratified by the $C_{avg,ss}$: quartiles: Table 49*	Acceptable
Overall Clinical Relevance for ER	*No statistically significant E R relationship was found for any of the safety endpoints examined (including Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, or IRR), except for the probability of diarrhea, where higher zanidatamab exposure was associated with an increased probability of diarrhea. Despite the apparent E R relationship for the occurrence of*	Acceptable

	diarrhea, there is no statistically significant ER relationship for Grade ≥ 3 diarrhea.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	*Cardiac Electrophysiology* (b) (4) [redacted]	The following modified version has been conveyed to the Sponsor: *A mean increase in the QTc interval > 20 ms was not observed at the recommended approved dosage.*

Abbreviations: %RSE = relative standard error expressed as a percent; AE = adverse event; BTC = biliary tract cancer; C_{avg} = average concentration; ; $C_{avg,ss}$ = average concentration at steady state; ECOG = Eastern Cooperative Oncology Group; ER = exposure-response; FDA = Food and Drug Administration; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IRR = infusion-related reaction; PK = pharmacokinetic(s); Q2W = every 2 weeks; Q3W = every 3 weeks; QTc = QT interval corrected for heart rate; QW = every week; SAE =-serious adverse event; TEAE = treatment=emergent adverse event.

Table 48: Summary Statistics of Demographic Characteristics for the ER Safety Analysis of AEs, by Study

Patient Characteristic	Statistic	Study		Overall
		ZWI-ZW25-101	ZWI-ZW25-203	
Age (y)	Mean (StD)	59.2 (11.8)	62.7 (9.5)	60.3 (11.2)
	Median	60.0	64.0	62.0
	Min, Max	24, 88	32, 79	24, 88
	n	192	87	279
Weight at Baseline (kg)	Mean (StD)	69.84 (17.27)	66.88 (15.72)	68.92 (16.83)
	Median	68.85	65.30	68.50
	Min, Max	35.4, 127.9	39.5, 112.9	35.4, 127.9
	n	192	87	279
Baseline LDH (U/L)	Mean (StD)	439.5 (402.9)	358.8 (397.0)	414.3 (402.1)
	Median	292.0	219.4	261.0
	Min, Max	71, 2677	125, 2500	71, 2677
	n	192	87	279
Baseline Sum of Diameters per ICR (mm)	Mean (StD)	82.78 (54.02)	77.12 (45.42)	81.02 (51.48)
	Median	69.50	68.00	69.00
	Min, Max	12.0, 312.0	13.0, 183.0	12.0, 312.0
	n	192	87	279
Race, n (%)	White	106 (55.2)	25 (28.7)	131 (47.0)

