25 April 2025
EMA/169374/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ziihera

International non-proprietary name: zanidatamab

Procedure No. EMEA/H/C/006380/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

%CV	Percent coefficient of variation
ΔQTcF	Change from baseline in QTcF
ADA	Antidrug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0-14,ss}$	Area under the curve from time 0 to 14 days at steady state
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
AUC_{0-t}	Area under the curve from time zero to last measurable concentration
AUC_{0-tau}	Area under the curve during the dosing interval
AUC_{ss}	Area under the curve within a dosing interval at steady state
BLQ	Below limit of quantification
BTC	Biliary tract cancer
C_{avg}/C_{ave}	Average concentration
$C_{avg,ss}$	Average concentration at steady state
CBR	Clinical benefit rate
CC	Cholangiocarcinoma
CDC	Complement-dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance

C_{max} Maximum concentration

$C_{max,ss}$ Maximum concentration at steady state

CMC Chemistry, Manufacturing, and Controls

C_{min} Minimum concentration

cORR Confirmed objective response rate

COVID-19 Coronavirus 2019

C-QT Concentration-QT

CR Complete response

CRC Colorectal cancer

CSR Clinical study report

CT Computed tomography

C_{trough} Trough concentration

$C_{trough,ss}$ Trough concentration at steady state

CV Coefficient of variation

CYP Cytochrome P450

DISH Dual In Situ Hybridization

DCO Data cut-off

DCR Disease control rate

Df Degrees of freedom

DLT Dose-limiting toxicity

DOR Duration of response

DP Drug product

EAP Extended access protocol

EBE Empirical Bayes Estimate

ECC Extrahepatic cholangiocarcinoma

ECD Extracellular domain

ECD2 Extracellular domain 2

ECD4 Extracellular domain 4

ECG Electrocardiogram

ECHO Echocardiography

ECL	Electrochemiluminescent
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EOT	End of treatment
E-R	Exposure-response
ESMO	European Society for Medical Oncology
EU	European Union
F	Female
FDA	Food and Drug Administration
FGFR2	Fibroblast growth factor receptor 2
FISH	Fluorescent in situ hybridization
GBC	Gall bladder cancer
GCP	Good Clinical Practice
GEA	Gastroesophageal adenocarcinoma
GLP	Good Laboratory Practice
GM	Geometric mean
GMR	Geometric mean ratio
Hct	Haematocrit
Hgb	Haemoglobin
HER2	Human epidermal growth factor receptor 2
HER3	Human epidermal growth factor receptor 3
HPC	High positive control
IC_{90}	90% inhibitory concentration
ICC	Intrahepatic cholangiocarcinoma
ICR	Independent central review
IDH1/2	Isocitrate dehydrogenase 1 and 2
IgG1	Immunoglobulin G isotope 1

IHC	Immunohistochemistry
IIV	Interindividual variability
IRR	Infusion-related reactions
ISH	In situ hybridization
IV	Intravenous
JZP598	Zanidatamab
KM	Kaplan Meier
LDGI	Ligand-dependent cellular growth inhibition
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LPC	Lower positive control
LPLV	Last patient last visit
LVEF	Left ventricular ejection fraction
M	Male
MAA	Marketing Authorization Application
mAb	Monoclonal antibody
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRI	Magnetic resonance imagery
MTD	Maximum tolerated dose
MUGA	Multigated acquisition
N or n	Number
N/A	Not applicable
Nab	Neutralizing antibody
NCA	Noncompartmental analysis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not estimable
NIH	National Institute of Health

NONMEM	Nonlinear Mixed Effects Modelling
OBD	Optimal biologic dose
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PC	Positive control
pcVPC	Prediction-corrected visual predictive check
PD	Pharmacodynamic
PFS	Progression-free survival
PI	Prediction interval
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PR	Partial response
PS	Performance status
PSC	Primary sclerosing cholangitis
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QC	Quality control
QTc	Corrected QT
QTcF	QT interval corrected for heart rate according to the Fridericia formula
QW	Once a week
RBC	Red blood cell
RC_{trough}	Accumulation index
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
sHER2	Soluble human epidermal growth factor receptor 2

sHER2-ECD	soluble HER2 extracellular domain
SMC	Safety Monitoring Committee
SMQ	Standardized MedDRA query
SOC	System organ class
StD	Standard deviation
$t_{½}$	Terminal half-life
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TMDD	Target-mediated drug disposition
TK	Toxicokinetic
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
US	United States
V_c	Central volume of distribution
V_d	Volume of distribution in the terminal elimination phase
V_p	Peripheral volume of distribution
VPC	Visual predictive check
V_z	Volume of distribution in the terminal elimination phase
ZW25	Zanidatamab

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Jazz Pharmaceuticals Ireland Limited submitted on 23 May 2024 an application for marketing authorisation to the European Medicines Agency for Ziihera, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Ziihera was designated as an orphan medicinal product EU/3/21/2458 on 19 July 2021 in the following condition: treatment of biliary tract cancer.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ziihera as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/ziihera

The applicant applied for the following indication:

Ziihera is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0433/2023 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation and accelerated assessment

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance zanidatamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
12 October 2023	EMA/SA/0000149077	*Dieter Deforce, Jens Reinhardt*
9 November 2023	EMA/SA/0000149081	*Dieter Deforce, Livia Puljak*

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Analytical comparability strategy for the active substance and finished product to support registration of a new commercial manufacturing site; need for additional non-clinical or clinical data to support such change; strategy to determine shelf life; active substance and finished product release and stability specifications; inclusion of a post-approval change management protocol in the initial MAA submission to qualify additional finished product manufacturers post- approval; use of a commercial kit to detect host cell protein in the active substance.
- Adequacy of the nonclinical development to support the MAA.
- Adequacy of the clinical pharmacology programme; proposed submission of a conditional MAA, in particular the intended evidence for efficacy and safety database and safety analyses; the proposed Phase 3 study as a confirmatory study; CDx strategy of immunohistochemistry testing for HER2.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

CHMP Rapporteur: Boje Kvorning Pires Ehmsen CHMP Co-Rapporteur: Robert Porszasz

The application was received by the EMA on	23 May 2024
The procedure started on	20 June 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	9 September 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	24 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 September 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 October 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 December 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	25 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	9 April 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Updated Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 April 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ziihera on	25 April 2025
The CHMP adopted a report on similarity of Ziihera with Tibsovo and Pemazyre on (see Appendix on similarity)	25 April 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	25 April 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant seeks a marketing authorisation for the medicinal product Ziihera (zanidatamab) with the following therapeutic indication:

"Ziihera is indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC)."

2.1.2. Epidemiology and risk factors

Biliary tract cancer (BTC) is a collective term for a group of rare, often fatal gastrointestinal tract cancers, accounting for approximately 1% of all adult cancers, and includes cholangiocarcinoma (CC) and gallbladder cancer (GBC) (Valle et al. 2017). Patients with BTC have a 5-year OS rate of 19.1% for regional disease and 3% for distant disease (NIH SEER, 2023; Koshiol et al. 2022). Newly diagnosed patients undergo surgical intervention with curative intent (approximately 15% to 40%; Jansen et al. 2020) or have unresectable disease requiring systemic interventions (60% to 85%). The relapse rate is high and survival for advanced disease is very poor (5-year survival rates: approximately 10% for stage III disease and 0% for stage IV disease per American Joint Committee on Cancer classification) (Valle et al. 2017; Yoo et al. 2021).

2.1.3. Biologic features and pathogenesis

Biliary tract cancers represent a heterogeneous group of diseases that likely arise from multifactorial processes and depend on familial genetic predisposition and environmental factors (Ishiguro et al. 2008; Bridgewater, et al. 2014; Marcano-Bonilla et al. 2016). Both CC and GBC and are associated with distinct risk factors, molecular characteristics, and symptoms at presentation. Infection with liver fluke Opisthorchis viverrini is a risk factor for ICC and ECC but not GBC, while cholelithiasis (gall stones) is one of the most strongly associated risk factors for GBC. Patients with GBC are less likely to present with jaundice than patients with ICC or ECC (Valle et al. 2017). Chronic liver disease (cirrhosis and viral hepatitis), obesity, diabetes, and alcohol are also recognized as risk factors, especially for the development of ICC (Bridgewater et al. 2014; Blechacz et al. 2017). A less commonly recognized cause of CC is biliary-enteric drainage, which can cause bile stasis, inflammation, and stone formation (Razumilava et al. 2013). However, many patients diagnosed with CC have no identifiable predisposing risk factor. Gallbladder cancer risk factors include gallstone disease (cholelithiasis, the strongest risk factor for GBC, present in 70-90% of GBC cases), porcelain gallbladder, gallbladder polyps, anomalous pancreaticobiliary duct junctions, inflammatory bowel disease, Primary sclerosing cholangitis (PSC), chronic infection (e.g. Salmonella typhi and paratyphi and Helicobacter bilis and pylori), congenital malformations, and obesity (Zhu et al. 2010; Kanthan et al. 2015; Bridgewater et al. 2016; Marcano-Bonilla et al. 2016).

The rates of BTC vary by geographical region, with the incidence of BTC several-fold higher in Asia, eastern Europe, and South America (Bridgewater et al. 2014; Hundal et al. 2014; Ayasun et al. 2023) than in North America and western Europe.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Cholangiocarcinoma accounts for 10% to 15% of primary liver cancers (Vogel et al. 2023). It is generally categorized as either intrahepatic (ICC) or extrahepatic (ECC) based on anatomic location. Approximately 5-10% of CCs are ICC and arise from peripheral bile ducts within the liver parenchyma (Kodali et al. 2021). The majority (60-70%) of ECCs are perihilar or Klatskin tumours involving the hepatic duct bifurcation; the remaining ECCs involve the distal common bile duct.

A published systematic literature review and meta-analysis of published data reporting HER2 status by IHC in BTC showed that among 38 studies (in a total of 3839 participants) the mean prevalence of HER2 overexpression was 26.5% (95%CI: 18.9, 34.1) (Galdy et al. 2017).

2.1.5. Management

Per current guidelines in the US and the EU, the current recommended first-line systemic therapy for patients with inoperable, locally advanced or metastatic disease now consists of combination chemotherapy with cisplatin and gemcitabine (CisGem) with or without the PD-L1 inhibitor durvalumab (CisGemDurva) or the PD-1 inhibitor pembrolizumab (Kelley et al. 2023; NCCN, 2023; Vogel et al. 2023). Despite the addition of immune checkpoint inhibitors to the standard of care, expected survival is still poor for patients with advanced BTC with only approximately one-quarter of patients alive at 2 years from the start of therapy (Oh et al. 2022).

There is significant unmet need for additional second-line treatments in BTC. No treatment method has been established yet as standard second-line therapy. Historically, chemotherapies have shown modest clinical benefit in the second-line or later setting and are associated with significant toxicity burden for these patients.

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 et al. 2018). The 2023 NCCN and ESMO guidelines include the combination of trastuzumab and pertuzumab as an option for pretreated HER2-positive advanced BTC (NCCN, 2023; Vogel et al. 2023), but none of these products are currently approved in the EU for such indication. The recently released 2025 ESMO guideline includes trastuzumab deruxtecan based on its FDA approval and zanidatamab based on its FDA accelerated approval (Vogel et al. 2025).

2.2. About the product

Zanidatamab is a dual HER2-targeted bispecific antibody that simultaneously binds extracellular domains 2 and 4 on separate HER2 monomers (binding in trans). Binding of zanidatamab with HER2 results in internalization leading to a reduction of the receptor on the cell surface. Zanidatamab induces complement-

dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumour growth inhibition and tumour cell death.

The final indication is:

"Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy (for biomarker-based patient selection, see section 4.2)."

Ziihera must be initiated by a physician experienced in the diagnosis and treatment of patients with biliary tract cancer.

Patients treated with Ziihera for BTC should have documented HER2-positive tumour status, defined as a score of 3 + by immunohistochemistry (IHC) assessed by a CE-marked *in vitro* diagnostic (IVD) medical device with the corresponding intended purpose. If a CE-marked IVD is not available, an alternate validated test should be used.

Posology:

The recommended dose of Ziihera is 20 mg/kg, administered as an intravenous infusion every 2 weeks (every 14 days) until disease progression or unacceptable toxicity.

Premedication should be administered 30 to 60 minutes prior to each Ziihera infusion to prevent potential infusion related reaction. Premedication is recommended to include a corticosteroid, antihistamine, and antipyretic.

Dose modifications for left ventricular dysfunction

Left ventricular function must be assessed at baseline and at regular intervals during treatment.

The recommendations on dose modifications in the event of left ventricular ejection fraction (LVEF) decrease are indicated in Table 1.

Table 1: Dose modifications for left ventricular dysfunction

Left ventricular dysfunction	Severity	Treatment modification
	Absolute decrease of ⩾ 16% points in LVEF from pre-treatment baseline	• Withhold Ziihera for at least 4 weeks. • Repeat LVEF assessment within 4 weeks. • Resume treatment within 4 to 8 weeks, if LVEF returns to normal limits and the absolute decrease is ⩽ 15% points from baseline. • If LVEF has not recovered to within 15% points from baseline, permanently discontinue.
	LVEF value below 50% and absolute decrease of ⩾ 10% points below pre-treatment baseline	

Dose modifications for infusion related reactions

Management of infusion related reaction (IRRs) may require reduced infusion rate, dose interruption, or treatment discontinuation of Ziihera as described in Table 2.

Table 2: Dose and infusion duration modifications for infusion-related reactions

Infusion related reactions	Severity	Treatment modification

	Mild (Grade 1)	• Reduce infusion rate by 50%. • Subsequent infusions should start at this reduced rate. • Infusion rate for subsequent Ziihera infusions may be increased gradually to the rate prior to symptoms, as tolerated.
	Moderate (Grade 2)	• Hold infusion immediately. • Treat with appropriate therapy. • Resume infusion at 50% of previous infusion rate once symptoms resolve. • Infusion rate for subsequent Ziihera infusions may be increased gradually to the rate prior to symptoms, as tolerated.
	Severe (Grade 3)	• Hold infusion immediately. • Promptly treat with appropriate therapy. • Resume infusion at the next scheduled dose at 50% of previous infusion rate once symptoms resolve. • Permanently discontinue for recurrent Grade 3 symptoms.
	Life threatening (Grade 4)	• Hold infusion immediately. • Promptly treat with appropriate therapy. • Permanently discontinue.

Dose modifications for pneumonitis

Management of pneumonitis may require treatment discontinuation of Ziihera as described in Table 3.

Table 3: Dose modifications for pneumonitis

Pneumonitis	Severity	Treatment modification
	Confirmed Grade ⩾ 2	• Permanently discontinue.

Missed dose

If a patient misses a dose of Ziihera, the scheduled dose should be administered as soon as possible. The administration schedule should be adjusted to maintain a 2-week interval between doses.

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that the claimed benefit from zanidatamab in the targeted population with advanced HER2+ biliary tract cancer (ORR ~41%) is not of sufficient magnitude to impel expeditious access to this product. Despite the unmet medical need, the rarity of this setting and the lack of approved HER2-targeted products, the caveats from uncontrolled data are not overcome by claimed benefits from this new anti-HER2 product, and thus it does not seem that zanidatamab is likely to be of major public health interest from the public health perspective.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

Zanidatmab, a dual HER2-targeted bispecific antibody, is a new and novel targeted agent for the treatment of subjects with unresectable locally advanced or metastatic HER2 positive BTC. This initial MAA is based on data from phase I study ZWI-ZW25-101 (study 101) and phase IIB study ZWI-ZW25-203 (study 203). Study 101 is a supportive study as it was performed in participants with locally advanced (unresectable) and/or

metastatic HER2-expressing cancer that progressed after receipt of all therapies known to confer clinical benefit with zanidatamab monotherapy (Part 1 and Part 2 of the study). Part 2 of the study included a zanidatamab monotherapy expansion cohort of participants with BTC (N=22), which is relevant to the proposed indication. Study 203 (N= 80 for Cohort 1), the pivotal study supporting this MAA, is an open-label single-arm study evaluating the antitumour activity of zanidatamab monotherapy in participants with HER2-gene-amplified, unresectable, and advanced or metastatic BTC, who had received at least 1 prior gemcitabine-containing regimen of systemic therapy for advanced disease and had experienced disease progression after or developed intolerance to the most recent prior therapy. The median duration was 21.9 months (range, 16 to 34 months). A clinically meaningful confirmed ORR (41.3%; 95% CI: 30.4, 52.8) including 2 CRs was demonstrated. The results also show sustained DOR (14.92 months; 95% CI: 7.39, NE; range, 1.5 to 20.6) with 84.8% of participants having a DOR of at least 16 weeks (the longest ongoing response as of the DCO was 20.3 months). Overall, the results of study 203, together with consistent supportive results from study 101, pooled data, and participant subgroups, provide substantial evidence of a positive benefit-risk assessment for zanidatamab treatment of patients with HER2+ BTC.

- It is likely that the applicant will be able to provide comprehensive data.

The applicant is proposing the ongoing phase III study JZP598-302 evaluating the efficacy and safety of the combination of zanidatamab plus cisplatin-gemcitabine with or without PD-1/L1 inhibitor (physician's choice of either durvalumab or pembrolizumab, where approved under local regulations) as compared with cisplatin-gemcitabine with or without PD-1/L1 inhibitor as first-line treatment for participants with HER2-positive locally advanced (unresectable) or metastatic BTC as a specific obligation to confirm the clinical benefit of zanidatamab in patients with HER2+ BTC in 2+L.

- Unmet medical needs will be addressed.

Standard of care first-line therapy for patients with BTC recurring after and/or not eligible for surgery consists of gemcitabine and platinum with or without durvalumab (Squadroni et al. 2017; Oh et al. 2022). Most patients have disease progression after treatment and patients with alteration in *ERBB2* (the gene that encodes the HER2 protein) have a markedly shorter time to progression on first-line therapy than do patients without this mutation (Lowery et al. 2018). The predictive and prognostic implications of HER2 expression in BTC have not been fully established for patients with metastatic disease, though most available data suggest worse or similar outcomes to combination chemotherapy (Lamarca et al. 2014; Lowery et al. 2019; Vivaldi et al. 2020; Roa et al. 2014; Albrecht et al. 2020; Kim et al. 2022). Historically, chemotherapies have shown modest clinical benefit in the second-line or later setting and are associated with significant toxicity burden for these patients. Options include capecitabine plus oxaliplatin; capecitabine plus irinotecan; gemcitabine plus oxaliplatin; gemcitabine plus capecitabine; capecitabine plus cisplatin; fluorouracil plus leucovorin (folinic acid) and irinotecan with or without bevacizumab; mFOLFOX; or liposomal irinotecan with fluorouracil and leucovorin. Overall, these treatment regimens have an ORR of approximately 3% to 15% and short DOR with a median time to failure of approximately 2.2 months (95% CI: 1.8-2.7) (Lowery et al. 2019; Brieau et al. 2015). The median PFS and OS with these chemotherapies were approximately 3 to 4 months and 6 to 7 months, respectively, depending on the particular regimen (Brieau et al. 2015; Fornaro et al. 2015; Lamarca, 2014 et al.; Lamarca et al. 2021; Yoo et al. 2021).