Patient Characteristic	Statistic	Study		Overall
		ZWI-ZW25-101	ZWI-ZW25-203	
	Black or African American	7 (3.6)	0 (0.0)	7 (2.5)
	Asian	67 (34.9)	57 (65.5)	124 (44.4)
	American Indian or Alaska Native	0 (0.0)	1 (1.1)	1 (0.4)
	Native Hawaiian or Other Pacific Islander	2 (1.0)	0 (0.0)	2 (0.7)
	Unknown	6 (3.1)	4 (4.6)	10 (3.6)
	Multiple	2 (1.0)	0 (0.0)	2 (0.7)
	Other	2 (1.0)	0 (0.0)	2 (0.7)
Sex, n (%)	Male	89 (46.4)	40 (46.0)	129 (46.2)
	Female	103 (53.6)	47 (54.0)	150 (53.8)
Baseline Number of Lesions per ICR, n (%)	1	7 (3.6)	1 (1.1)	8 (2.9)
	2	18 (9.4)	7 (8.0)	25 (9.0)
	3	33 (17.2)	21 (24.1)	54 (19.4)
	4	28 (14.6)	18 (20.7)	46 (16.5)
	5	34 (17.7)	10 (11.5)	44 (15.8)
	6	23 (12.0)	11 (12.6)	34 (12.2)
	7	18 (9.4)	6 (6.9)	24 (8.6)
	8	9 (4.7)	5 (5.7)	14 (5.0)
	9	9 (4.7)	4 (4.6)	13 (4.7)
	10	8 (4.2)	1 (1.1)	9 (3.2)
	11	1 (0.5)	1 (1.1)	2 (0.7)
	12	1 (0.5)	1 (1.1)	2 (0.7)
	13	1 (0.5)	1 (1.1)	2 (0.7)
	15	1 (0.5)	0 (0.0)	1 (0.4)
	20	1 (0.5)	0 (0.0)	1 (0.4)
IHC HER2 Central Results, n (%)	0	2 (1.0)	4 (4.6)	6 (2.2)
	1+	12 (6.3)	3 (3.4)	15 (5.4)
	2+	44 (22.9)	18 (20.7)	62 (22.2)
	3+	134 (69.8)	62 (71.3)	196 (70.3)
Standard Toxicity Grade, n (%)	Mild	80 (41.7)	23 (26.4)	103 (36.9)
	Moderate	16 (8.3)	14 (16.1)	30 (10.8)
	Severe	1 (0.5)	3 (3.4)	4 (1.4)
	NA	95 (49.5)	47 (54.0)	142 (50.9)

Abbreviations: AEs = adverse events; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; n = number of patients; NA = not applicable; StD = standard deviation.
Source: ER Report Table 27.

Table 49: Summary Statistics of Demographic Characteristics for the ER Safety Analysis of AEs, by Steady-State C_{avg} Quartiles

Patient Characteristic	Statistic	Zanidatamab Steady-State C_{avg} (µg/mL)				
		[69.61, 211.13)	[211.13, 281.17)	[281.17, 349.29)	[349.29, 701.8]	Overall
Age	Mean (StD)	59.0 (12.2)	60.4 (11.0)	61.5 (11.0)	60.4 (10.8)	60.3 (11.2)
	Median	60.0	62.0	61.5	63.0	62.0
	Min, Max	24, 86	27, 79	31, 88	27, 79	24, 88
	n	69	70	70	70	279
Weight at Baseline (kg)	Mean (StD)	63.84 (14.47)	63.16 (15.25)	74.26 (18.03)	74.33 (16.10)	68.92 (16.83)
	Median	61.50	60.15	72.40	72.80	68.50
	Min, Max	36.2, 107.5	35.4, 116.9	47.0, 127.9	48.1, 108.8	35.4, 127.9
	n	69	70	70	70	279
Baseline LDH (U/L)	Mean (StD)	575.9 (531.7)	365.7 (360.6)	380.0 (298.6)	338.0 (343.5)	414.3 (402.1)
	Median	361.0	254.5	250.0	215.5	261.0
	Min, Max	71, 2366	111, 2677	141, 1632	133, 2500	71, 2677
	n	69	70	70	70	279
Baseline Sum of Diameters per ICR (mm)	Mean (StD)	96.93 (63.19)	76.06 (44.55)	82.66 (49.22)	68.65 (43.59)	81.02 (51.48)
	Median	82.00	68.50	74.50	59.50	69.00
	Min, Max	15.0, 312.0	16.0, 199.0	15.0, 187.0	12.0, 247.0	12.0, 312.0
	n	69	70	70	70	279
Race, n (%)	White	35 (50.7%)	25 (35.7%)	33 (47.1%)	38 (54.3%)	131 (47.0%)
	Black or African American	3 (4.3%)	0 (0%)	3 (4.3%)	1 (1.4%)	7 (2.5%)
	Asian	28 (40.6%)	42 (60.0%)	30 (42.9%)	24 (34.3%)	124 (44.4%)
	American Indian or Alaska Native	0 (0%)	0 (0%)	1 (1.4%)	1 (1.4%)	2 (0.7%)
	Native Hawaiian or Other Pacific Islander	1 (1.4%)	2 (2.9%)	3 (4.3%)	4 (5.7%)	10 (3.6%)
	Unknown	1 (1.4%)	1 (1.4%)	0 (0%)	0 (0%)	2 (0.7%)
	Multiple	1 (1.4%)	0 (0%)	0 (0%)	1 (1.4%)	2 (0.7%)
	Other	0 (0%)	0 (0%)	0 (0%)	1 (1.4%)	1 (0.4%)
Sex, n (%)	Male	30 (43.5%)	31 (44.3%)	37 (52.9%)	31 (44.3%)	129 (46.2%)
	Female	39 (56.5%)	39 (55.7%)	33 (47.1%)	39 (55.7%)	150 (53.8%)