In recent years, molecularly targeted agents have been approved by the EMA for second-line or later treatment for patients with advanced/metastatic BTC. These agents include:

- Pembrolizumab (Keytruda, 2022), for the treatment of adult patients with metastatic MSI-H or dMMR

solid tumours that have progressed following previous treatment.

- Two kinase inhibitors, pemigatinib (Pemazyre, 2021) and futibatinib (LYTGOBI, 2023), that are indicated for the treatment of patients with previously treated, unresectable locally advanced or metastatic CC with a FGFR2 fusion or other rearrangement.
- An IDH1 inhibitor, ivosidenib (TIBSOVO, 2023), which is indicated for the treatment of patients with locally advanced or metastatic refractory CC that bears a susceptible IDH1 mutation.

Although HER2 is a validated therapeutic target, there are no approved agents specifically for HER2 amplified or expressing BTC. Drugs targeting HER2 have been evaluated previously in small studies as a potential treatment for BTC. The combination regimen of trastuzumab and pertuzumab has been studied in MyPathway (NCT02091141), a non-randomised, phase IIa multi-basket study in which subjects with advanced solid tumours bearing HER2 gene (*ERBB2*) amplification and/or overexpression were treated with a combination regimen of trastuzumab and pertuzumab (Javle et al. 2021). In this study, 9 of 39 previously-treated patients with advanced/metastatic BTC achieved a PR (ORR 23% [95% CI: 11–39]). Median DOR was 10.8 months (95% CI: 0.7–25.4) and estimated OS at 1 year was 50% (95% CI: 33–64). But such combination is not yet approved.

Thus, significant and urgent unmet medical needs exist for effective treatment options for patients with advanced/metastatic HER2-positive BTC who have progressed on prior systemic therapy.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Zanidatamab, which has a well characterised mechanism of action and a manageable safety profile, can fill the treatment gap that exists for HER2-amplified BTC patients and represents a substantial benefit improvement over existing non-targeted therapies for BTC in the second-line setting. Zanidatamab consistently demonstrated clinically meaningful efficacy benefits in subjects with previously treated advanced/metastatic HER2 positive BTC in study 203 (28 July 2023 DCO preliminary data) and in study 101.The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Acknowledging the challenges of conducting large clinical trials in such a relatively rare malignancy, the applicant considers the totality of the data presented sufficient to evaluate the benefit/risk profile of zanidatamab. The promising results demonstrate a favourable benefit/risk profile with clear clinical benefit in the treatment of patients with HER2-positive BTC, which greatly outweighs associated risks. The existing data presented herein are sufficiently compelling to warrant a rapid approval (with the goal of providing broad access to patients) while confirmatory evidence is being generated in the phase III study JZP598-302. The applicant considers it in the best interest of the public to bring this therapeutic option to patients as expeditiously as possible and is thus seeking a conditional marketing authorisation.

2.1. Quality aspects

2.1.1. Introduction

The finished product (FP) is presented as a powder for concentrate for solution for infusion containing 300 mg of zanidatamab as active substance (AS).

Other ingredients are: polysorbate 20, disodium succinate, succinic acid, sucrose and water for injections.

The product is available in a 20 mL Type I glass vial with a chlorobutyl stopper and flip-off cap, containing 300 mg zanidatamab, in a pack size of 1 or 2 vials.

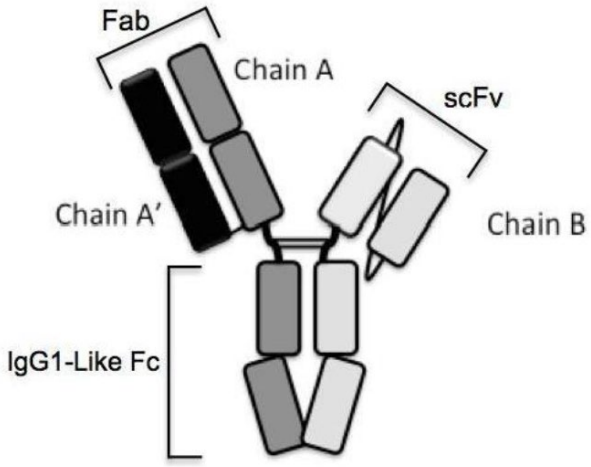
2.1.2. Active Substance

2.1.2.1. General Information

Zanidatamab is a recombinant, humanised, bispecific IgG1 monoclonal antibody recognising two non-overlapping epitopes of the extracellular domain of the human HER2 antigen. It is expressed in a genetically engineered Chinese hamster ovary (CHO) cell line. The Fc region of zanidatamab contains complementary mutations in each CH3 domain that impart preferential pairing to generate a heterodimeric molecule. Chain A is otherwise a normal IgG1 heavy chain and forms a Fab through pairing with IgG Kappa light Chain A'. Chain A binds to ECD2 of HER2. Chain B has an IgG1-like hinge, CH2 and CH3 domains but contains a single chain variable fragment (scFV) domain rather than a Fab arm. Chain B binds to ECD4 of HER2. In place of the CH1 domain, it has a VL domain, an unstructured 20 amino acid linker of glycine and serine residues, followed by a VH domain to form a scFV antibody variable domain. Two N-linked glycosylation sites are present in the CH2 domain on each heavy chain. Zanidatamab is predominantly core fucosylated.

The two binding arms bind to separate HER2 receptor molecules, translinking them, and inducing the formation of receptor clusters and receptor internalisation, resulting in downregulation. This downregulation inhibits growth factor-dependent and -independent tumour cell proliferation. Antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) also contribute to zanidatamab's overall effect of tumour cell death and growth inhibition *in vitro* and *in vivo*.

Figure 1 Structure of zanidatamab



2.1.2.2. Manufacture, process controls and characterisation

The zanidatamab active substance is produced and tested at WuXi Biologics Co. Ltd., Jiangsu, China. Additional sites are indicated for working cell bank (WCB) production, and WCB/master cell bank (MCB) storage. Adequate documentation has been provided to demonstrate compliance with GMP.

The active substance manufacturing process is using a standard upstream process for a monoclonal antibody based on culturing of recombinant CHO cells. The production bioreactors content is harvested to remove cells and cell debris and filtered using a guard filter and bioburden reduction filters prior to further purification.

The purification steps are typical for monoclonal antibody manufacturing including a series of chromatography steps and virus reduction steps.

Critical and key process parameters (CPPs and KPPs) have been identified for the manufacturing process. The proposed CPPs and KPPs, and associated proven acceptable ranges (PARs), are considered acceptable.

In-process testing for safety attributes includes minute virus of mice, *in vitro* assay for adventitious virus, mycoplasma and bioburden at harvest and bioburden, and bacterial endotoxins on the harvest clarified pool. For the downstream process in-process testing for bioburden and bacterial endotoxins is performed at each process operation step. Safety parameters are considered adequately tested, and the proposed acceptance criteria are found acceptable.

The analytical procedures used for in-process testing are described. Sufficient information on method validation is provided.

Controls of process/performance attributes are in place for both the upstream and downstream processes. These include cell viability and viable cell density performed at different steps of the upstream process, titer, pH, conductivity, step yield, filter integrity, and product concentration. Attributes are classified as critical process attribute (CPA) or key process attribute (KPA) with an associated acceptance criterion and an action limit. This is found acceptable.

Hold times are proposed and found adequately validated. Cleaning procedures are described

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications for non-compendial raw materials are presented. Raw materials of animal or human origin used in the manufacture of active substance are the production cell line and a component in the cell culture media. A certificate of origin and BSE/TSE statement from the supplier are provided.

Zanidatamab is produced through stable expression in a recombinant CHO cell line. Historically, two production cell lines were generated. As the productivity of the first generation GEN1 cell line was low, a second generation GEN2 cell line was developed for late-stage clinical and commercial production.

Screening and subcloning procedures have been described in sufficient detail.

The generation of MCB and working cell bank (WCB) has been described adequately. Cells from the WCB are used to initiate the production process. An end-of-production (EOP) cell bank was also generated to demonstrate the stability of the cell line.

MCB, WCB and EOP cell banks were characterised according to ICH Q5A, Q5B and Q5D guidelines, addressing microbial and viral purity, host cell identity and genetic stability. It is confirmed that the methods used for genetic characterisation of cell banks have been appropriately validated/qualified. A procedure to establish future WCBs is described.

Process validation

Process validation studies were conducted both at the commercial manufacturing scale and in qualified scale-down models (SDM).

The qualification of the zanidatamab active substance manufacturing process was performed at WuXi Biologics. Consecutive process CMP-WX-W batches originating from independent thaws were manufactured in the process performance qualification (PPQ) campaign.

CPPs and KPPs were monitored to demonstrate that the manufacturing process could be executed within the established PARs/normal operating ranges (NORs). CPAs and KPAs were evaluated to assure the process performed as designed. In summary, the data presented demonstrate that all CPPs and KPPs were within NOR and PAR, and all CPAs and KPAs were within their predefined acceptance criterion. There was no deviation to a CPP, CPA, KPP, or KPA with a process-related cause. All deviations were investigated and it was concluded that they did not impact process performance and product quality. Assessment for each deviation is endorsed and it can be agreed that the deviations did not have any impact on the overall qualification of the active substance manufacturing process.

Resin lifetime studies

Sufficient information is provided on the reuse of chromatography resins. The number of reuse cycles was evaluated based on small-scale reuse studies and is concurrently verified at manufacturing scale, which is considered acceptable. Resin performance was assessed by measuring the evolution of the yield, eluate volume, process-related impurities, and product-related impurities. No correlation in the variation of these parameters with column usage was found, except for minor trends.

Blank cycles were performed at regular intervals to assess the efficiency of the cleaning procedures and potential carryover.

Process hold times

Biochemical stability was evaluated. In addition to the hold study for each intermediate, a cumulative hold study was conducted in which each intermediate was held for the maximum allowable time before being forward processed. Relevant quality and process attributes were evaluated. In general, it is found that product quality is acceptable for the duration of the proposed hold times.

The strategy for the microbial hold time study was to use a surrogate approach. An evaluation summary is provided and concluded that the representative containers and hold times are included in the platform database and no additional hold studies or sampling were required. The approach taken and the evaluation of the risk assessment can be supported. Overall, the proposed hold times can be considered validated.

Impurity clearance

Clearance of the process-related impurities was evaluated in the in-process pools of the PPQ batches. From the data submitted, it is agreed that the purification process is capable of reducing process-related impurities to low levels to result in minimal safety risk. Reduction of product-related impurities is also demonstrated.

Impurity clearance was also evaluated in small-scale studies. Overall, it is considered demonstrated that the purification process provides effective and consistent clearance capacity of process- and product-related impurities.

Limit of in vitro cell age (LIVCA)

The LIVCA was established. All in-process performance results were within the acceptance criteria and the active substance release results met the specifications. Genetic stability testing results on the EOP cell bank were comparable to MCB and WCB, and the safety testing results met the acceptance criteria.

Extractables and leachables

All plastics and elastomers in direct or indirect contact with the active substance were evaluated for their impact on product quality and patient safety. All items with a medium risk were further evaluated using a toxicological assessment based on the maximum daily intake of impurities. The results of the assessment are submitted and all items are below the safety concern threshold. This is considered acceptable.

Manufacturing process development

The original process was developed from the MCB of GEN1 cell line and with G1 formulation and generated material used for toxicological studies and phase 1 clinical studies. The process was transferred and was used to produce material for phase 1 and phase 2 clinical studies. Development was transferred to another site which established a new process with a new production cell line (GEN2) and a new formulation. This process, was initiated from the MCB of GEN2 cell line, and generated material for toxicological and phase 1 clinical studies as well as for the pivotal phase 2 trial. The process was further developed into a version which started from the WCB of GEN2 cell line. In view of commercialisation, the process was transferred to WuXi Biologics and scaled-up to process G2-WX-W. Finally, process CMP-WX-W was developed as the commercial process at WuXi Biologics. This process generated the PPQ batches.

The changes made during development reflect changes to improve process robustness, increase productivity or changes related to the development of GEN2 cell line and formulation change, as well as facility fit and batch scale up. The changes implemented have been adequately described and justified.

The comparability exercise encompasses several studies to compare material from the different processes. As material for the pivotal clinical trial was not manufactured with the commercial process, emphasis is made to compare these processes.

In conclusion, comparability across the different manufacturing processes is considered sufficiently demonstrated.

Process characterisation

Quality attributes for zanidatamab were assessed for their potential impact on biological activity, PK/PD, immunogenicity, and safety to determine their criticality. Clinical experience, product knowledge, and process understanding, as well as industry standards, were considered. A numerical scoring system, including scores for impact and uncertainty, was used based on data from all historical batches. The overall criticality rating of each attribute was the product of the impact and the uncertainty scores. The strategy used for identification and criticality assessment of the quality attributes is considered thorough, and the identified critical quality attributes (CQAs) are endorsed. A control strategy for each attribute based on process characterisation and manufacturing experience or process development data is proposed and found acceptable.

A failure mode and effects analysis (FMEA) was conducted for each unit operation to assess the criticality of all process parameters. Historical process data, knowledge from similar processes and literature data were used in the assessment. The FMEA identified potential critical and key parameters, each parameter's final risk rating was confirmed after process characterisation.

Process characterisation studies were either univariate or multivariate studies planned and evaluated using design of experiment (DOE) concepts.

Overall, the strategy applied for process characterisation, including the process parameters selected for investigation, the qualification strategy of the SDMs, and the conduction of the process characterisation studies, is considered comprehensive and appropriate. Identified KPPs and CPPs are considered adequate.

Characterisation

Zanidatamab consists of an A-half, formed by IgG1 heavy chain A (HA) and kappa light chain A' (LC), and the B-half, formed by IgG1 heavy chain B (HB), engineered to contain an scFv arm. The Fc domains are mutated to facilitate A:B heterodimerisation.

Overall, the structure and other characteristics of zanidatamab are considered well characterised. Tested quality attributes include: Primary structure, glycosylations, molecular weight, secondary and higher-order structure, size variants, charge variants, and biological activity. The characterisation methods are confirmed to be fit for purpose.

Primary structure

Experimental extinction coefficient: The extinction coefficient was determined. The result was considered sufficiently close to the theoretical value to keep using that value when measuring protein concentration. This is considered acceptable.

Sequence confirmation: Peptide mapping was carried out. Peptides with masses corresponding to the expected sequence were detected, and no amino acid mis-incorporation was observed in the data.

Post translational modifications (PTMs): The peptide mapping MS/MS data were also used to evaluate the occurrence of PTMs.

Disulfide bonds: The predicted pattern was confirmed by peptide mapping LC-MS/MS.

Glycosylations

N-glycosylation sites: The presence was confirmed using peptide mapping LC-MS/MS.

N-glycoform profiling: species were detected by HILIC-HPLC and HILIC-MS/MS.

Molecular weight

Molecular integrity by non-reduced LC-MS: Molecular mass data have been provided.

Quaternary structure: SEC-MALS was carried out. Ultracentrifugation-sedimentation velocity (AUC-SV) was also used.

Secondary and higher-order structure

CD spectroscopy was carried out. In addition, thermal transition points were determined by DSC.

Free sulfhydryls were tested

Size variants

Data generated using SE-HPLC and

CE-SDS was provided.

Charge variants

CEX-HPLC: Each charge group, i.e. acidic, main, and basic, was enriched and tested for composition by SEC-HPLC and peptide mapping MS. Each charge group was found to have activity comparable to unfractionated active substance, as measured by any of the potency assays used at release.

Biological activity

Activity was tested using the potency release methods, i.e. pertuzumab and trastuzumab competition binding activity ELISA, anti-proliferation cell-based assay, and ADCC cell-based assay.

Forced degradation

Tested conditions are thermal stress (high pH), oxidative stress and light stress.

Product-related impurities

The applicant considers the product related impurities to be well controlled by the manufacturing process, and through specification testing. It is agreed that the species in question are overall sufficiently controlled. Information on post-translational modification impurities has been provided in the dossier.

Process-related impurities

The process-related impurities identified by the applicant are: Cell-substrate derived impurities (HCP, DNA), process reagents/materials/leachates and microbial and viral impurities and contaminants. HCP, DNA, endotoxin, and bioburden are controlled by the active substance release specification. PPQ batch results demonstrate clearance to low and acceptable levels. Small scale studies to evaluate clearance of several process-related impurities have also been conducted, and demonstrated robust clearance

2.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The release and shelf-life specification for the active substance is provided. The release specification includes the general tests for Appearance (Colour, Clarity), pH and Osmolality, test for identity, purity and impurity tests for product-related variants test for protein content (Spectroscopy), tests for potency, test for residual Host cell protein, Residual DNA (qPCR) as well as tests for safety (Bioburden and Bacterial endotoxins).

The panel of methods used to assure the quality of the active substance is in accordance with ICH Q6B and Ph. Eur. Overall, the parameters included in the active substance specification are found acceptable to control the quality of the active substance at release and during shelf life.

The active substance specifications have been set based on data from pivotal clinical trial batches and PPQ batches considered to appropriately incorporate clinical experience and commercial process capability. For setting the acceptance criteria, release data, statistical analysis and stability trends have been employed. In general, it is considered that the acceptance criteria are clinically justified.

Analytical procedures

The analytical procedures used are a combination of compendial and non-compendial methods. Methods applied to both active substance and finished product are described in the active substance section.

The analytical procedures are described in sufficient details. The compendial methods Appearance (Color, Clarity), pH, Osmolality, Bioburden and Bacterial endotoxins are performed in accordance with the methods described in Ph. Eur.

Method suitability verification has been presented for all compendial methods and the methods are considered suitable for their intended use.

For Bacterial Endotoxins, method suitability verification has been performed for both AS and FP and in-process samples demonstrating endotoxin recovery in the presence of the samples. Low endotoxin recovery hold time study has been additionally performed on the FP.

System suitability testing of the bioburden membrane filtration method was performed for both AS and FP and in-process samples.

The non-compendial analytical procedures are appropriately described and validated.

System suitability criteria, based on the applied reference standards and controls, are specified and found adequate to confirm that the methods are in control during routine testing.

Reference standards

Different reference standards (RS) were used during development. Comparability has been demonstrated between the different manufacturing processes. The RS are stored as aliquots.

Release testing and extended characterisation were performed to qualify each RS. The acceptance criteria for release tests were those in place at the time of release.