Patient Characteristic	Statistic	Zanidatamab Steady-State C_{avg} (µg/mL)				
		[69.61, 211.13)	[211.13, 281.17)	[281.17, 349.29)	[349.29, 701.8]	Overall
Baseline Number of Lesions per ICR, n (%)	1	0 (0%)	1 (1.4%)	1 (1.4%)	6 (8.6%)	8 (2.9%)
	2	5 (7.2%)	9 (12.9%)	5 (7.1%)	6 (8.6%)	25 (9.0%)
	3	5 (7.2%)	9 (12.9%)	21 (30.0%)	19 (27.1%)	54 (19.4%)
	4	14 (20.3%)	13 (18.6%)	11 (15.7%)	8 (11.4%)	46 (16.5%)
	5	14 (20.3%)	8 (11.4%)	12 (17.1%)	10 (14.3%)	44 (15.8%)
	6	6 (8.7%)	11 (15.7%)	10 (14.3%)	7 (10.0%)	34 (12.2%)
	7	7 (10.1%)	8 (11.4%)	3 (4.3%)	6 (8.6%)	24 (8.6%)
	8	4 (5.8%)	3 (4.3%)	4 (5.7%)	3 (4.3%)	14 (5.0%)
	9	5 (7.2%)	5 (7.1%)	1 (1.4%)	2 (2.9%)	13 (4.7%)
	10	5 (7.2%)	1 (1.4%)	2 (2.9%)	1 (1.4%)	9 (3.2%)
	11	0 (0%)	1 (1.4%)	0 (0%)	1 (1.4%)	2 (0.7%)
	12	0 (0%)	1 (1.4%)	0 (0%)	1 (1.4%)	2 (0.7%)
	13	2 (2.9%)	0 (0%)	0 (0%)	0 (0%)	2 (0.7%)
	15	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
	20	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
IHC HER2 Central Results, n (%)	0	1 (1.4%)	1 (1.4%)	2 (2.9%)	2 (2.9%)	6 (2.2%)
	1+	2 (2.9%)	7 (10.0%)	3 (4.3%)	3 (4.3%)	15 (5.4%)
	2+	19 (27.5%)	13 (18.6%)	19 (27.1%)	11 (15.7%)	62 (22.2%)
	3+	47 (68.1%)	49 (70.0%)	46 (65.7%)	54 (77.1%)	196 (70.3%)
ECOG at Baseline, n (%)	Normal	7 (10.1%)	15 (21.4%)	26 (37.1%)	25 (35.7%)	73 (26.2%)
	Symptoms/ambulatory	62 (89.9%)	55 (78.6%)	44 (62.9%)	45 (64.3%)	206 (73.8%)