A procedure to establish and qualify future primary or secondary RS is presented and found acceptable.

Batch analysis

Batch analysis data have been provided for the Wuxi Commercial Scale PPQ Batches and active substance batches manufactured by earlier processes.

The test methods employed and the specification for release testing of the batches were those valid at the time of testing. All batch data complied with the specifications valid at the time of testing.

Overall, it is found that the batch data confirm batch-to-batch consistency and process comparability.

Container closure

The active substance is stored in sterile single-use bags. Compatibility between the container closure system and the active substance was evaluated through stability studies. Safety of the container closure system was evaluated by extractables and leachables studies.

2.1.2.4. Stability

The proposed shelf life for Zanidatamab active substance is 24 months at -70°C ± 10°C.

The stability studies are designed in accordance with the ICH Q5C guideline. The proposed shelf life is supported by real-time stability data from primary studies and supporting studies.

The stability studies at the long term storage condition are ongoing. Testing intervals are in accordance with ICH Q5C.

The panel of tests conducted in the stability program is found comprehensive and appropriate.

The provided stability commitment and a post-approval stability protocol are found acceptable.

All stability data provided at the long-term storage condition at -70°C ± 10°C are within specification, with no substantial changes in any attribute assessed. In general, parallel shifts have been observed at accelerated and stressed conditions for both the primary and supporting stability data.

The data provided by the applicant support the suggested shelf-life of 24 months at -70°C ± 10°C for the active substance.

2.1.3. Finished Medicinal Product

2.1.3.1. Description of the product and pharmaceutical development

The finished product is formulated at 50 mg/mL in succinate, sucrose, and polysorbate 20. It is supplied as a sterile, preservative free, lyophilised, white cake. The labelled content is 300 mg of zanidatamab. All used excipients are well-known and compendial, and their functions are indicated.

For administration, the product is reconstituted with sterile water for injection. To ensure a withdrawable volume of 6.0 mL, an overfill is applied. A reconstitution volume of 5.7 mL is used. The reconstituted finished product is colourless to light yellow, clear to slightly opalescent, and essentially free of particles. Overages are not applied.

Table 4 Finished product composition

Component [a]	Quality Standards	Pharmaceutical Function	Strength	
			Labeled Qty (mg) per Vial [b]	Concentration after Reconstitution [c]
Zanidatamab	In-house	Active ingredient	300	50 mg/mL
Disodium succinate (sodium succinate anhydrous)	USP-NF	Buffering agent	[redacted]	[redacted]
Succinic acid	USP-NF, JP	Buffering agent	[redacted]	
Sucrose	USP-NF, Ph Eur, JP	Thermal stabilizer	[redacted]	[redacted]
Polysorbate 20	USP-NF, Ph Eur	Surfactant	[redacted]	[redacted]
Water for injection	USP, Ph Eur	Aqueous solvent	qs to target volume	qs to target volume

USP: United States Pharmacopeia; Ph. Eur.: European Pharmacopoeia; JP: Japanese Pharmacopoeia; qs: quantity sufficient

[a] Sterile filtered nitrogen gas is used to backfill the lyophilized drug product vial.

[b] The quantities per vial are based on the 300 mg of labeled content and does not include the overfill.

[c] The composition reflects the product reconstituted in 5.7 mL of sterile water for injection for a withdrawable volume of 6.0 mL.

Information on the Quality Target Product Profile (QTPP) is considered sufficient. The QTPP is based on the properties of the active substance, characterisation and configuration of the finished product, and the intended patient population. It includes dosage form, route of administration, dosage strength and concentration, patient population, quality criteria (appearance, excipients, viscosity, comparability with manufacturing process, impurities, in-use compatibility, microbial limits), climate zone, and shelf life.

Formulation development

Justifications for the choice of each excipient are provided.

Two different formulations have been used during development. The steps taken for development of the generation 1 formulation and further through to the generation 2 formulation are outlined. For each step, changes being explored, conditions tested, and test methods are listed, and the conclusions from each step are summarised.

Forced degradation studies were carried out on both lyophilised finished product (thermal, light) and liquid active substance (thermal, low, pH, high pH, oxidation, agitation, freeze-thaw). Observed degradation pathways are summarised.

Manufacturing process development

The manufacturing process changes, including changes in site and scale, are considered adequately described.

Data has been provided to demonstrate comparability between processes used during the development and the proposed commercial process.

Process characterisation

The process parameters of the finished product manufacturing process were initially evaluated using failure mode effect analysis. Based on the results, risk was categorised as low, medium or high. For medium and high-risk parameters, scaled-down process characterisation studies were carried out. For lyophilisation, two studies were carried out. An initial study where all parameters were set as for the intended commercial process, and a second study where parameters with initial risk ranking of medium or high were varied in a DoE setup. Characterisation studies were also carried out for compatibility of finished product with materials (prefilter, filter, tubing). Results are acceptable.

Post-characterisation risk ranks were assigned for process performance and product quality and then combined, to classify the process parameters as nKPP, KPP, or CPP.

Controls and limits (action limit, alert limit, acceptance criteria) are defined. For each defined KPP and CPP, NOR or PAR ranges are declared and justified based on process characterisation and/or PPQ. The control strategy is acceptable.

Container closure system

The finished product is supplied as a sterile product in a single-dose clear Type I glass vial with an elastomeric stopper and an aluminum overseal with a polypropylene flip-off cap. Compatibility of the container closure system with the finished product is supported by stability data. Suitability of the container closure system is further supported by demonstration of container closure integrity of lots placed on stability, and by extractables/leachables studies, identifying no potential safety risks. The current container closure system has been in use since implementation of the generation 2 formulation. The information is considered sufficient.

Compatibility

The finished product is administered by intravenous (IV) infusion. It is first reconstituted in the vial with sterile water for injection. The reconstituted finished product is added to an IV infusion bag containing 0.9% saline or 5% dextrose, whereby it is diluted to between 0.4 mg/mL and 6.0 mg/mL. The diluted dosing solution is then administered through an infusion set. A 0.2-µm or 0.22-µm in-line filter must be used.

For the reconstituted finished product in vial, physicochemical stability data have been provided. In lieu of microbial challenge data, the applicant has set the in-use stability of reconstituted finished product as maximum 4 hours at room temperature (18-24°C) under ambient light or 4 hours at 2-8°C.

For the diluted product, compatibility was confirmed for a range of closed system transfer devices (CSTDs). IV infusion compatibility was tested for the two applicable diluents, the dilution extremes, and with/without filtration, while varying the contact materials of filters, IV bag, and infusion set. A wide range of commonly used product contact materials was evaluated. The diluted dosing solutions prepared with 0.9% saline or 5%

dextrose at 0.4 mg/mL and 6.0 mg/mL demonstrated physiochemical stability Overall, the in-use stability claims are deemed acceptable.

2.1.3.2. Manufacture of the product and process controls

Jazz Pharmaceuticals Ltd., Dublin, Ireland, carries out quality oversight, importation and QC batch release.

The finished product manufacturing process is typical for a lyophilised biological product. It consists of thawing of the active substance, pooling and compounding, pre-filtration (bioburden reduction), sterile filtration, aseptic vial filling and partial stoppering, lyophilisation and full stoppering, capping, visual inspection, packaging, and storage. The finished product is shipped and stored at 2-8°C. There are no reprocessing steps. For each step, information is provided on in-process controls and tests, in-flows of materials, and process parameter ranges.

All product contact materials are single use and disposable, including filling needles. Information on sterilisation of product contact materials is provided. Bioburden reduction is done and sterilising filtration is carried out The information provided is sufficient.

In-process tests (IPTs) and in-process controls (IPCs) are listed along with their acceptance criteria. There are no intermediates. The information provided is sufficient.

Defined manufacturing limits (processing times, hold times) are presented. The cumulative time out of refrigeration is considered acceptable as based on stability data. The remaining entries are hold times covered by the process validation. A process development study has been carried out to investigate the potential impact of light exposure during routine manufacturing. A worst-case light dose relative to routine manufacturing conditions was applied and no significant changes have been observed in the monitored quality attributes over the course of the study. The study is considered to sufficiently support the manufacturing time limits.

Process validation

PPQ was performed. Process parameters (CPPs, KPPs, nKPPs) and the in-process controls/tests (IPCs, IPTs) were monitored. All parameters are within their PAR/NOR and the acceptance limits were met for the IPCs and IPTs. Hold times were also validated during the PPQ, and the results are considered acceptable.

Media fill study design and results are presented and considered acceptable.

Capping qualification was carried out, and study design and results are considered acceptable.

For both pre-filter and sterilising filter, compatibility with the finished product was tested, and extractable studies using model solvents are presented. For the sterile filter, microbial retention capacity was studied using an appropriate indicator organism. Filter validation is considered acceptable.

Data are also presented for extractables and leachables studies (for product-contact materials of the finished product manufacturing process), cleaning validation (for lyophiliser), decontamination qualification (for washer, depyrogenation tunnel, autoclave, steam-in-place of lyophiliser, vaporised hydrogen peroxide treatment of isolator), and shipping validation (where studies encompassed real-world transport, -20°C to 40°C temperature cycling, and physical stress simulation). The data are considered acceptable.

2.1.3.3. Product specification, analytical procedures, batch analysis

A finished product release and stability specification for Zanidatamab has been proposed. The release specification includes tests for Appearance, Reconstitution Time, Water, Test for Visible and Subvisible Particulates, pH, osmolality, test for Polysorbate 20, test for identity, purity and impurity tests for product-related variants, test for protein content and Extractable volume, tests for potency (Competition binding ELISA against Trastuzumab and Pertuzumab as well as the cell-based Antiproliferation Bioassay and ADCC Bioassay), test for Uniformity of Dosage Units and tests for safety.

Overall, the parameters included in the finished product specification are found acceptable to control the quality of Zanidatamab finished product at release and during shelf life. The specifications have been established based on data from pivotal clinical trial batches and PPQ batches considered to appropriately incorporate clinical experience and commercial process capability. For setting the acceptance criteria, release data, statistical analysis and stability trends have been employed. The establishment of acceptance criteria was additionally supported by characterisation data. It is in general considered that the acceptance criteria for the finished product specification tests are clinically justified.

Overall, the finished product specification and the acceptance criteria have been established in accordance with ICH Q6B.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed, covering raw materials, reagents, and container closure system, as well as pH and temperature. Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical procedures

Methods applied to both active substance and finished product are described in the active substance section.

The compendial methods (Visual Appearance including colour and clarity for the reconstituted solution, Reconstitution time, Water Determination, Visible Particulates, Subvisible Particulates, Extractable volume, Sterility, Container Closure Integrity and Uniformity of dosage units) are performed in accordance with the methods described in Ph. Eur. Data from method suitability verification have been presented for all compendial methods.

The non-compendial methods have been described and validated. The applicant provided the genealogy of method changes occurred per the FP lots, which has been used to establish the specifications. The historical methods and changes have been adequately described. The suitability of the methods for the intended purpose has been confirmed. All methods have been validated after the changes.

Reference standards

The reference standard used for finished product testing is the same as that used for the active substance (refer to the active substance section).

Batch analysis

Batch analyses data have been provided for finished product batches, i.e. Wuxi Commercial Scale (from process P3) batches, including Engineering, Stability and PPQ/stability batches, and Legacy batches. The test methods employed and the specification for release testing of the batches were those valid at the time of testing.

All batch data complied with the specifications valid at the time of testing. It is also found that the batch data confirm batch-to-batch consistency.

Container closure system

The container closure system for the finished product is a 20R clear type I borosilicate glass vial with a coated chlorobutyl stopper, and a flip-off aluminium overseal. Specifications, technical drawings, and example quality certificates are provided. The vial adheres to Ph.Eur. 3.2.1, and the stopper adheres to Ph. Eur. 3.2.9. The information provided is sufficient.

Validation of the sterilisation methods is presented in the of process validation section.

2.1.3.4. Stability of the product

A shelf life of 24 months at 2°C to 8°C is proposed for the finished product.

The stability program includes testing at the long-term condition (2°C to 8°C), accelerated condition (25°C ±2°C, 60% ±5% RH) for 12 months, and stressed condition (40°C ±2°C, 75% ±5% RH) for up to 6 months. Testing intervals are declared, and are in accordance with ICH Q5C.

The batches included in the stability program are four primary stability batches manufactured using the commercial process P3, and three supportive batches from the former processes. The containers used in the stability studies are the same as the commercial containers.

The long-term studies are still ongoing. There have so far been no out of specification results. Plots of the data are shown for stability indicating methods. No clear trends are observed.

The accelerated and stressed studies are completed for all batches in the stability program. All results were within the specifications.

Photostability of the finished product was evaluated during development per ICH Q1B and the data shows no impact to product quality when exposed to light.

In-use stability of the reconstituted finished product and the diluted dosing solution is addressed as part of pharmaceutical development (see above).

A stability commitment and a post-approval stability protocol have been provided and are acceptable.

The proposed shelf life of 24 months at 2°C to 8°C is considered acceptable. The in-use shelf-life as outlined in the SmPC is also considered acceptable.

2.1.3.5. Adventitious agents

Materials of animal origin are the CHO-derived production cell line and a raw material used in the cell culture process. A certificate of origin and a BSE/TSE statement from the supplier of the raw material are provided.

All raw materials are TSE/BSE free and none of the medium components contain serum. Overall, the product is considered safe with regard to non-viral adventitious agents.

Cell banks have been tested for non-viral and viral adventitious agents according to ICH Q5A and ICH Q5D. The MCB, WCB and EOP cell banks were shown to be free of detectable bacterial, fungal and mycoplasma contamination. The MCB and EOP cell banks were tested for viral safety including general *in vitro* assay for adventitious viruses (28 days in MRC-5, Vero and CHO cells as detector cells), *in vivo* assay for inapparent viruses (adult mice, suckling mice, guinea pigs and embryonated eggs), reverse transcriptase activity, detection of retroviruses by cocultivation assay, detection of virus-like particles (transmission electron microscopy in 200 cells) and PCR assay for minute virus of mice. In addition, the MCB was found negative for murine virus by the mouse antibody production test and negative for hamster virus by the hamster antibody production test. The cell banks are therefore considered safe for use in the manufacture of zanidatamab with regard to the risk of viral and non-viral adventitious agents and endogenous retroviruses.

Additionally, the unprocessed pre-harvest bulk of each batch manufactured is tested for bioburden, mycoplasma*, in vitro* adventitious virus and minute virus of mice. A brief description of the methods used for virus testing is provided.

The viral clearance capacity of the zanidatamab downstream purification process was evaluated by conducting virus clearance studies using qualified SDMs in accordance with ICH Q5A. The scale down procedure is considered acceptable and the SDMs are representative of the commercial scale.

The selected model viruses represent a wide range of particle size, genome type, and degree of resistance to chemical treatments as required by ICH Q5A. The assays were conducted under non-cytotoxic and non-interfering conditions.

The virus clearance obtained across the process steps investigated in the virus clearance validation studies is considered acceptable.

End of resin lifetime study and virus carryover study were performed with the four model viruses. In addition, the efficiency of the resin sanitisation procedures for avoiding virus carryover was evaluated.

Overall, the risk of contamination with adventitious agents, including TSE, mycoplasma, bacteria, fungi, and viruses, is considered well contained based on selection of safe raw materials, demonstration of absence of adventitious agents in cell banks, testing at relevant stages of the process, and finally the substantial virus clearance capacity, demonstrated for the zanidatamab purification process. In conclusion, zanidatamab is considered safe for commercial purposes with regard to risk of contamination with adventitious non-viral or viral agents or with endogenous viruses.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

The manufacture of active substance is standard for monoclonal antibody production. Overall, the manufacturing process is considered adequately described and the applied process parameters and in-process controls, as well as their ranges, and the control of starting materials are considered appropriate to control the process and ensure manufacture of active substance of consistent quality. The active substance manufacturing process has been in general appropriately validated, including impurity removal, extractables and leachables, resin lifetime studies and reprocessing. The process development, including development of the control strategy, is considered sufficiently described and justified. Comparability of the proposed

commercial manufacturing process with the earlier processes has overall been adequately demonstrated. The batch data provided demonstrate that the commercial process is capable of manufacturing an active substance of consistent quality.

The selection of the attributes included in the active substance and finished product specifications is based on the control strategy. In general, the approach for selecting attributes and setting acceptance criteria is found acceptable.

The applicant provided data supporting the suggested shelf-life of 24 months at -70°C ± 10°C for the AS.

The finished product manufacturing process is standard and consists of thawing of the active substance, pooling and compounding, bioburden reduction filtration, sterile filtration, aseptic vial filling and partial stoppering, lyophilisation and full stoppering, capping, visual inspection, packaging, and storage. Formulation development is in general appropriate. Comparability studies between the various manufacturing processes that have been in use during development are overall acceptable. The process development studies and the established control strategy, are overall considered sufficiently described and justified. The submitted validation data demonstrate that the process is generally well controlled.

The finished product is presented as a sterile, preservative-free, lyophilised white cake in a 20R Type I glass single-dose vial with a chlorobutyl stopper and a flip off aluminium overseal. The finished product is composed of 50 mg/mL zanidatamab in 10 mM succinate, 9% (w/w) sucrose, and 0.01% (w/w) polysorbate 20, at pH 4.6. For administration, the product is reconstituted with sterile water for injection.

The Applicant presented stability data supporting shelf-life of 24 months at 2-8°C for the finished product. In-use stability for reconstituted finished product and in-use stability of the diluted finished product are acceptable. The presented shelf-life extension plan is endorsed.

At the time of the CHMP opinion, there was one unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the implementation of a two-tiered reference standard. This point is put forward and agreed as a recommendation for future quality development.

2.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.1.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

- To establish a two-tiered reference standard system.

2.2. Non-clinical aspects

2.2.1. Introduction

The non clinical development of zanidatamab was conducted as per International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 Guidelines and Q&As : Nonclinical Evaluation for Anticancer Pharmaceuticals and the M3(R2) guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.

Safety pharmacology, including an assessment of zanidatamab's effect on cardiovascular and respiratory function, was conducted as part of the pivotal GLP-compliant toxicology study. Zanidatamab was evaluated in a comprehensive toxicology program (non-GLP and GLP studies) for IV administration. Intravenous dosing was utilized in all pivotal toxicology studies, as it is the intended route of administration in the clinic, and dosing schedules were adjusted to support the anticipated clinical regimen. The toxicology program was carried out in cynomolgus monkeys, as it was demonstrated that the cynomolgus monkey and human have relevant HER2 sequence homology and affinity. Other toxicology studies, including genotoxicity and reproductive toxicology studies have not been conducted, in accordance with ICH S9 and ICH S6.

EMA Protocol Assistance on the adequacy of the nonclinical package was received on the 9 November 2023.

2.2.2. Pharmacology

2.2.2.1. Primary pharmacodynamic studies

In vitro pharmacology

Table 5 Zanidatamab Affinity for HER2 ECD

HER2 Species	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
Dog	1.03E + 05	4.19E -04	4.07
Rat	No binding	No binding	No binding
Mouse	No binding	No binding	No binding

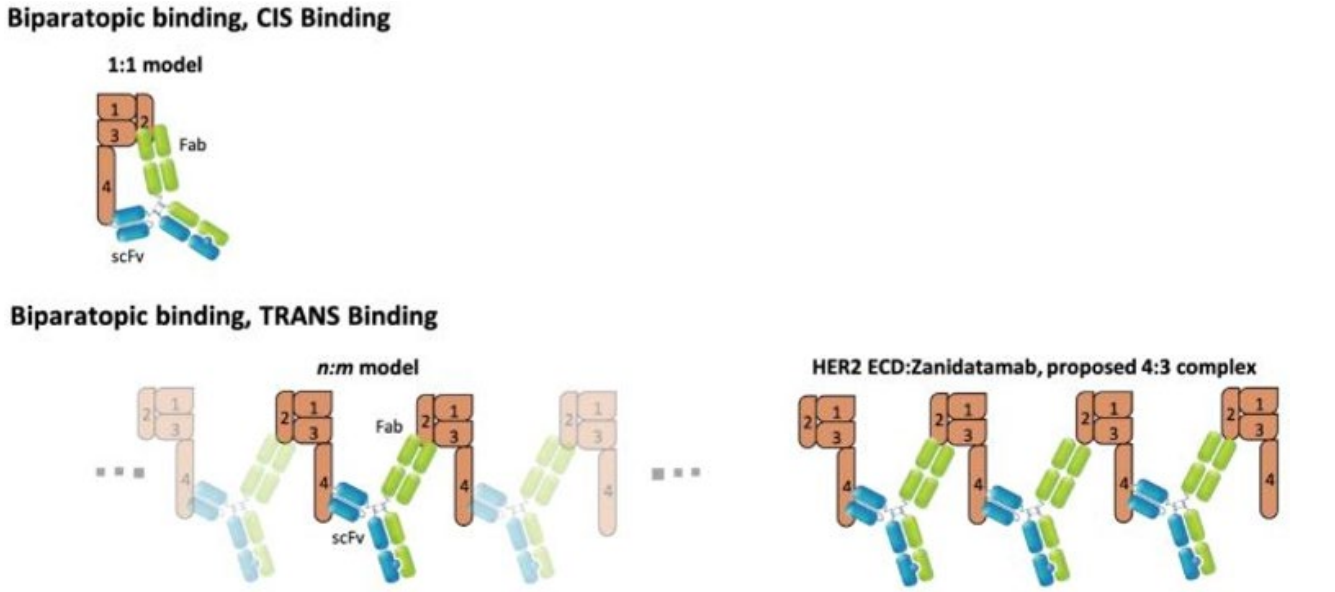
Abbreviations: ECD = extracellular domain; HER2 = human epidermal growth factor receptor 2; k_a = rate constant of drug association to the receptor; k_d = rate constant of drug dissociation from the receptor; K_D = dissociation constant at equilibrium (k_d/k_a); Ms = mole second; s = second.

Zanidatamab (also known as ZW25 and JZP598) is a humanized, immunoglobulin G isotype 1 (IgG1)-like human epidermal growth factor receptor 2 (HER2)-targeted bispecific antibody (Ab).

The applicant investigated the binding affinity of zanidatamab for HER2 extracellular domain (ECD) in various species (ZW25-07). It was demonstrated that zanidatamab binds with similar affinity to human and cynomolgus monkey HER2 ECD (Kd = 0.74 and 0.47 nM, respectively), while the affinity for dog was lower (Kd = 4.07 nM) and no affinity was demonstrated for rodents (see table above). The data justifies the choice of cynomolgus monkey as the most relevant non-clinical species.

Part of the mode of action of zanidatamab is biparatopic binding in *trans* configuration in the HER2 extracellular domain by binding both ECD 2 and ECD 4 on two different HER2 molecules, resulting in large cell surface HER2 clusters. Meanwhile, clusters will not form if zanidatamab binds in *cis* configuration through engagement of both epitopes on a single HER2 molecule (see figure below). The applicant demonstrated the formation of clusters higher than 2:1 complexes at equimolar concentrations of zanidatamab and HER2 ECD as well as when HER2 ECD was in large excess (up to 5-fold), confirming *trans* binding as the predominant configuration resulting in clustering into large complexes (ZW25-42). Unlike trastuzumab, zanidatamab and its precursor exhibited a reduction in off-rate (koff) as the surface density of the antibody increased, indicating stronger binding affinity at higher concentrations. This was not observed with trastuzumab, where the off-rate remained constant. No significant changes in the on-rate (kon) were noted for any of the antibodies. The decreasing off-rate for zanidatamab suggests that at higher concentrations, it binds HER2 in a trans-configuration, enabling cross-linking of HER2 receptors through anti-ECD2 and anti-ECD4 paratopes. This behaviour was consistent with previous trans-binding assessments, implying that zanidatamab's biparatopic binding mechanism enhances its affinity at higher antibody densities (ZW25-44).

Figure 2 Cis and Trans Binding Modes of Zanidatamab to HER2 ECD (ZW25-42)



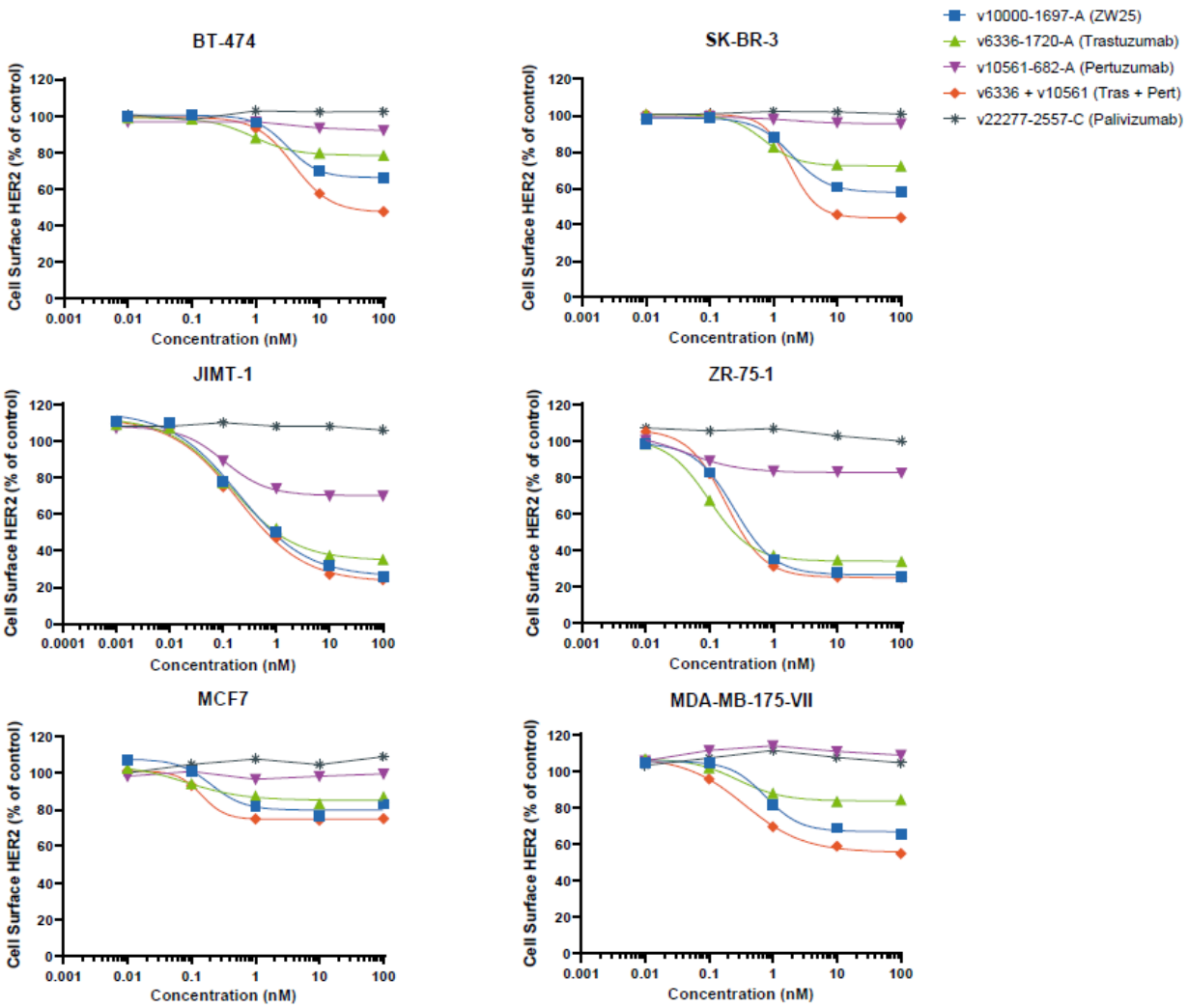
Abbreviations: ECD = extracellular domain; HER2 = human epidermal growth factor receptor 2. Cis binding: HER2 ECD in orange, with each of the 4 numbered subdomains. Schematic of biparatopic antibody zanidatamab binding to HER2 in cis binding configuration. Trans binding: (Left) Trans binding as a cluster size of n:m, where n represents n HER2 ECD molecules and m represents m zanidatamab molecules, or (Right) trans binding of an example cluster with a specific size of 4:3 with 4 HER2 ECD molecules and 3 zanidatamab molecules.

Table 6 Binding of Zanidatamab and Trastuzumab to HER2-Expressing Human Cancer Cell Lines

Cell Line	HER2 (IHC)	B_{max} (MFI)			K_D (nM)		
		Zanidatamab	Trastuzumab	Fold Difference	Zanidatamab	Trastuzumab	Fold Difference
MDA-MB-231	0/1 +	559	396	1.4	5.6	4.8	1.2
MCF-7	0/1 +	1016	650	1.6	4.2	2.3	1.9
JIMT-1	2 +	4791	2840	1.7	8.4	3.6	2.3
ZR-75-1	2 +	28.2	20	1.4	0.9	0.4	2.6
SKOV-3	3 +	46222	26465	1.7	15.2	5.5	2.8
NCI-N87	3 +	41859	28139	1.5	10.3	8.7	1.2
BT-474	3 +	38543	22451	1.7	16.1	7.9	2.1
SK-BR-3	3 +	39436	23854	1.7	10.8	5.3	2.0

Abbreviations: B_{max} = maximal binding; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; K_D = dissociation constant at equilibrium (k_{off}/k_{on}); MFI = mean fluorescence intensity.

Figure 3 Zanidatamab Mediates HER2 Downregulation in Cancer Cell Lines

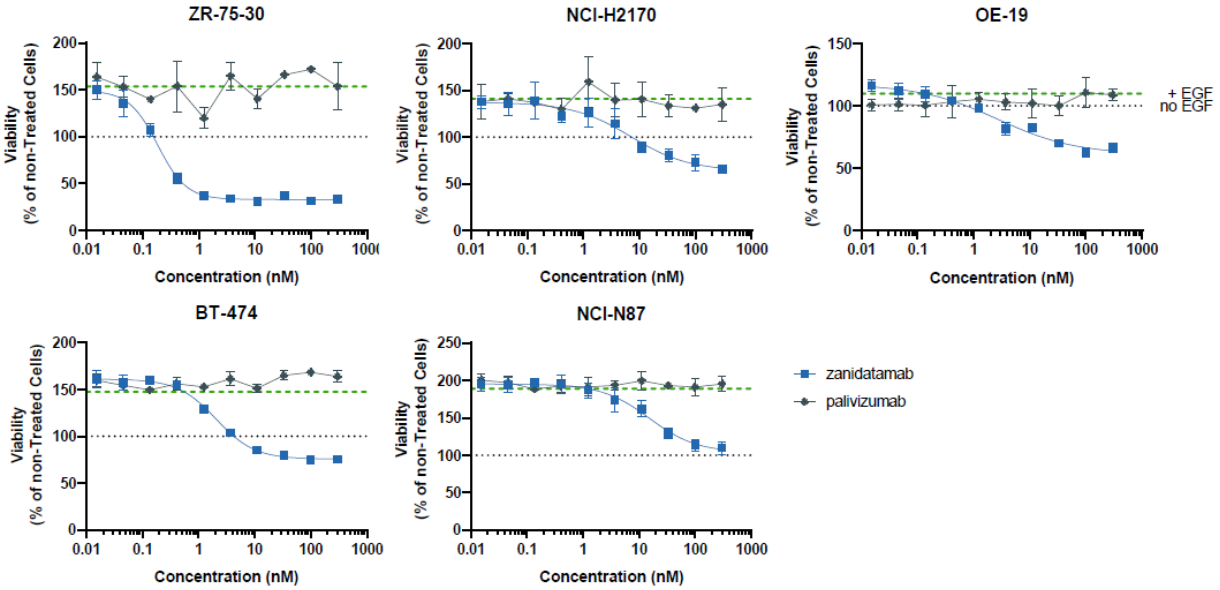


Abbreviations: HER2 = human epidermal growth factor receptor 2; Pert = pertuzumab; tras = Trastuzumab; ZW25 = zanidatamab (also known as JZP598).
Cell surface HER2 downregulation mediated by zanidatamab (blue squares), trastuzumab (green upward triangles), pertuzumab (purple downward triangles), the combination of trastuzumab and pertuzumab (orange diamonds), and palivizumab, a non-binding control anti-respiratory syncytial virus antibody (gray asterisks). Data graphed are single data points.

Concentration-dependent ligand-independent growth inhibition was observed for zanidatamab with mean IC_{50} values ranging from 0.18 to 2.0 nM and decreased the percent of viable cells ranging from 20%-66% in high HER2 receptor (HER2 3+)-expressing breast, gastric, oesophageal, and lung cancer cell lines as well as in one HER2-negative (HER2 0+) breast cancer cell line. At the highest concentration tested, zanidatamab mediated a greater decrease in the percentage of viable cells in 8 of 11 cell lines compared to the combination of trastuzumab + pertuzumab, in all 11 cell lines tested compared to trastuzumab alone and in 10 of 11 cell lines compared to pertuzumab alone. When ligand-dependent cell growth was investigated using epidermal growth factor (EGF) in various HER2 3+ cancer cell lines, zanidatamab induced a concentration dependent inhibition

compared to EGF+-controls, reducing cell viability to 33%-38% in ZR-75-30 breast cancer cells, 43% in NCI-H2170 lung cancer cells, 61%-66% in OE-19 oesophageal cells, 48%-76% in BT-474 breast cancer cells, and 91%-113% in NCI-N87 gastric cells (see figure below).

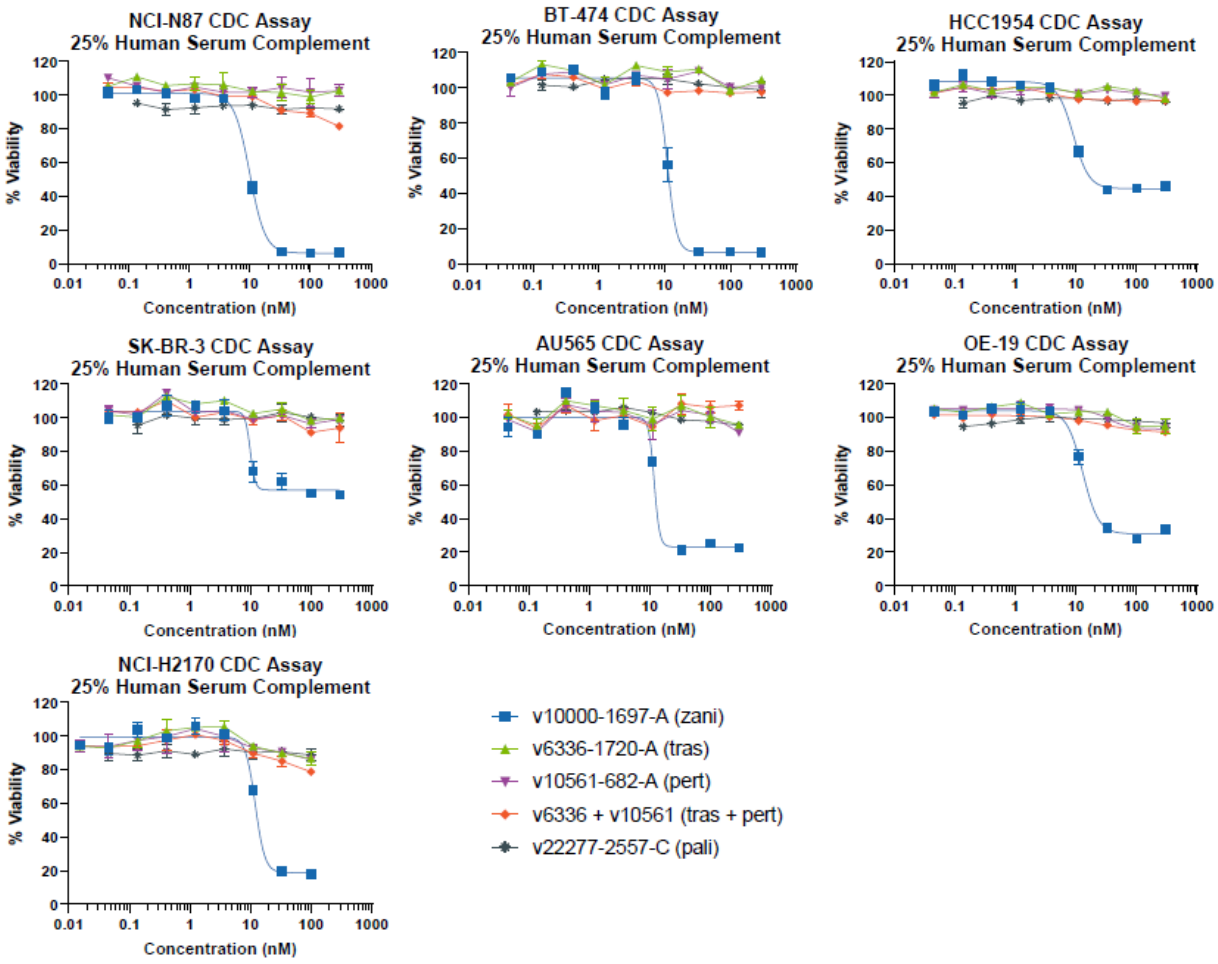
Figure 4 Zanidatamab Mediated Inhibition of EGF-Dependent Growth in HER2-Positive (HER2 3+) Cancer Cell Lines



Abbreviations: EGF = epidermal growth factor; HER2 = human epidermal growth factor receptor 2.
Inhibition of EGF-dependent cell growth mediated by zanidatamab (blue squares) and palivizumab (gray asterisks). The upper horizontal dashed line (green) represents % viable cells upon EGF stimulation (% Viability [+EGF]) under indicated assay conditions. The lower horizontal dotted line (grey) marks the viability of non-treated cells that was referenced at 100%. Data are graphed as mean viability (% of non-treated cells) ± standard deviation.