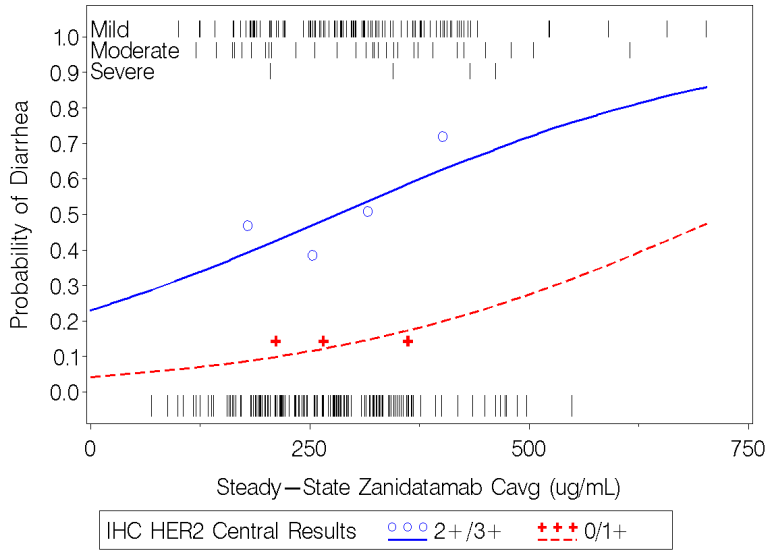
Abbreviations: AEs = adverse events; C_{avg} = average concentration; ECOG = Eastern Cooperative Oncology Group; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; n = number of participants; StD = standard deviation.
Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.
Source: ER Report Table 36.

Table 50: Parameter Estimates and Standard Errors From the Refined (Final) ER Safety Model for the Occurrence of Diarrhea in Studies ZWI-ZW25-101 and ZWI-ZW25-203

Parameter		Final Parameter Estimate	
		Population Mean	%RSE
SLP	Slope for Steady-State Zanidatamab C_{avg} (1/(ug/mL))	0.00429	29.2
INT	Additive Shift for HER2 Status of 0/+1 (HER01 = 1)	-1.91	34.5
Minimum Value of the Objective Function = 363.022			

Abbreviations: %RSE = relative standard error expressed as a percent; C_{avg} = average concentration; ER = exposure-response; HER01 = indicator variable for HER2 status of 0/1+ versus 2+/3+; HER2 = human epidermal growth factor receptor 2.
Source: ER Report Table 39.

Figure 17: Observed and Model-Predicted Probability of Diarrhea Versus Zanidatamab Steady-State C_{avg}, by HER2 Status, for the Final ER Model for the Occurrence of Diarrhea in Studies ZWI-ZW25-101 and ZWI-ZW25-203



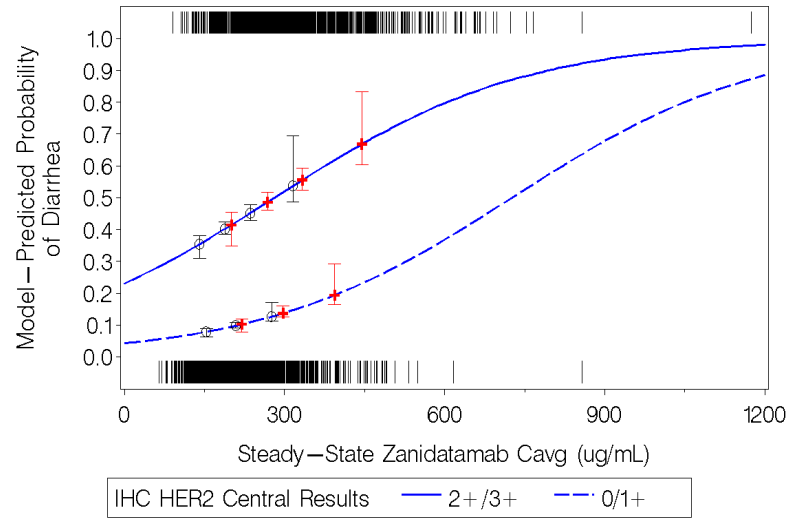
Abbreviations: C_{avg} = average concentration; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; n = number of participants.
Note: The number of participants stratified by HER2 IHC were as follows: 0 (n = 6), 1+ (n = 15), 2+ (n = 62), and 3+ (n = 196).
Source: ER Report Figure 26.