Another part of the mechanism of action of zanidatamab is activation of Fc-dependent immune effector mechanisms, specifically the complement-dependent cytotoxicity (CDC) system. In cancer cell line assays with added human complement serum, concentration-dependent CDC was observed for zanidatamab in high HER2 expressing cancer cell lines (HER2 3+) in terms of a decrease in the percent of viable cells ranging from 9%-60%. No activation of CDC was, however, observed in low expressing HER2 cell lines (HER2 2+, 1+ and 0). When the same cell lines were tested with trastuzumab and pertuzumab alone, limited CDC activation was observed, with far less reduction in cell viability. The combination of trastuzumab + pertuzumab mediated concentration-dependent CDC in NCI-N87 (gastric cells) only, however, to a much lesser extent than zanidatamab (see figure below).

Figure 5 Complement-Dependent Cytotoxicity of Zanidatamab, Trastuzumab, Pertuzumab, and the Combination of Trastuzumab Plus Pertuzumab in HER2-Positive (HER 3 +) Cancer Cell Lines HCC1954, AU565, BT-474, SK-BR-3, NCI-H2170, OE-19, and NCI-N87



Abbreviations: CDC = complement-dependent cytotoxicity; HER2 = human epidermal growth factor receptor 2; pali = palivizumab; pert = pertuzumab; tras = trastuzumab; zani = zanidatamab (also known as ZW25 and JZP598).
CDC mediated by zanidatamab (blue squares), trastuzumab (green upward triangles), pertuzumab (purple downward triangles), the combination of trastuzumab and pertuzumab (orange diamonds), and palivizumab (gray asterisks). Data are graphed as mean % viability ± standard deviation.

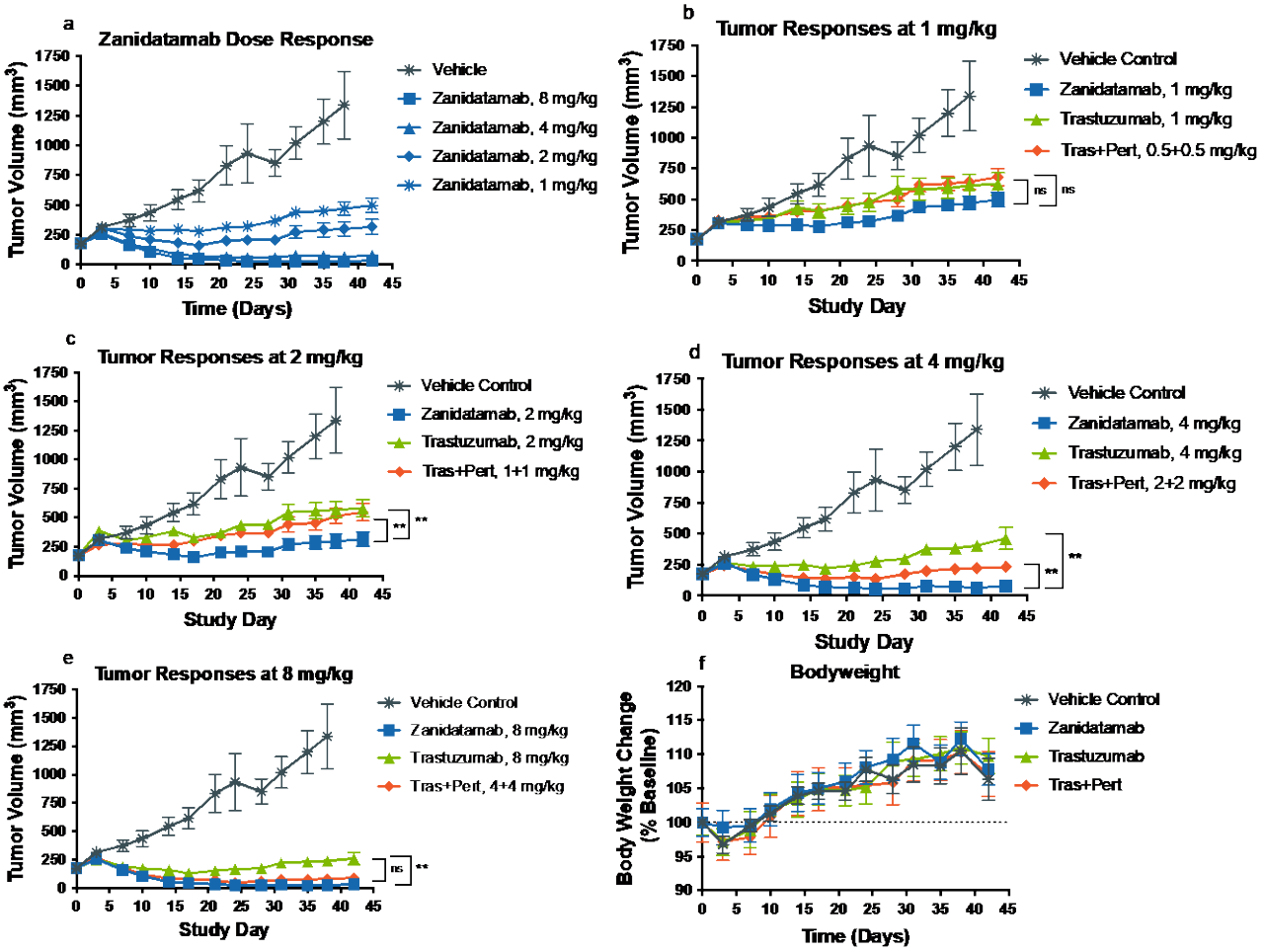
Zanidatamab may also mediate both Antibody-Dependent Cellular Cytotoxicity (ADCC) and Antibody-Dependent Cellular Phagocytosis (ADCP), and the applicant investigated the extent in various cancer cell assays. The applicant confirmed that zanidatamab mediates both ADCC and ADCP in NCI-N87 (HER2 3+), SK-BR-3 (HER2 3+) and JIMT-1 (HER2 2+) cancer cell lines in the presence of human PBMC effector cells. However, it appears that zanidatamab exerts ADCC to a similar extent as observed for pertuzumab and trastuzumab either alone or in combination, except for in one donor of NCI-N87, where zanidatamab induced a higher response compared to the other treatments. Trastuzumab, pertuzumab, and the combination of trastuzumab and pertuzumab demonstrated concentration-dependent ADCP similar to zanidatamab in NCI-N87 and SK-BR-3 cells. The combination of trastuzumab and pertuzumab demonstrated concentration-dependent ADCP similar to zanidatamab in JIMT-1 cells. No ADCC or ADCP was observed with any test articles in HER2-negative MDA-MB-468 tumour cells.

In vivo pharmacology

Zanidatamab was evaluated in xenograft models in nude mice using different human cancer cell lines. First, zanidatamab was tested against human immunoglobulin G (IgG) as a negative control in the HER2 3+ SKOV-3 ovarian cancer cell line as well as two precursor bispecific HER2-targeting antibodies (v5019 and v7091) (ZW25-25). Zanidatamab was administered at 0.1, 0.3, 1, 3, or 10 mg/kg twice weekly for 4 weeks. Zanidatamab mediated dose-dependent tumour growth inhibition of SKOV-3 xenografts by 6%, 53%, and 78% at 1, 3, and 10 mg/kg, respectively. Compared to human IgG, zanidatamab at 10 mg/kg significantly inhibited the rate of tumour growth by 48.7% *(P* = 0.0135). All other groups treated with lower doses zanidatamab failed to show significant tumour inhibition compared with human IgG control. When compared to the precursor antibodies (v5019 and v7091), no significant differences in tumour growth inhibition were observed at a dose of 3 mg/kg. Importantly, all treatments were well tolerated, with no significant weight loss or adverse reactions.

In a second assay, efficacy of zanidatamab was evaluated in comparison to trastuzumab and the combination of trastuzumab plus pertuzumab in BALB/c nude mice bearing subcutaneous NCI-N87 tumours, a HER2 3+ cell line derived from human gastric adenocarcinoma (ZW25-46). Mice were dosed intravenously (IV) twice weekly with zanidatamab at 1, 2, 4, or 8 mg/kg; trastuzumab at 1, 2, 4, or 8 mg/kg; or 0.5+0.5, 1+1, 2+2, or 4+4 mg/kg of trastuzumab + pertuzumab combination for 4 weeks. The efficacy of zanidatamab was dose-dependent at 1, 2, 4, and 8 mg/kg and resulted in significantly higher inhibition of tumour growth rates of 52%, 136%, 268% and 309% at 1, 2, 4 and 8 mg/kg, respectively, compared to vehicle control ($p< 0.01$) (see figure below). Zanidatamab treatment at 1 mg/kg did not result in higher tumour growth inhibition compared to trastuzumab alone or the combination of trastuzumab and pertuzumab. Zanidatamab however performed significantly better compared to trastuzumab alone at 2, 4 and 8 mg/kg, which resulted in 55%, 86% and 77% tumour growth inhibition, respectively ($p < 0.01$). When compared against treatment with trastuzumab in combination with pertuzumab, which resulted in growth inhibition of 34%, 155% and 264% at 1+1, 2+2 mg/kg and 4+4 mg/kg, respectively, zanidatamab however only resulted in a statistically significant increase in tumour growth inhibition at 2 or 4 mg/kg ($p< 0.01$) while the difference was not significant at the 8 mg/kg dose level ($p=0.41$). No differences in mean body weight changes were observed in any group.

Figure 6 Zanidatamab Inhibits Tumour Growth in the NCI-N87 Gastric Cancer Cell Line Xenograft Model



Abbreviations: Pert = pertuzumab; SEM = standard error of mean; Tras = trastuzumab.
Note: **a** dose-dependent zanidatamab-mediated tumour growth inhibition. **b-e** tumour growth inhibition comparison between zanidatamab, trastuzumab, and trastuzumab + pertuzumab combination at **b** 1 mg/kg, **c** 2 mg/kg, **d** 4 mg/kg, and **e** 8 mg/kg. **f** shows bodyweight changes in all groups. **, p<0.01 vs trastuzumab or trastuzumab + pertuzumab. Data are mean ±SEM.

In a third assay, the antitumour activity of a single high dose level of zanidatamab was evaluated in GXA 3054, a patient-derived HER2 3+ gastric cancer xenograft model in nude mice (ZW25-29). Human IgG, trastuzumab, or zanidatamab at 30 mg/kg IV was administered twice weekly for 5 weeks. Treatment with zanidatamab reduced the mean tumour volume and significantly inhibited the growth rate of GXA 3054 tumour xenografts by 307.6% compared to human IgG ($P = 2.91 \times 10^{-11}$) and trastuzumab ($P = 3.17 \times 10^{-7}$).

When zanidatamab was administered to nude mice at 30 mg/kg twice weekly for 4 weeks in a HER2 negative xenograft model using ST803, a human pancreatic cancer cell line, zanidatamab monotherapy did not demonstrate a significant ability to attenuate tumour growth or prolong host survival compared to human IgG control in this model (ZW25-23-ST803). The same lack of efficacy was observed for trastuzumab monotherapy. Zanidatamab combined with nab-paclitaxel significantly delayed tumour growth by 26%, with a improvement in median survival beyond 73 days compared to the hIgG control (p=0.00264) and the hIgG

plus nab-paclitaxel group (p=0.0127). The combination treatment resulted in a tumour growth inhibition of 40% compared to the control group, rendering it the most effective treatment in the study.

2.2.2.2. Secondary pharmacodynamic studies

No secondary pharmacology studies have been conducted with zanidatamab.

2.2.2.3. Safety pharmacology programme

The applicant performed an ex vivo study of immunogenicity to investigate potential undesired immunological responses of zanidatamab compared to other antibodies, using human peripheral blood mononuclear cells (PBMCs) from 8 randomly selected donors, in which B cells were used as antigen-presenting cells to establish a potential stimulation of proliferation of the PBMCs (study ZW25-34). For each donor, a stimulation index (SI) was calculated based on cell proliferation after exposure to test antibodies. The positive control (Candida albicans) showed a Max SI (MSI) ranging from 0.81 to 37.54 across donors, while the negative control (HSA) ranged from 0.94 to 1.91. A proliferation threshold of 1.83 was set to determine positive responses. Test antibodies were compared against these controls to assess whether they induced proliferation. The results revealed that most donors did not experience significant proliferation in response to zanidatamab (MSI of 1.20) nor for Herceptin, or Perjeta. Zanidatamab's proliferation profile was not significantly different from Herceptin, but both were significantly different from the positive control (Candida albicans). This suggests that neither zanidatamab nor Herceptin triggered immune proliferation at levels comparable to an immune-stimulating pathogen like Candida albicans. One donor had an extreme proliferation response to zanidatamab, which skewed the normal distribution analysis. The analysis was re-run with and without this donor's data to explore if the extreme response was a biological effect or a measurement error. In both cases, zanidatamab's profile remained comparable to Herceptin but different from Perjeta and A5SU buffer, suggesting the response seen may be related to the buffer used in Zanidatamab and Perjeta. Statistical tests, including the Wilcoxon sign-ranked test and t-tests, were used to compare proliferation across batches and different antibodies. Results showed no significant batch effects, confirming that donor responses were consistent. When analyzing the Max SI values, neither zanidatamab nor Herceptin significantly induced PBMC proliferation compared to the negative control (HSA), while their responses differed from the positive control. The extreme value from one donor was investigated with parametric and non-parametric tests. Both approaches confirmed that zanidatamab's proliferation profile was consistent with Herceptin but different from Perjeta. Overall, none of the tested antibodies induced a statistically different response in proliferation of cells compared to the negative control (human serum albumin, p>0.000001).No dedicated safety pharmacology studies were submitted. Safety pharmacology endpoints were incorporated into the GLP-compliant 8- or 13-week repeat-dose toxicity study in cynomolgus monkeys intravenously administered with zanidatamab at doses of 5, 50 and 150 mg/kg once weekly (QW) (study id: ZW25-04-13WTOX (2363-002)). This approach is acceptable in accordance to ICH S6(R1) and S9.

The effect of zanidatamab on the cardiovascular (ECG and blood pressure), respiratory, renal/urinary, and central nervous systems was evaluated. Endpoints were assessed for all dose groups, twice pre-dose, two to three times during the treatment phase (day 1, 50 and 85) and once in the last week of the recovery phase (week 15 or 21).

Electrocardiographic (ECG) measurements revealed sinus tachycardia (> 270 beats per minute) in 5 animals at 9 intervals, whereof only 2 were post-dose. Sinus bradycardia (<160 beats per minute), occurred in 2

animals but only on pre-test ECG measurements. Hence, none of the diverging rhythms were considered test article related, which is agreed by the assessor. Aside from the described instances of sinus tachycardia and bradycardia, all of the remaining electrocardiograms were qualitatively and quantitatively within normal limits and no direct effect of infusion was noted.

No notable test-related effects of zanidatamab were observed on blood pressure, respiratory rate or in the central nervous system assessed by lack of neurobehavioral changes and histopathological findings in the brain. Of note, a statistically significant decrease in mean systolic blood pressure compared to control was observed on day 1 in females at 5 mg/kg. However, this was considered incidental, as no effects were seen at higher doses or at similar doses in male animals. This conclusion is accepted.

It was addressed by the applicant that no effect was noted in the renal/urinary system. An increase in blood urea nitrogen (BUN) from day 22 was noted but without correlating histopathological findings in the kidneys. Hence, the lack of effect on the renal system is agreed.

2.2.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted by the applicant.

2.2.3. Pharmacokinetics

Analytical methods

Cynomolgus monkey serum was analysed for both zanidatamab concentration and the presence of anti-zanidatamab antibodies and the bioanalytical methods are presented in the below table.

Table 7 Bioanalytical Methods

Validation Study /Method Type	Matrix	Analyte	Drug tolerance	Detection range (LLQ - ULQ)	Studies Supported	GLP/Testing Facility
In-house qualified ELISA	Serum, cynomolgus monkey	Zanidatamab	-	20 to 150 ng/mL	ZW25-01-PKTol Single dose PK	No Centre national de biologie experimentale INRS
2363-004 VALIDATION OF A LIGAND BINDING ASSAY TO DETECT ZW25 ECL	Serum, cynomolgus monkey	Zanidatamab	-	1.95 to 125 ng/mL	ZW25-02-28D TOX (2363-001) Repeat dose TK	No MPI Research Inc.
			-	3.91[a] to 125 ng/mL	ZW25-04-13WTOX (2363-002) Repeat dose TK	Yes MPI Research Inc.
2363-005 VALIDATION OF A LIGAND BINDING	Serum, cynomolgus monkey	Anti-zanidatamab antibodies	PC low (5 µg/mL) drug tolerance: 31.15 µg/mL	0.5 to 10 µg/mL[b]	ZW25-02-28D TOX (2363-001) Repeat dose TK	No MPI Research Inc.

Validation Study /Method Type	Matrix	Analyte	Drug tolerance	Detection range (LLQ - ULQ)	Studies Supported	GLP/Testing Facility
ASSAY TO DETECT ANTI-ZW25 ANTIBODIES Bridging ECL		(ADA)	PC high (10 µg/mL) drug tolerance: 187.62 µg/mL		ZW25-04-13WTOX (2363-002) Repeat dose TK	Yes MPI Research Inc.

Abbreviations: ECL = electrochemiluminescence; ELISA = enzyme linked immunosorbent assay; PC = positive control; LLQ = lower limit of quantification; ULQ = upper limit of quantification; GLP = good manufacturing practice; TK = toxicokinetic; PK = pharmacokinetics; ADA = anti-drug antibody.

[a] lower limit of quantification adjusted from 1.95 in the validation study to 3.91 following the repeat dose studies.

[b] calibration range determined with positive control. The following is in place for the ADA assay validation study: screening assay cut point: 795, confirmatory assay cut point factor: 47.66%, sensitivity: 8.59 ng/mL (anti-trastuzumab [range: 6.46-11.6]).

The first bioanalytical method (conventional ELISA) was developed for a dedicated single dose pilot study (ZW25-01-PKTol) to determine zanidatamab concentration within a detection range of 20 to 150 ng/mL and qualified using an in-house protocol.

Two additional bioanalytical methods were developed to detect zanidatamab or anti-zanidatamab antibody concentrations from monkey serum in the 28-days and 13-weeks repeat dose toxicity studies (non-GLP ZW25-02-28D TOX [2363-001] and pivotal GLP-compliant ZW25-04-13WTOX [2363-002]).

Zanidatamab concentrations were determined using an electrochemiluminescence assay with a meso scale discovery platform (ECL/MSD®). Full method validation was performed in monkey serum as described in study ZW25-2363-004 in support of the repeat dose studies. According to the validation run history, several runs were rejected as they failed to meet acceptance criteria (run QC samples and stability samples under-recovered). The cause was due to a dilution error, and when corrected in a new run, all acceptance criteria were met. An assessment of the pivotal repeat dose studies reveals a program in good control and with both validation and study-related bioanalysis in compliance with GLP. Incurred sample reproducibility was found to comply with guidelines.

The presence of anti-zanidatamab antibody in monkey serum was furthermore determined using an ECL/MSD bridging assay and validation of the assay was evaluated in study ZW25-2363-005 in support of the repeat dose studies. Overall, the method appears robust with a mean sensitivity of 8.59 ng/mL and interpolated drug tolerance level of 31.147 µg/mL and 187.619 µg/mL for low and high positive controls (5 and 10 mg/mL, respectively). The positive control consisted of human anti-trastuzumab, but it is noted that also anti-pertuzumab has been used (data not shown). It is assumed that similar conclusions have been reached with anti-pertuzumab with respect to assay sensitivity to detect drug (drug tolerance). Mean serum concentrations at dose levels 50 and 150 mg/kg at the 168 h post-dose measurement on Day 50 are, however, measured to 748 µg/mL and 2560 µg/mL, which significantly exceeds the drug tolerance levels. Thereby, the conclusion that animals are negative for the presence of ADA is a potentially false negative, as the ADA assay is not considered valid at the measured serum concentration levels to evaluate ADAs. Moreover, ADA-positive control and pre-dose samples in the pivotal 13-week study indicate interference, potentially caused by endogenous HER-2, as also supported by a high confirmatory cut point of app. 48% in the validation study.

Absorption

A series of PK and toxicology studies (with a TK component) have been conducted for zanidatamab. These studies included non-GLP single- and repeat-dose IV studies and a GLP repeat-dose IV study up to 13 weeks in cynomolgus monkeys with doses ranging from 5 to 150 mg/kg. A summary of the pharmacokinetics of zanidatamab is presented in the below table.

Single-dose IV

In a non-GLP pharmacokinetic pilot study (ZW25-01-PKTol) female cynomolgus monkeys were administered a single IV dose of 0, 10 or 30 mg/kg. Following IV single-dose administration, zanidatamab displayed dose-dependent kinetics with a relatively dose-proportional increase in systemic from 10 to 30 mg/kg exposure based on C_{max} and $AUC_{0\text{-}168h}$ (slightly greater than dose-proportional). Serum concentrations of zanidatamab declined in a biphasic exponential manner with a rapid decline within the first 24 hours. Mean t½ of zanidatamab from a single dose was 65.5- and 114-hours following administration of 10 and 30 mg/kg, respectively, and thus, zanidatamab demonstrated a long serum half-life. Estimated serum clearance of zanidatamab via hepatic blood flow and glomerular filtration was low, ranging from 0.394 to 0.518 mL/h/kg between the two doses, and the estimated volume of distribution (Vss) ranged from 48.5 to 65.0 mL/kg and approximated the serum volume in monkey, suggesting that zanidatamab did not distribute extensively outside of the serum compartment. It is noted that serum samples for ADA analysis were collected, but not tested in this study.

Repeat-dose IV

Two repeat dose studies using the same dosing regimen have been carried out for zanidatamab with similar results. In the 13-week GLP toxicology study (ZW25-04-13WTOX (2363-002) male and female cynomolgus monkey were administered IV infusion once weekly of 5, 50 and 150 mg/kg for 8 or 13 weeks in two different cohorts. There were no significant gender-related differences observed in exposure parameters and thus male and female results are combined. Following administration with zanidatamab, systemic exposure increased slightly more than dose-proportional manner, based on mean C_{max} and mean $AUC_{0\text{-}168h}$, in both the 8- and 13-week dosing cohorts from 5-50 mg/kg, and dose-proportionate from 50-150 mg/kg. High variability was noted in the high dose groups.

Median time of maximum observed concentration (T_{max}) at mean C_{max} occurred app. at 1.5 hours, which was within 30 minutes of the end of infusion. The mean t½ values after repeated dosing were similar between cohorts, but displayed great variability, ranging between 74 and 215 hours (app. 3 to 9 Days). These results were according to the applicant similar to the reported half-life of trastuzumab in monkeys, wherein the terminal half-lives ranged from 3 to 14 days (EMA, 2005). Half-life values for zanidatamab should however be interpreted with caution since they were determined from limited data (approximately one half-life of data). Of note, several PK parameters/values could not be determined due to insufficient data and especially the secondary parameters from the repeat dose studies like clearance and volume of distribution are fraught with uncertainties. Available mean clearance values for both dosing cohorts on the first day of dosing were 0.537 and 0.418 mL/h/kg, indicating slow to moderate clearance. However, mean clearance values decreased with time and fell between a range of 0.181 and 0.323 on the last day of sampling in both cohorts (Day 50 and 85, all doses). The mean volume of distribution in both cohorts were between 13.9 and 77.3 mL/kg, which is consistent with or is slightly less than the serum volume of the monkey, as also indicated in the previous single dose PK study. The mean C_{max} occurred at a median T_{max} mostly ranging from 1.0 to 1.5 hours.

In accordance with the more than dose-proportional increase in exposure observed between 5-50 mg/kg, accumulation was observed with the accumulation ratio being ≥2- fold (ranging from 1.99 to 3.15) for the 5 and 50 mg/kg dosing groups across 8- and13-week dosing cohorts. While this could be expected with repeat dosing for a monoclonal antibody with a long half-life and weekly dosing, the accumulation ratio decreased between doses 50 and 150 mg/kg (from 3.15 and 2.15 to 2.30 and 1.65, respectively), indicating a clearing effect of ADA on zanidatamab at higher doses measured at late time points.

With respect to ADA, all dosing cohorts were screened and several findings indicated both formation of ADA and possible inadequacies of the ADA-assay. Seven animals were ADA-positive during screening and were tested further in the confirmatory assay. Of these, only two animals were confirmed positive in pre-treatment samples, but none were positive for ADA in subsequent samples post-treatment. One animal was positive for ADA in the screening assay after administration of zanidatamab; however, positivity was not confirmed in the confirmatory assay at any timepoint. Of importance, zanidatamab concentrations were below the level of quantification in all samples collected during the last weeks of the study for this specific animal, which anyhow coincided with the majority of zanidatamab-treated animals, since serum concentrations was shown to exceed the specific drug tolerance level of the assay (31.1 µg/mL). Thus, ADA may had been present but undetectable. Regardless, exposure levels remained sufficient at all doses and time points.

Table 8 Pharmacokinetics of Zanidatamab Following Intravenous Administration of Zanidatamab to Cynomolgus Monkeys

Study	Dose (mg/kg)	N/Sex	Day	T½ Mean h (SD)	Tmax Median h (range)	Cmax µg/mL (SD)	AUC0-168h hR*µg/mL (SD)	R (AUC0-168hr Day 22/AUC0-168hr Day 1)
Single dose study ZW25-01-PKTol	10	2F	1	65.5	NA	246	16,100	NA
	30	2F	1	114	NA	882	47,800	NA
4-week study ZW25-02-28dTOX (2363-001)	5	2F+2M	1	56.9 (9.71)	1.5	127 (16)	6,240 (376)	NA
			22	94.2 (30.7)	1.5	161 (8)	10,100 (1,820)	1.63
	50	2F+2M	1	182 (47.6)	1.5	1,390 (220)	83,900 (4,380)	NA
			22	207 (36.7)	1.5	1,850 (123)	140,000 (16,700)	1.68
	150	2F+2M	1	185 (58.9)	1.5	3,720 (296)	233,000 (22,100)	NA
			22	169 (NA)	1.5	5,790 (878)	473,000 (110,000)	2.02
13-week study ZW25-04-13WTOX (2363-002)	5[a]	3F+3M	1	75.6 (14.9)	1.5	145 (9)	8,060 (1,310)	NA
			50	112 (24.4)	1.5	165 (82)	16,400 (3,820)	1.99
	50[a]	3F+3M	1	153 (32.3)	1.5	1,760 (133)	96,300 (5,060)	NA
			50	99.7 (34.6)	1.5	3,920 (1,490)	300,000 (93,500)	3.15
	150[a]	5F+5M	1	203 (38.6)	NA (0.5-2)	4,780 (374)	297,000 (19,400)	NA
			50	175 (49.3)	1.5	8,610 (2,270)	687,000 (237,000)	2.30
	5[b]	4F+4M	1	74.3 (12.4)	1.5	173 (25)	9,950 (979)	NA
			85	117 (21.2)	1.5	315 (116)	23,200 (4,390)	2.33
	50[b]	4F+4M	1	183 (42.2)	1.5	1,720 (391)	95,600 (11,400)	NA
			85	130 (21.9)	1	2,460 (218)	203,000 (28,600)	2.15
	150[b]	7F+7M	1	172 (49.9)	NA (1-24)	4,760 (963)	334,000 (87,100)	NA
			85	215 (112)	NA (1-4)	6,680 (1,100)	534,000 (67,500)	1.65

Abbreviations: $AUC_{0\text{-}168h}$ = area under the serum concentration-time curve from time zero to 168 hours; C_{max} = maximum observed concentration; F = female; h = hours; IV = intravenous; M = male; N = number of animals; NA = not applicable; R = accumulation ratio; SD = standard deviation (SD not applicable for group size of ≤ 2 animals.); $t_{½}$ = terminal elimination half-life; T_{max} = time of maximum observed concentration.

[a] 8-week cohort

[b] 13-week cohort

Distribution

No dedicated tissue distribution studies have been performed with zanidatamab in accordance with ICH S6(R1) (ICH, 2011), The Vss values described in the repeat dose studies indicate that zanidatamab is mainly contained in the serum compartment and that tissue distribution in monkeys is limited, as would be expected with the generally limited ability of mAbs to leave the vascular space due to the large molecular weight and

polarity. Tissue cross-reactivity using human tissue indicate that zanidatamab staining was mostly consistent with HER2 expression in normal human tissues reported in the literature.

Distribution to blood cells and across the blood brain barrier has not been investigated, but is expected to be marginal or without clinical outcome based on the toxicological profile. Placental transfer end excretion into milk has not been investigated but is considered probable based on clinical cases with other HER2-directed antibodies. Appropriate warnings against use during pregnancy and in women of childbearing potential without the use of contraception and precautions for breastfeeding women have been listed in the SmPC, which is considered sufficient.

Metabolism

No specific metabolism and/or excretion studies were performed for zanidatamab in accordance with ICH S6(R1) (ICH, 2011).

Excretion

No dedicated excretion studies have been performed for zanidatamab as it is expected to be catabolized.

Pharmacokinetic Drug Interactions

No formal drug-drug interaction studies have been conducted with zanidatamab. Zanidatamab is an antibody that is not expected to impact the cytochrome P450 enzymes. Also, zanidatamab is not known to target mechanisms that may impact the pharmacokinetics of concomitant medicines.

Other Pharmacokinetic Studies

No additional PK studies were performed for zanidatamab.

2.2.4. Toxicology

Zanidatamab was evaluated in a toxicology program as outlines in the below table. Studies (non-GLP and GLP) were conducted in line with the ICH S9 and S6(R1) guidelines in member countries of the OECD Mutual Acceptance Data Program.

Table 9 Overview of the toxicology program for zanidatamab

Species	Route	Duration	Dose (mg/kg)	GLP Status	Study name (Report Number) [batch]	Location in CTD	Reference used in toxicology assessment (by assessor)
Single Dose Toxicity							
Cynomolgus Monkey	IV	Single Dose	0, 10, 30	No	ZW25-01-PKTol [711-A]	4.2.2.7	ZW25-01-PKTol
Repeat Dose Toxicity							
Cynomolgus Monkey	IV	4 weeks	0, 5, 50, 150	No	ZW25-02-28D TOX (2363-001) [886-A]	4.2.3.2	28DTOX

	IV	8/13 weeks	0, 5, 50, 150	Yes	ZW25-04-13WTOX (2363-002) [ENGR15-33]	4.2.3.2	13WTOX - 8W-cohort - 13W-cohort
Tissue Cross Reactivity							
Human	In vitro	-	-	No	ZW25-03-TCR (20059441)	4.2.3.7	-
	In vitro	-	-	Yes	ZW25-09-GLP-TCR (20085010) [ENGR15-33]	4.2.3.7	ZW25-09-GLP-TCR
Antigenicity							
Cynomolgus Monkey	In vitro	4 weeks	0, 5, 50, 150	No	ZW25-02-28D TOX (2363-001) [886-A]	4.2.3.2	28DTOX
	In vitro	8/13 weeks	0, 5, 50, 150	Yes	ZW25-04-13WTOX (2363-002) [ENGR15-33]	4.2.3.2	13WTOX 1. 8W-cohort 2. 13W-cohort

Based on HER2 sequence homology and binding affinity of zanidatamab, the cynomolgus monkey was selected as the pharmacologically relevant species for none-clinical safety assessment and is the only species used in the toxicology program. Intravenous administration was used in all in vivo toxicology studies since it is the intended route of administration in the clinic.

2.2.4.1. Single dose toxicity

No dedicated single dose toxicity studies were performed. However, a non-GLP single-dose study (ZW25-01-pktol) with iv administration of zanidatamab at doses up to 30 mg/kg were conducted in female cynomolgus monkeys in order to assess pharmacokinetics, general tolerability and determine the dose levels used in the repeat-dose toxicity studies. Evaluation proceeded for 28 days post administration of zanidatamab. Single dose exposure multiples were below or equivalent to clinically relevant exposure with C_{max} of 0.5 and 1.9-fold and $AUC_{0\text{-}168h}$ of 0.3 and 0.9-fold for the 10 mg/kg and 30 mg/kg groups, respectively. Treatment at both dose levels was well tolerated. No mortalities or evidence of treatment-related toxicity were observed in daily clinical observations, body weight, haematology, clinical chemistry, ECG, or respiratory parameters.

In repeat-dose toxicity studies in cynomolgus monkeys (28DTOX and 13WTOX), no mortality or signs of acute toxicity was noted following the first administration of zanidatamab at dose levels up to 150 mg/kg resulting in exposure multiples approximately 10-fold higher than clinically relevant exposure. The maximum tolerated dose (MTD) was not reached in any of the studies but this is considered acceptable due to the relatively high safety margin of 10-fold for an anti-cancer product.

Table 10 Single dose PK and general tolerability study

Study details	No:Sex	Dose (mg/kg)	Exposure		Major (alt. Salient) findings
			C_{max} (ng/ml) Geometric mean	$AUC_{0\text{-}168h}$ (h·ng/mL) Geometric mean	
Single-dose toxicity studies					
Cynomolgus monkey, single iv injection, 28 days follow-up, non-GLP (ZW25-01-PKTol)	1F (vehicle)	0	-	-	≤30 mg/kg: No mortalities and no evidence of treatment-related effects was observed in clinical signs, body weight, hematology, clinical chemistry, ECG, or respiratory parameters. **MTD not established**
	2F	10	246,000	16,100,000	
	2F	30	882,000	47,800,000	

Abbreviations: $AUC_{0\text{-}168h}$ = area under the concentration-time curve from time 0 to 168 hours; C_{max} = maximum observed concentration; F = female; GLP = Good Laboratory Practice; IV = intravenous; MTD = maximum tolerated dose.

2.2.4.2. Repeat dose toxicity

Repeat dose toxicity, safety pharmacology, ADA formation and the toxicokinetic profile of zanidatamab were evaluated after intravenous (iv) administration once weekly (QW) in a pivotal GLP-compliant repeat-dose study of up to 13 weeks duration (13WTOX). Study 13WTOX was supported by a non-GLP 4 week iv (QW) repeat dose study (28DTOX). In both studies, zanidatamab was intravenously (iv) administered once weekly (QW) at doses 0, 5, 50, and 150 mg/kg via 1-hour iv infusion at a dose volume of 15 ml/kg. Female and male adult monkeys were used. In 13WTOX, a treatment-free recovery period of 8 weeks was included (control, high-dose groups). Further, 13WTOX-animals were divided into two cohorts receiving either 8 or 13 treatments (8W- and 13W-cohorts). With exception of the recovery animals, monkeys were terminated 7 days following the last dose. Toxicity endpoints were mortality, changes in clinical signs, body weight, food consumption, blood pressure, respiratory rate, electrocardiographic parameters, ophthalmic parameters, clinical pathology, organ weights, and macroscopic and microscopic findings. The repeat dose toxicity studies are summarized in the below table.

Slight decreases in red blood cell count (RBC), haematocrit (Hct) and haemoglobin (Hgb) levels compared to baseline were seen in all groups, including controls, from day 22. Maximum differences were found in female animals prior to terminal necropsy, namely 18%, 15%, and 13%, respectively. In parallel, increases of about 20-65% in reticulocyte (Retic) count were observed compared to baseline levels, which are likely due to a compensatory bone marrow response. The alterations in RBC, Hct, and Hgb levels were normalized in most recovery controls and partially in the dosed recovery females. The elevation in Retic level was resolved in most recovery animals. No microscopic correlates were observed in the bone marrow.