Table 51: Summary of Simulated Model-Predicted Probability of Diarrhea for Virtual Patients, by Quartiles of Zanidatamab $C_{avg,ss}$

15 mg/kg Q2W						
Steady-State Zanidatamab C_{avg} (µg/mL)	**Statistic**	**[64.3, 169.8]**	**[169.8, 211.4]**	**[211.6, 263]**	**[263.2, 857.1]**	**Overall**
Probability of Diarrhea	Mean (StD)	0.33 (0.07)	0.38 (0.09)	0.42 (0.09)	0.53 (0.12)	0.42 (0.12)
	Median	0.35	0.40	0.45	0.53	0.42
	Min, Max	0.1, 0.4	0.1, 0.4	0.1, 0.5	0.1, 0.9	0.1, 0.9
	n	250	250	250	250	1000
20 mg/kg Q2W						
Steady-State Zanidatamab C_{avg} (µg/mL)	**Statistic**	**[90.8, 242.3]**	**[242.3, 299.2]**	**[299.3, 371.9]**	**[372.5, 1174.5]**	**Overall**
Probability of Diarrhea	Mean (StD)	0.39 (0.09)	0.46 (0.10)	0.53 (0.11)	0.66 (0.13)	0.51 (0.15)
	Median	0.41	0.48	0.55	0.66	0.51
	Min, Max	0.1, 0.5	0.1, 0.5	0.1, 0.6	0.2, 1.0	0.1, 1.0
	n	250	250	250	250	1000

Abbreviations: C_{avg} = average concentration; $C_{avg,ss}$ = average concentration at steady state; Max = maximum; Min = minimum; n = number of patients; StD = standard deviation; Q2W = every 2 weeks.
Source: ER Report Table 61.

Figure 18: Simulated Model-Predicted Probability of Diarrhea Versus Zanidatamab $C_{avg,ss}$ for the Final ER Model for the Occurrence of Diarrhea, by HER2 Status and Regimen



The lines represent the model—based predicted probability of diarrhea for each HER2 grouping. The black (15 mg/kg Q2W) and red (20 mg/kg Q2W) symbols and bars represent the associated predicted median probabilities and 5th and 95th percentiles, respectively, at the median steady—state Cavg values of each quartile or tertile. The hash marks at the top (20 mg/kg Q2W) and bottom (15 mg/kg Q2W) of the figure represent the individual steady—state Cavg for 1000 virtual patients.

Abbreviations: C_{avg} = average concentration; $C_{avg,ss}$ = average concentration at steady state; ER = exposure-response; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; Q2W = every 2 weeks.
Source: ER Report Figure 40.

The FDA's Assessment:

In this submission, the exposure-response (E-R) relationships for both efficacy and safety endpoints of zanidatamab were evaluated using data from Study 203 (efficacy and safety) and Study 101 (safety). Predicted zanidatamab pharmacokinetic (PK) exposures, along with efficacy and safety data, were explored using logistic regression models and survival models. In these studies, zanidatamab was administered at different dose regimens of 5, 10, and 15 mg/kg QW, 20, 25, and 30 mg/kg Q2W, or 30 mg/kg Q3W as a single agent.

E-R relationship for Efficacy

The E-R relationship for efficacy was assessed for confirmed OR and PFS from Study 203 (N = 87) in participants with HER2-amplified BTC.

The analysis showed a trend indicating that the probability of confirmed OR as assessed by independent central review (ICR), increased with higher zanidatamab exposures (steady-state Cavg or Cycle 1 Cmin), but approached a plateau at the second quartile and beyond.