Table 11 Summary of repeat dose toxicity studies

Study details	Dose mg/kg	N/Sex	Day	C_{max} ng/mL (SD)	$AUC_{0\text{-}168h}$ hR*ng/mL (SD)	Major findings & NOAEL
Cynomolgus monkey 4-week (QW) 1-h iv infusion non-GLP (no statistical analysis. Descriptive statistics, incl. means and StD) ZW25-02-**28DTOX** [2363-001] Batch: 886-A	5	2F+2M	1	127,000 (16,000)	6,240,000 (376,000)	***Mortality***: None ***Clinical observations***: ≥5 mg/kg: ↑ incidence of watery/soft faeces (non-dose dependent) (M and F) 5 mg/kg: sporadic discolored (red) skin, vomitus (2F), inappetence (M) 150 mg/kg: inappetence (F), petechial-like skin reaction (orange discoloration) ventral body and left axillary from d26 (1F), tremor (1M, one episode (d8)) ***Body weight***: no ZW25-related effects ***Food consumption (qualitative)***: 150 mg/kg: ↓F (day 17-28) ***Clinical pathology***: ≥5 mg/kg: tendency of ↑ BUN (day 15 + terminal) ***Necropsy***: ≥5 mg/kg: mild catherization/infusion/venipuncture reactions (2F, macro- and microscopically confirmed + multiple animals with microscopically confirmed injection site findings) 150 mg/kg: Microscopically identified minimal lung adhesion, inflammation and pleural fibrosis correlated with macroscopic thoracic cavity adhesion (1M) **NOAEL: 150 mg/kg**
			22	161,000 (8,370)	10,100,000 (1,820,000)	
	50	2F+2M	1	1,390,000 (220,000)	83,900,000 (4,380,000)	
			22	1,850,000 (123,000)	140,000,000 (16,700,000)	
	150	2F+2M	1	3,720,000 (296,000)	233,000,000 (22,100,000)	
			22	5,790,000 (878,000)	473,000,000 (110,000,000)	
Cynomolgus monkey 8-week (QW) 8-week recovery 1-h iv infusion GLP	5	3F+3M	1	145,000 (9,400)	8,060,000 (1,310,000)	***Mortality***: None ***Clinical observations*:** ≥5 mg/kg: ↑ incidence of watery/soft faeces (non-dose dependent) (M+F) correlated to ↑ BUN, ↓ albumin in some animals. Sporadic inappetence (mostly F). 5 mg/kg: hunched posture (1M) 150 mg/kg: vomitus (1M), hunched posture (1F)
			50	165,000 (82,300)	16,400,000 (3,820,000)	
	50	3F+3M	1	1,760,000 (133,000)	96,300,000 (5,060,000)	

ZW25-04-**13WTOX** [2363-002]) Batch: ENGR15-33			50	3,920,000 (1,490,000)	300,000,000 (93,500,000)	***Body weight*** *(1+2=13W-cohort; 3=8W-cohort):* 1. 50 mg/kg (M): ↓ week 1+2+6+11+13 compared to 13W-controls 2. 150 mg/kg (M): ↓ week 1-13 compared to 13W-controls 3. 150 mg/kg (F): ↑ week 6+7 compared to 8W- controls ***Food consumption (qualitative), indirect blood pressure, RR, ECG, indirect ophthalmoscopy***: no ZW25-related effects ***Clinical pathology***: <u>≥5 mg/kg</u>: ↑ BUN (non-dose dependent, persistent from D22 but not progressing during treatment, M+F) ↓ albumin (non-dose dependent, M+F) ***Hematology***: <u>≥5 mg/kg</u>: ↓RBC/Hct/Hgb (mild but persistent from D22). ↑ Retic ***Necropsy***: 150 mg/kg: Microscopically: minimal lung adhesion, inflammation and pleural fibrosis (1F) ***ADA formation***: <u>5 mg/kg:</u> ↓ ZW25 conc. D29-50 (1M) **<u>Recovery (150 mg/kg):</u>** Soft/watery faeces reversed towards normality and generally resolved but persisted in some animals ↑ BUN, ↓ albumin persisted in some animals ↓RBC/Hct/Hgb reversible in most animals ↑ Retic reversible in most animals **NOAEL: 150 mg/kg**
	150	5F+5M	1	4,780,000 (374,000)	297,000,000 (19,400,000)	
			50	8,610,000 (2,270,000)	687,000,000 (237,000,000)	
Cynomolgus monkey 13-week (QW) 8-week recovery 1-h iv infusion GLP ZW25-04-**13WTOX** [2363-002] Batch: ENGR15-33	5	4F+4M	1	173,000 (24,800)	9,950,000 (979,000)	
			85	315,000 (116,000)	23,200,000 (4,390,000)	
	50	4F+4M	1	1,720,000 (391,000)	95,600,000 (11,400,000)	
			85	2,460,000 (218,000)	203,000,000 (28,600,000)	
	150	7F+7M	1	4,760,000 (963,000)	334,000,000 (87,100,000)	
			85	6,680,000 (1,100,000)	534,000,000 (67,500,000)	

2.2.4.3. Genotoxicity

No genotoxicity studies were conducted in support of this application.

2.2.4.4. Carcinogenicity

No carcinogenicity studies were conducted in support of this application.

2.2.4.5. Reproductive and developmental toxicity

No dedicated reproductive and developmental toxicity studies with zanidatamab were conducted in support of this application. Fertility studies have not been performed with zanidatamab but its potential to impair fertility was assessed by histopathology and organ weight analysis as part of the pivotal repeat dose toxicity study.

A weight-of-evidence (WoE) approach was applied in order to provide evidence for a potential class effect of HER2-targeting agents on embryo-foetal development. The WoE assessment, based on published literature, reveal broad expression of HER2 in epithelial tissues of the developing foetus including the placenta and several vital organs in humans. Further, embryonic lethality due to heart and brain malformations is reported in ERBB2-deficient/mutated mice. In support, clinical case reports indicate that HER2-antibodies might be linked to cases of oligohydramnios and oligohydramnios sequelae manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

2.2.4.6. Toxicokinetic data

Toxicokinetics of zanidatamab was evaluated as part of single and repeat-dose toxicity studies. The assessment of toxicokinetics focuses on the pivotal 13WTOX study and is briefly presented here in the toxicology section while the main assessment can be found above under section 2.5.3 Pharmacokinetics.

Blood samples were collected for toxicokinetic analysis; for the 8W-cohort on Days 1 and 50 and for the 13W-cohort on Days 1 and 85 prior to dosing. In both cohorts, samples were also collected at 0.5, 1, 1.5, 2, 4, 8, 24, 72, 120, and 168 hours post dosing, and for recovery animals also at 336, 672, 1008, and 1344 hours. Blood was also collected from all animals (as appropriate) prior to dosing on Days 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78.

Individual serum concentration-time profiles, AUC, and C_{max} values were similar between males and females and the systemic exposure to zanidatamab and toxicokinetics were based on males and females combined. A summary of the toxicokinetics of zanidatamab is provided in the below table.

Table 12 Summary of Toxicokinetics of Zanidatamab Following Intravenous Administration of Zanidatamab to Cynomolgus Monkeys

Study	Dose mg/kg	N/Sex	Day	Cmax ng/mL (SD)	AUC $_{0\text{-}168h}$ hR*ng/mL (SD)	R ($AUC_{0\text{-}168hr}$ Day 22/50/85 : $AUC_{0\text{-}168hr}$ Day 1)
Single dose study	10	2F	1	246,000	16,100,000	NA
ZW25-01-PKTol	30	2F	1	882,000	47,800,000	NA
Cynomolgus monkey 4-week (QW) 1-h iv infusion	5	2F+2M	1	127,000 (16,000)	6,240,000 (376,000)	NA
			22	161,000 (8,370)	10,100,000 (1,820,000)	1.63
	50	2F+2M	1	1,390,000 (220,000)	83,900,000 (4,380,000)	NA

non-GLP			22	1,850,000 (123,000)	140,000,000 (16,700,000)	1.68
ZW25-02-28DTOX [2363-001] Batch: 886-A	150	2F+2M	1	3,720,000 (296,000)	233,000,000 (22,100,000)	NA
			22	5,790,000 (878,000)	473,000,000 (110,000,000)	2.02
Cynomolgus monkey 8-week (QW) 8-week recovery 1-h iv infusion GLP ZW25-04-13WTOX [2363-002]) Batch: ENGR15-33	5	3F+3M	1	145,000 (9,400)	8,060,000 (1,310,000)	NA
			50	165,000 (82,300)	16,400,000 (3,820,000)	1.99
	50	3F+3M	1	1,760,000 (133,000)	96,300,000 (5,060,000)	NA
			50	3,920,000 (1,490,000)	300,000,000 (93,500,000)	3.15
	150	5F+5M	1	4,780,000 (374,000)	297,000,000 (19,400,000)	NA
			50	8,610,000 (2,270,000)	687,000,000 (237,000,000)	2.30
Cynomolgus monkey 13-week (QW) 8-week recovery 1-h iv infusion GLP ZW25-04-13WTOX [2363-002] Batch: ENGR15-33	5	4F+4M	1	173,000 (24,800)	9,950,000 (979,000)	NA
			85	315,000 (116,000)	23,200,000 (4,390,000)	2.33
	50	4F+4M	1	1,720,000 (391,000)	95,600,000 (11,400,000)	NA
			85	2,460,000 (218,000)	203,000,000 (28,600,000)	2.15
	150	7F+7M	1	4,760,000 (963,000)	334,000,000 (87,100,000)	NA
			85	6,680,000 (1,100,000)	534,000,000 (67,500,000)	1.65

Abbreviations: $AUC_{0\text{-}168h}$ = area under the concentration-time curve from time 0 to 168h; C_{max} = maximum observed concentration; QW = once weekly.

For interspecies comparison and exposure margins to clinical exposure please refer to the below table.

Table 13 Safety Margin Calculation (Males and Females Combined)

Study ID/ Species	**NOAEL mg/kg**	**Study day**	**AUC (ng·h/ml) (M + F)**	**Corrected AUC (ng·h/ml) (M + F)**	**C_{max} (ng/ml) (M + F Combined)**	**Animal:Human Exposure Multiple (AUC=corrected)**
ZW25-04-13WTOX Cynomolgus monkey	150	Day 1[a]	333,500,000	47,642,857	4,760,000	10.3[a] (C_{max}, first dose)
		Day 85[a] (SS)	534,000,000[a]	76,285,714	6,685,000	10.4[b] (C_{max}, first dose)
		Day 1[b]	296,500,000	42,357,143	4,775,000	10.9[a] (C_{max}, steady state)

		Day 50[b] (SS)	686,500,000	98,071,429	8,595,000	14[b] (C_{max}, steady state)
ZWI-ZW25-203 Human		Cycle 1	56,016,000	4,001,143	461,100	11.9[a] (AUC, first dose) 10.6[b] (AUC, first dose)
		SS (≥cycle 4)	97,420,800 h·ng/mL	6,958,629	612,100	11[a] (AUC, steady state) 14.1[b] (AUC, steady state)

Abbreviations: AUC = area under the curve; C_{max} = maximum observed concentration; F = female; M = male; NOAEL = no observed adverse effect level; SS = Steady state.
[a] Monkey 13W-cohorte. [b] Monkey 8W-cohorte. Cynomolgus monkeys received 150 mg/kg QW for 8/13 weeks and humans received 20 mg/kg Q2W. Human data from Study ZWI-ZW25-203, data cutoff date: 28 July 2023.

2.2.4.7. Local tolerance

Local tolerance was evaluated as part of the 13-week GLP compliant repeat-dose study following intravenous infusion of zanidatamab in cynomolgus monkeys. No changes were observed that indicated local intolerance.

2.2.4.8. Other toxicity studies

Tissue-cross Reactivity

Tissue binding specificity of zanidatamab was evaluated in vitro in two tissue cross-reactivity (TCR) studies (non-GLP + GLP) with human tissues. A TCR study with a panel of human tissues is a recommended component of the safety assessment package supporting initial clinical dosing to provide evidence for predicting primary target organs and clinical adverse drug reactions. However, no in vitro TCR studies nor in vivo tissue distribution studies were performed with/in cynomolgus tissue/monkeys. The lack of TCR studies in monkey tissue limit the ability to demonstrate comparable distribution of HER2 epitopes and to evaluate toxicity arising from unintentional tissue cross-reactivity of zanidatamab.

This assessment focuses on the GLP compliant study in human tissue (ZW25-09-GLP-TCR). Binding specificity of zanidatamab (batch ENGR15-33) was evaluated in cryosections of 36 normal human tissues at low and high zanidatamab concentrations. Test tissues were selected in accordance with current guidance and 3 samples of each tissue, from 3 unique individuals, were stained. Binding of zanidatamab was evaluated by immunohistochemistry and visualized under light microscopy. Positive and negative controls were included in each experiment, and Human $IgG1_{Kappa}$ was used as control antibody. CD31 staining was used to qualify the adequacy of the tissue samples.

Table 14 Summary of study ZW25-09-GLP-TCR

Study: ZW25-09-GLP-TCR	
Test Article (vehicle/formulation): ZW25	**Method of Administration**: In vitro
Test Article Lot No.: ENG15-33	**Dose**: 1 and 10 µg/mL
Species / Strain: Human	**Duration of Dosing:** n/a
Gender and No. per Group: n/a	
Noteworthy Findings: The ZW25 staining pattern was generally consistent with expression of HER2 reported in the published literature for human tissues (Press, 1990; Liu, 2001), with the exception of the following: lung (type II pneumocytes), pituitary pars (intermedia glandular epithelium), spinal cord (ependymal epithelium) and thyroid (follicular epithelium). While the spinal cord exhibited membrane staining, the existence of the blood-spinal-cord barrier should limit in vivo exposure of these tissues to ZW25 (Rossi, 2013).	

Abbreviations: HER2 = human epidermal growth factor receptor 2; n/a = not applicable; ZW25 = zanidatamab (also known as JZP598).

Antigenicity

Antigenicity was assessed as part of the pivotal GLP 13WTOX study supported by the non-GLP 28DTOX study. No ADA formation was noted at any dose levels in the 28DTOX study. 8W-cohort data is marked with a and 13W-cohort data with b (see table above). Blood samples were collected for anti-zanidatamab-antibody (ADA) analysis at pretestab, day 29ab, 57a/92b, 106a/141b. A total of 292 samples were screened for ADA. Post-dose, ADAs were detected during screening in a single low dose 8W-cohort male monkeya on day 29 and 57. Despite a negative confirmatory assay, zanidatamab concentrations were below the level of quantification from day 29-50. ADA positives were also reported at screening in a total of 4ab control or pre-test samples of which 2 were confirmed positive. Nevertheless, post-dose bioanalytical results of zanidatamab levels were within the variation range for other animals in the respective treatment groups. Further, the majority of treated animals had zanidatamab serum concentrations that exceeded the specific tolerance level of the used assay, and ADAs can have been present but undetectable due to high zanidatamab concentrations.

Immunotoxicity

In the conducted primary pharmacodynamic studies evidence of CDC, ADCC and ADCP activation by zanidatamab was seen as a result of Fcγ receptor cross-linking on immune cells leading to induction of nontargeted immune cell activation. When occurring locally by zanidatamab-binding on the HER2-expressing tumour cell, this is considered a part of the mode of action (MoA). However, if occurring off-target it would be considered immunotoxicity. Additionally, a PBMC proliferation assay (study id: ZW25-34) was conducted in order to evaluate potential systemic immunogenic activation.

The immunotoxic potential of zanidatamab was evaluated, as a part of the 8- or 13-week GLP compliant repeat-dose study. No histopathological findings of inflammation and no changes in immune-related organs were noted, expect for minimal to moderate thymic lymphocyte depletion in female animals across all dose groups including controls accompanied by a >50% reduction in thymic weight in the 150 mg/kg group. The thymic findings were assigned to biologic variation/physiologic involution by the applicant, however, the clinical relevance of the thymic changes is unclear.

Decreases in serum albumin of up to 12% were observe from day 22 but not considered a result of immunotoxicity. Additionally, a non-severe reversible anaemia was noted.

ADA formation was observed .

Studies on metabolites

No traditional metabolism studies were performed for zanidatamab.

Studies on impurities

No original data on impurities were presented in the toxicology part of the dossier. The applicant referred to Module 3 (quality) for details, but stated that the impurity profile of the GLP lot (ENGR15-33, also known as DEVASAA-6) was within the specifications and impurities were at equivalent or greater levels compared to the impurities in the clinical lot. There were no impurities that would require qualification in toxicological studies.

Phototoxicity studies

No phototoxicity studies were conducted in support of this application.

Excipient studies

Lot ENGR15-33 (also known as DEVASAA-6) used as test material in the 13WTOX GLP study was formulated in 10 mM acetate, 0.01% polysorbate 20 and 9% sucrose 13WTOX GLP study. Of note, during later stages of drug development, acetate was substituted with succinate.

2.2.5. Ecotoxicity/environmental risk assessment

Zanidatamab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no environmental risk assessment for zanidatmab is required.

2.2.6. Discussion on non-clinical aspects

Pharmacology

Zanidatamab (also known as ZW25 and JZP598) is a humanized, immunoglobulin G isotype 1 (IgG1)-like human epidermal growth factor receptor 2 (HER2)-targeted bispecific antibody (Ab) which binds to the HER2 extracellular domain (ECD) to a similar extent in humans and cynomolgus monkeys but with lower affinity in dogs. No binding is observed in rodents. It is therefore agreed that cynomolgus monkeys appears to be the most relevant non-clinical species.

Zanidatamab was investigated in terms of binding affinity and mode of action. It was demonstrated that zanidatamab is a biparatopic antibody (Abs) that binds in trans configuration in the HER2 extracellular domain by binding both ECD2 and ECD4 on two different HER2 molecules. Biparatopic binding of HER2 receptors is a defining characteristic of zanidatamab, leading to cross-links between receptors and resulting in large cell surface HER2 clusters, which facilitates Fc-mediated cytotoxicity via complement-dependent cytotoxicity (CDC), in contrast to monoparatopic binding Abs, which do not induce this effect. Binding affinity studies with different cancer cell lines demonstrated that zanidatamab binds with higher affinity to tumour cells expressing high levels of HER2 receptors (HER2 3+), whereas affinity to tumour cells negative for HER2 receptors or expressing low levels (2+, 1+, 0) was reduced. As part of its mode of action, zanidatamab mediates internalization of surface HER2 as well as downregulation of cell surface HER2, total HER2 and intracellular phosphorylating signalling pathways. Zanidatamab induces both a ligand-independent and ligand EGF-dependent inhibition of tumour cell growth in vitro in HER2 3+-expressing cancer cell lines, including

breast, gastric, oesophageal, and lung cancer cell lines. The inhibitory response varied depending on the cancer type, with the highest activity observed in the NCI-N87 gastric cell line. As part of its mode of action, in vitro results demonstrated that zanidatamab activates Fc-dependent immune effector mechanisms, including complement-dependent cytotoxicity (CDC), Antibody-Dependent Cellular Cytotoxicity (ADCC) and Antibody-Dependent Cellular Phagocytosis (ADCP). It was demonstrated that zanidatamab only induces CDC in HER2 3+ expressing cancer cell lines and not lower HER2 expressing cell lines while ADCC and ADCP was induced in both HER3+ and 2+-expressing cell lines, but not in HER negative cell lines. CDC was not observed for trastuzumab or pertuzumab alone, while the combination of trastuzumab and pertuzumab only mediated CDC in cell line NCI-N87 to a much lesser degree than zanidatamab. Comparable levels of ADCC and ADCP was induced by zanidatamab, trastuzumab and pertuzumab as well as the combination in vitro. These immune-mediated responses support zanidatamab's ability to recruit the immune system in targeting HER2-positive tumours, complementing its direct effects on tumour cell proliferation.