However, this positive exposure-efficacy trend and the model predicted ORR for lower dose of 15 mg/kg should be interpreted with caution for the following reasons:

- The relatively lower percentage of participants with IHC 3+ in the first quartile may have contributed to the lower confirmed OR in this group, potentially confounding the E-R assessment.
- This exposure-response for efficacy analysis was conducted using only one dosing regimen and limited total participants (n = 80 in cohort 1, where HER2 expression of IHC 2+ or 3+ and ISH+)

The exposure-efficacy relationship of zanidatamab for PFS investigation results are inconclusive due to inconsistencies across exposure quartiles based on daily Cavg.

E-R relationship for Safety

The E-R relationship for safety was assessed for AEs including diarrhea, Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, IRRs, Grade ≥ 3 IRRs, and SAEs using data from 279 participants: Study 101 (N = 192) involving participants with HER2-expressing cancers, and Study 203 (N = 87) in participants with HER2-amplified BTC.

No statistically significant E-R relationship was identified for any of the safety endpoints examined (including Grade ≥ 3 diarrhea, Grade ≥ 3 TEAEs, or IRR), except for the probability of diarrhea, where higher zanidatamab exposure was associated with an increased probability of diarrhea. Despite the apparent E-R relationship for the occurrence of diarrhea, there is no statistically significant E-R relationship for Grade ≥ 3 diarrhea.

Additionally, extrapolating the observed E-R relationships for efficacy and safety to untested dosing regimens is unwarranted due to the narrow exposure range from the single dose level included in the analysis and the confounding effects of time-dependent clearance.

Reviewer's comments:

> *The Sponsor's exposure-response analyses appear acceptable. However, the E-R analyses on the limited data from a single arm study should be interpreted with caution.*
>
> *The Cmin at Cycle 1 was used in the final E-R for efficacy (confirmed OR) model. The primary consideration for this PK metric selection was to prioritize the PK in Cycle 1 and try to eliminate confounding effects due to nonspecific catabolism, which may lead to the interaction between post-treatment effect and drug exposure and bias the E-R at later cycles (Liu, 2017).*
> *For certain approved therapeutic antibodies, such as pembrolizumab, while a significant E-R relationship is demonstrated for efficacy (CR, PR or OS) using steady-state PK, but using Cycle 1 PK reveals a flat relationship, which has been consistent to the clinical observations. In contrast, for zanidatamab, positive E-R trends were observed when using both Cycle 1 and steady-state PK data (**Figures 8, 9, and 10**). This suggests that nonspecific catabolism may not play a dominant role on the overall drug clearance of zanidatamab. These findings may be interpreted by the following two hypotheses:*
>
> *1). **True E-R efficacy relationship**: The presence of a true E-R efficacy relationship for zanidatamab at the current dose level.*
>
> *Or,*
>
> *2). **TMDD confounded E-R efficacy relationship**: Similar to the well-known case of trastuzumab (Chen, 2017), in the investigated patient population, a subgroup of non-responders exhibited significantly higher baseline clearance, likely due to elevated HER2 receptor expression on tumor cells. This led to increased TMDD and total clearance, resulting in lower drug exposure within this small subgroup of patients. Consequently, this contributed to an erroneous overall positive E-R relationship across the entire population studied.*

Due to the narrow exposure range from the single dose level included in the analysis and the confounding effects of time-dependent clearance, the ER relationship for efficacy remains inconclusive. We recommend that the applicant continue assessing the appropriateness of dosing in specific subgroups of patients as additional data become available from the ongoing or future controlled clinical trials.

REFERENCES

Liu C, Yu J, Li H, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. *Clin Pharmacol Ther*. 2017; 101:657-666.

Chen SC, Quartino A, Polhamus D, et, al. Population pharmacokinetics and exposure–response of trastuzumab emtansine in advanced breast cancer previously treated with ≥2 HER2-targeted regimens. Br J Clin Pharmacol (2017) 83 2767–2777.

19.5. Additional Safety Analyses Conducted by FDA

Table 52: Case narrative summary of deaths within 30 days of last dose zanidatamab in Study 203.

Patient ID	Patient Summary and FDA Reviewer Comments
(b) (6) 32-year-old Female Preferred Term: Hepatic Failure	32-year-old female patient with a diagnosis of gallbladder carcinoma (GBC), was hospitalized on Cycle 1 Day 10, for management of multiple concomitant adverse events including Grade 3 sepsisoral candidiasis, and hepatic failure. The patient's baseline liver function tests on Cycle 1 Day 1 were ALT 38 U/L (ref: 4-51 u/L), AST 106 U/L (ref. 5-46 u/L), and total bilirubin 17.1 umol/L (ref: 1.71-25.65). During the course of the admission the patient was initiated on broad spectrum antibiotics, antifungals, and antiviral treatments, vasopressor support and underwent endoscopic retrograde cholangiopancreatography (ERCP) with stent placement. During the course of her admission, her LFTs worsened (Day 27: AST: 149 U/L, ALT: 1091 U/L, and T. Bili 53.01 umol/L). The patient died on Day 30. *FDA Reviewer Comment: The patient had Grade 1 elevation of ALT prior to initiating treatment, and her clinical course was confounded by septic shock. Given the timeline of LFT worsening, the onset of "hepatic failure" is possibly related to the initial zanidatamab infusion. A description of the fatal adverse event was listed in the zanidatamab US prescribing information.*
(b) (6) 73-year-old Female Preferred Term: Bacteremia Cholangitis	73-year-old female with a diagnosis of extrahepatic cholangiocarcinoma experienced a Grade 2 IRR with her initial dose of zanidatamab. The patient required dose interruption with resolution of symptoms the same day. She had no recurrence of her IRR when retreated on Cycle 2 Day 1. She was admitted on Day 33, for staphylococcus aureus bacteremia, requiring the removal of port-a-cath. She received her next infusion on Study Day 57. She was admitted on Study Day 62, with an ERCP demonstrating worsening

	common bile duct obstruction secondary to local ingrowth, the patient subsequently withdrew from the study and died on Study Day 75. *FDA Reviewer Comments: The patient had evidence local disease progression complicated by cholangitis and this is likely related to underlying condition.*
(b) (6) 77-years-old Male Preferred Term: Cholangitis	77-year-old male with a diagnosis of GBC, experienced a Grade 2 IRR with his initial infusion of zanidatamab, resolving the same day, and was able to receive the subsequent dose on Study Day 15. The patient was admitted on Study Day 22 with clinical concerns for cholangitis and acute kidney injury, requiring percutaneous biliary drainage. His clinical course was complicated by pneumocystis jirovecii pneumonia and patient subsequently died on Study Day 37. *FDA Reviewer Comment: This patient's clinical course was complicated by cholangitis, which has high associated morbidity and did not resolve with percutaneous drainage. This is likely related to the underlying condition.*
(b) (6) 58-years-old Female Preferred Term: Asthenia	58-year-old female with a diagnosis of intrahepatic cholangiocarcinoma (IHCC), with past medical history notable for cancer pain, ascites, decreased appetite, and peripheral edema. She had Grade 3 asthenia following her second dose of zanidatamab on Day 16. The patient had no other adverse events listed and subsequently withdrew from the study and died on Day 30. *FDA Reviewer Comment: There is no clinical evidence from the information provided to suggest that the withdrawal of patient consent was as a result of an adverse reaction to zanidatamab.*
(b) (6) 54-years-old Male Preferred Term: Cholangiocarcinoma	54-year-old female with a diagnosis of IHCC. The patient received his second infusion of zanidatamab on Study Day 15. He was subsequently diagnosed with hypercalcemia and worsening abdominal lymphadenopathy on Day 27 and discontinued treatment due to disease progression on Day 28. He died Day 42. *FDA Reviewer Comment: The description of worsening abdominal lymphadenopathy and hypercalcemia is consistent with disease progression.*

APPEARS THIS WAY ON ORIGINAL

Discipline	Reviewer	Office/Division	Section	Authored Approved
Nonclinical Team Leader	Matthew Thompson	OOD/DHOT	Section: 5	**Select one:** _x_ Authored _x_Approved
Signature:	Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2024.10.30 11:21:09 -04'00'			
Nonclinical Division Director	Haleh Saber	OOD/DHOT	Section: 5	**Select one:** __ Authored _x_Approved
Signature:	Haleh Saber -S Digitally signed by Haleh Saber -S Date: 2024.10.30 12:08:10 -04'00'			
Clinical Pharmacology Reviewer	Dapeng Cui	OCP/DCPII	Section: 6, 19.4	**Select one:** _x_ Authored __Approved
Signature:	Dapeng Cui -S Digitally signed by Dapeng Cui -S Date: 2024.10.30 13:38:43 -04'00'			
Clinical Pharmacology Team Leader	Jason Moore	OCP/DCPII	Section: 6, 19.4	**Select one:** _x_Authored _x_Approved
Signature:	JASON N. MOORE JR -S Digitally signed by JASON N. MOORE JR -S Date: 2024.10.31 09:37:34 -04'00'			
Pharmacometrics Reviewer	Da Zhang	OCP/DPM	Section: 6, 19.4	**Select one:** _x_ Authored __Approved
Signature:	Da Zhang -S Digitally signed by Da Zhang -S Date: 2024.10.31 13:11:35 -04'00'			
Pharmacometrics Team Leader	Youwei Bi	OCP/DPM	Section: 6, 19.4	**Select one:** __ Authored _x_Approved
Signature:	Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.10.31 13:33:02 -04'00'			
Clinical Pharmacology Division Director	Atiqur Rahman	OCP/DCPII	Section: 6, 19.4	**Select one:** **Select one:** __Authored _x_Approved
Signature:	Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2024.10.31 14:54:45 -04'00'			
Clinical Reviewer	Vaibhav Kumar	OND/DO3	Section: 2, 7, 8, Appendix	**Select one:** X Authored
Signature:	VAIBHAV KUMAR -S Digitally signed by VAIBHAV KUMAR -S Date: 2024.11.01 09:39:49 -04'00'			

Discipline	Reviewer	Office/Division	Section	Authored Approved
Clinical Team Leader	Sandra Casak	OND/DO3	Section: 2, 7, 8, Appendix	**Select one:** __ Authored x_Approved
Signature: See final signature in Assessment Aid				
Statistical Reviewer	Sirisha Mushti	OB/DB-V	Sections: 7, 8.1, 8.3 1	**Select one:** _x_ Authored _x_Approved
Signature: Sirisha Mushti -S Digitally signed by Sirisha Mushti -S Date: 2024.11.01 10:41:46 -04'00'				
Statistical Team Leader	Chi Song	OB/DB-V	Section: 7, 8.1, 8.3 1	**Select one:** __ Authored _X_Approved
Signature: Chi Song -S Digitally signed by Chi Song -S Date: 2024.11.03 00:32:32 -04'00'				
Statistical Division Director	Shenghui Tang	OB/DB-V	Section: 7, 8.1, 8.3 1	**Select one:** __ Authored _x_Approved
Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2024.11.04 08:11:17 -05'00'				
Associate Director for Labeling (ADL)	Doris Auth	OCE	Section:11	**Select one:** X Authored X Approved
Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2024.11.04 09:25:13 -05'00'				
Cross-Disciplinary Team Leader (CDTL)	Sandra Casak	OND/DO3	Section: All	**Select one:** __ Authored _x_Approved
Signature: See final signature in Assessment Aid				
Division Director	Steven Lemery	OND/DO3	Section: All	**Select one:** __ Authored _x_Approved
Signature: See final signature in Assessment Aid				

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/

SANDRA J CASAK
11/20/2024 07:40:39 AM

STEVEN J LEMERY
11/20/2024 09:11:38 AM

PAUL G KLUETZ
11/20/2024 04:50:12 PM