Zanidatamab was investigated in vivo in different HER2 3+ expressing cancer cell line xenograft models in BALB/c nude mice against negative controls, trastuzumab alone or the combination of trastuzumab + pertuzumab. Zanidatamab generally displayed a dose-dependent response in the investigated cell lines, however, lack of an increased response compared to the negative control was observed in an ovarian cancer cell line (SKOV-3), as zanidatamab was only superior against IgG (negative control) at the highest dose level of 10 mg/kg, but not at 0.1, 0.3, 1 or 3 mg/kg. When tested against IgG as a negative control in the GXA 3054 gastric adenocarcinoma cell line at the single dose level of 30 mg/kg that was included, zanidatamab demonstrated a superior response compared to IgG. Zanidatamab showed superior efficacy against trastuzumab alone or the combination of trastuzumab and pertuzumab at 2 and 4 mg/kg in a human gastric adenocarcinoma cell line (NCI-N87). Zanidatamab was however not superior at the highest dose level of 8 mg/kg against the combination of trastuzumab and pertuzumab. The non-clinical in vivo data therefore indicates that higher dose levels of zanidatamab is needed to induce a significant clinical response, but also that zanidatamab may not be superior to the combination of trastuzumab and pertuzumab, depending on the setting and tumour type. It was confirmed in vivo that zanidatamab elicits no efficacy in HER2 negative cancer cells.

From the non-clinical in vitro and in vivo pharmacology results, there is a large variation in tumour growth inhibition and efficacy in general, depending on the HER2 expression level of the investigated cancer cell lines. Tumour cells expressing high levels of HER2 receptors (HER 3+) was by far the most responsive cell types. Mechanistically, in vitro studies demonstrated that zanidatamab seems to have a higher binding affinity and effect in tumour cells with high expression of HER2 receptors (HER2 3+) in terms of ligand-dependent and -independent reduction in cell viability and CDC activation, compared to tumour cells with low expression of HER2 receptors (HER2 2+, 1+ and negative). Specifically, concerning the HER2 Downregulation: Zanidatamab is noted for mediating strong HER2 downregulation, but in some cases, the trastuzumab + pertuzumab combination outperforms zanidatamab (e.g. SK-BR-3 and BT-474 cells). The varying results observed in the non-clinical pharmacology are relevant for the assessment of efficacy in humans.

The applicant performed an ex vivo study of immunogenicity to investigate potential undesired immunological responses of zanidatamab compared to other antibodies, using human peripheral blood mononuclear cells (PBMCs) (study ZW25-34). None of the tested antibodies induced a statistically different response in proliferation of cells compared to the negative control. Furthermore, no immunotoxic effects were observed in the 13-weeks monkey study (seeToxicology section below). Hence, this supports a low immunogenic potential of zanidatamab.

In studies conducted with zanidatamab, CDC, ADCC, and ADCP were most consistently and reproducibly observed in vitro in cells with higher expression of HER2 (≥2+) (studies ZW25-36, ZW25-37 and ZW25-38). No antibody-mediated effector function is expected in low HER2-expressing non-malignant adult tissues.

Safety pharmacology endpoints were incorporated into the GLP-compliant 8- or 13-week repeat-dose toxicity study in cynomolgus monkeys (study ZW25-04-13WTOX (2363-002)), which is considered acceptable in accordance with ICH S6(R1) and S9. No notable zanidatamab-related effects were observed in cardiovascular (ECG and blood pressure), respiratory or central nervous systems.

Pharmacokinetics

The methods developed to measure zanidatamab and anti-zanidatamab antibody in cynomolgus monkey serum have been suitably validated and support the non-GLP and GLP pivotal toxicology studies. The ECL assay for detection of zanidatamab was validated across a calibration range of 3.91 to 125 ng/mL.

The validated anti-zanidatamab bridging ECL assay had a screening assay cut point of 795 and a confirmatory assay cut point factor of 47.66%. The relative sensitivity was 8.59 ng/mL (assessed using a surrogate positive control HER2 antibodies). In this assay the drug tolerance was 31.15 µg/mL (low positive control) and 187.62 µg/mL (high positive control).

Zanidatamab is by definition fully absorbed into the circulation as it is administered by intravenous infusion. Overall, with respect to absorption, there were no significant gender-related differences observed in exposure parameters across single or repeat-dose studies using both male and female cynomolgus monkeys. Systemic exposure based on Cmax and AUC0-168h increased with dose from 50-150 mg/kg with a notable deviation from proportionality in exposure levels following both single and repeated doses. Accumulation of zanidatamab was observed between 5-50 mg/kg dosing. Interestingly, accumulation ratio was reduced again from 50-150 mg/kg, indicating increased clearance at higher doses, which was also supported by decreasing serum concentration of zanidatamab occurring at and above 50 mg/kg. As expected due to the IV route of administration, Tmax was rapid and occurred within 1-2 hours upon infusion in both single dose and repeat-dose studies, except for the high dose group after repeated dosing Day 1 and 85, where Tmax ranged from 1-4 hours and 1-24, possibly as a consequence of imprecise administration to the surrounding tissue. The mean half-life showed noticeable variation, which could have been due to limited half-life data or due to the observed (treatment related) diarrhoea, and ranged between 3- and 9-days after repeated dosing. Nonetheless, the terminal half-life for zanidatamab was similar to the reported half-life of trastuzumab from repeated-dose studies in monkey wherein the terminal half-lives ranged from 3 to 14 days. Clearance for zanidatamab was slow and reasonably similar between groups with mean values ranging between 0.181 and 0.537 mL/h/kg in the 13-week repeat-dose study and 0.394 to 0.518 mL/h/kg in the single dose study. Corresponding mean volume of distribution was consistent with the serum volume of monkey (between 13.9 and 77.3 mL/kg in the 13-week repeat-dose study and 48.5 to 65.0 mL/kg in the single-dose study), suggesting that zanidatamab did not distribute extensively outside of the serum compartment.

No ADA-formation was noted in the 28-day repeat-dose study but animals in the pivotal 13-week study were confirmed positive for ADA formation against zanidatamab during the screening of control, pre-dose and post-dose samples, some of which were not confirmed in the confirmatory assay. The validity of the ADA-assay, more specifically the sensitivity and drug tolerance level, has been questioned, as the assay may not properly detect or quantify the presence of ADA. Assay interference is indicated and is made possible by either high zanidatamab concentrations or by the presence of endogenous soluble HER-2 in pre-dose samples. Indeed, with respect to the former, the majority of zanidatamab-treated animals had serum

concentrations that exceeded the specific drug tolerance level of the assay (31.1 µg/mL); thus, ADA may have been present but undetectable. The possible presence of undetected ADA and the possible presence of soluble HER2 in pre-dose samples causing false negatives may explain the higher TK variability seen in some animals following repeated dosing of zanidatamab. ADA did however not affect exposure levels greatly and sufficient exposure is considered sustained after repeated dosing with zanidatamab.

No dedicated distribution, metabolism, excretion or pharmacokinetic drug interaction studies were performed with zanidatamab in line with ICH guideline S6(R1) which is considered acceptable.

Toxicology

Single dose toxicity

The maximum tolerated dose (MTD) was not reached in any studies. This is considered acceptable due to the exposure multiple of at least 10-fold and in the view of the advanced cancer indication.

Repeat dose toxicity

The overall study design of the 13-week repeat-dose toxicity study (13WTOX) in cynomolgus monkeys is considered adequate with an exposure margin of approximately 10-fold at the highest dose of 150 mg/kg administred once weekly. Of note, the recommended clinical dose of zanidatamab is 20 mg/kg (iv-infusion, Q2W). Hence, the treatment interval is different between monkeys (QW) and patients (Q2W).

Zanidatamab was generally well tolerated at all dose levels showing a low level of toxicity. The main finding was a drug-associated but non-dose dependent increase in the incidence of soft/watery faeces across treatment groups compared to controls. No noteworthy test-related effects were noted on body weight or general clinical appearance. Except for a few animals receiving fibre supplementation, no intervention was required, indicating that the gastrointestinal (GI) condition was non-severe. No GI macro- or microscopic correlates were observed. Full recovery was not obtained for all recovery animals but the incidence of soft/watery faeces was reported to be more sporadic in recovery animals and generally comparable to the incidence of soft/watery faeces in controls which indicate reversibility. However, recovery data were not presented schematically, making it difficult to confirm this claim.

It is well-known that diarrhea is a common side effect of EGFR-inhibitors with a mechanism that is still unclear, and that diarrhea may occur independently of intestinal tissue damage in experimental animals. Thus, it is agreed that the GI effect is a result of a pharmacological effect related to zanidatamab. As the condition was transient, no dose-dependency was noted in frequency or severity, and no effect were seen on body weight, it is considered acceptable that the applicant omitted the GI findings when determining the NOAEL. Nevertheless, diarrhea is sufficiently described in the repeat dose toxicology paragraph in section 5.3 of the SmPC.

In some animals, soft/watery faeces were correlated to increased blood urea nitrogen (BUN) and/or decreased blood albumin levels. It is agreed that increases in BUN were minimal and may be secondary to mild subclinical dehydration, but not all cases of increased BUN correlated with soft/watery faeces. From day 22, BUN was generally increased up to 45% and persisted in recovery animals despite a reduction in the incidence of soft/watery faeces. Therefore, a direct effect of zanidatamab on BUN cannot be ruled out. However, increases in BUN were non-dose dependent, did not progress in magnitude, and were within the historical control range at the test facility except of slight exceedances in a few animals. Furthermore, zanidatamab did not significantly affect creatinine levels, BUN:creatinine ratios or urinalysis parameters, and histopathological findings raised no concern of kidney toxicity. Of note, in patients treatment-emergent

increases in creatinine (<grade 3) were reported, whereas changes in BUN were not. Based on this, the BUN changes are considered of limited clinical concern. Nevertheless, inclusion of the BUN changes in section 5.3 of the SmPC is considered relevant.

Non-dose dependent decreases in blood albumin of up to 12% were reported throughout the dosing phase. Decreases were observed at all dose levels but were generally most pronounced in animals at 5 and 50 mg/kg QW and in males. It was stated that loss in the GI tract secondary to watery faeces may have contributed to the observed changes, however, no GI histopathological changes were noted. Other potential underlying causes were not discussed. Changes in albumin persisted throughout the recovery period in some animals despite a significant reduction in the incidence of diarrhoea. The diarrhoea-status of animals with decreased albumin levels were not specified. However, it is agreed that the observed changes in albumin may be considered mild and non-severe. According to the applicant, albumin levels in recovery animals (150 mg/kg) were generally within the range of individual values reported in recovery controls and/or historical control reference range. For a few low dose (1M/4M) and mid-dose (2M/4M and 1F/4F) animals, albumin levels were slightly below the historical control reference range. Based on the presented data, it cannot be excluded that the persistent decrease in recovery albumin levels in some animals may be a consequence of zanidazamab. However, it is accepted that only limited clinical concern exists considering the indication of Ziihera and the fact that clinical decreases in albumin levels were non-severe (< grade 3).

Slight decreases in red blood cell count (RBC), haematocrit (Hct) and haemoglobin (Hgb) levels compared to baseline were seen in all groups, including controls. Based on the presented data, the anaemia can be classified as a non-severe and reversible effect. The underlying mechanism of anaemia is unknown. Nevertheless, mentioning of the observed hematologic changes is important as anaemia is a very common side effect in human patients according to section 4.8 in the SmPC. Although anaemia seen in monkeys possibly has a clinical correlate, it does not raise significant clinical concern, as it is a non-severe, reversible effect and is sufficiently monitored in human patients.

Short-term hunched posture, vomitus, and inappetence were observed at limited incidences and in inconsistent patterns. However, the observations are relevant as abdominal pain, nausea and vomiting are very common adverse reactions in treated patients. Hence, a treatment-related component cannot be ruled out. Sporadic observations of alopecia, dry skin and erythema were also noted. Overall, it is agreed that these observations may be considered procedural or incidental but it is noted that rash is a very common adverse effect in humans.

In 13WTOX, microscopic evaluation showed minimal lung adhesion, inflammation and pleural fibrosis (1 high-dose female). Similar findings were seen in 28DTOX (1 high-dose male), which correlated macroscopically with thoracic cavity adhesion. Individual clinical examinations and respiratory evaluations did not predict pneumonia in these monkeys. The lung inflammation was observed with limited incidence and also appeared in historical control data. Of note, the GLP tissue-cross reactivity study in human tissue showed only cytoplasmic staining in the lung. Altogether, it is likely that the observed findings in monkeys are not zanidatamab-related.

The NOAEL was established at the highest dose level of 150 mg/kg. The GI, BUN- and albumin-findings were adequately included in section 5.3 of the SmPC.

Genotoxicity, carcinogenicity, and phototoxicity

No mutagenic, carcinogenic or phototoxic potential is expected and the waiving of such studies is considered acceptable in accordance to ICH S6(R1), S9, and S10.

Fertility and early embryonic development

In accordance with ICH S9 and S6(R1), a dedicated fertility and a reproductive and development toxicity studies have not been conducted with zanidatamab. However, antibodies that bind to HER2 have been observed to cause severe embryo-foetal toxicity. Embryo-foetal Toxicity is an important potential risk in the RMP. Based on the mechanism of action, zanidatamab may cause embryo-foetal harm when administered during pregnancy. There are no animal data on the use of zanidatamab in pregnancy. Female patients should use effective contraception during treatment with Ziihera and for 4 months following the last dose of zanidatamab. To exclude pregnancy, women of childbearing potential should undergo pregnancy testing before initiation of Ziihera.

Potential impairment of fertility was evaluated by histopathology and organ weight analysis in general toxicology studies. No male reproductive organ weight or microscopic alterations were observed. Statistically significant decrease in absolute uterus weight was seen in all dosed females. The decrease was less pronounced when adjusted for body or brain weight and there were no microscopic correlates. No specific concerns regarding impaired fertility based on the pharmacological activity of zanidatamab and/or previous findings, e.g. from other HER2 inhibitor procedures, were raised by the applicant. Based on this, it is agreed that zanidatamab had no effect on male and female reproductive organs at doses up to 150 mg/kg/week when evaluated by organ weights and histopathology. The wording regarding reproduction and developmental toxicity in section 5.3 of the SmPC is considered adequate.

Toxicokinetics

In accordance with current guidance, toxicokinetics of zanidatamab was evaluated as part of single and repeat-dose toxicity studies. The high dose of 150 mg/kg zanidatamab resulted in acceptable systemic exposure margins based on mean AUC corrected for dose-intervals and C_{max}.

Interspecies comparison and exposure margins to clinical exposure

In vitro studies demonstrated that zanidatamab binds to cynomolgus HER2. However, no tissue cross-reactivity studies nor tissue distribution studies were performed with/in cynomolgus tissue/monkeys. The lack of such studies limits the ability to assess the comparability in distribution of HER2 epitopes and toxicity arising from unintentional tissue cross-reactivity between the two species.

In monkeys, $C_{max,\ day50}$ (8,595,000 ng/mL, 8W-cohort) and $C_{max,\ day85}$ (6,685,000 ng/mL, 13W-cohort) compared to the clinical $C_{max,\ steady\ state}$ (612,100 ng/mL) provide exposure multiples of 14 and 10.9, respectively, which is considered acceptable in accordance with ICH S6(R1).

The applicant used human AUC_{∞} following the first dose to calculate exposure multiples at steady state. However, it seems more relevant to use the actual mean $AUC_{0-\tau,\ steady\ state}$ (cycle 4 or later) of 4059.2 days*µl/mL equivalent to 97,420,800 h·ng/mL. Using this value, the exposure multiple for AUC at steady state for the 13W-cohort was 5.5 and not 7.3 as stated. However, due to differences in the dosing intervals between monkeys (7 days) and humans (14 days) it is suggested to calculate and compare corrected $AUC_{steady\ state}$ values. Comparisons based on $AUC_{0-168h,\ day\ 50/85}$ divided by 7 and human $AUC_{0-\tau,\ steady\ state}$ divided by 14 provide safety margins of 14.1 and 11 for the 8W- and 13W-cohorts, respectively, which is considered acceptable.

Local tolerance

Local tolerance was evaluated as part of the 13-week GLP compliant repeat-dose study following intravenous infusion of zanidatamab in cynomolgus monkeys. No changes were observed that indicated local intolerance.

Tissue-cross reactivity

Tissue binding specificity of zanidatamab was evaluated at two concentrations (optimal and high) in vitro in tissue cross-reactivity (TCR) studies with human tissues. In a panel of normal human tissues, HER2 epithelial binding was unexpected in lung (type II pneumocytes), pituitary pars (intermedia glandular), spinal cord (ependymal), and thyroid (follicular). Of these tissues, only the spinal cord showed membrane staining, which is agreed to be considered of minimal clinical concern due to the limited in vivo exposure of the spinal cord protected by the blood-spinal cord barrier. In general, the cytoplasm is not typically accessible to antibodies in vivo. Hence, it is agreed that the unexpected epithelial cytoplasmatic binding of zanidatamab in lung, pituitary pars, and thyroid tissues most likely is of no clinical relevance. The clinical relevance of zanidatamab-specific membranous staining consistent with HER2 expression in the following human tissues was questioned: eye, placenta, prostate, skin, tonsil, ureter, and cervix. No clear relationship exists between zanidatamab interaction at HER2 membranous receptors and clinical or non-clinical effects. However, clinical observations of skin rash cannot be excluded as a potential consequence of zanidatamab binding to HER2 receptors in the skin. Rash is a very common adverse drug reaction in section 4.8 of the SmPC.

Antigenicity

The provided data support that ADA activity did not significantly affect the systemic exposure levels of zanidatamab.

Immunotoxicity

No signs of unexpected general immunotoxicity were seen in the conducted 8- or 13-week repeat-dose toxicity study except for ADA-formation.

Studies on metabolites

Zanidatamab is expected to be catabolized in vivo into small peptides and individual amino acids, hence it is accepted that no traditional metabolism studies were performed for zanidatamab.

Studies on impurities

In the pivotal W13TOX study, lot ENGR15-33 (also known as DEVASAA-6) of zanidatamab was used as test material. The impurity profile of the non-clinical batch was within the specifications, and impurities were at equivalent or greater levels compared to the impurity levels in clinical lots. No impurities required qualification in toxicological studies.

Excipient studies

All excipients are all well-known and commonly used in drug production. No toxicology concerns are raised.

Environmental risk assessment (ERA)

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, zanidatamab is not expected to pose a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the available pharmacological, pharmacokinetics and toxicological data are considered appropriate and sufficient for approval of zanidatamab for the treatment of HER2+ BTC patients.

2.3. Clinical aspects

2.3.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 15 Clinical Study Overview

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
ZWI-ZW25-101	Phase 1, 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[a]: combination therapy expansion cohorts treated at zanidatamab MTD, OBD, or RD plus selected antineoplastic agents	Locally advanced (unresectable) and/or metastatic HER2 expressing (HER2 1+, 2+, or 3+ by IHC) cancers Part 1: M/F: 22/24 Part 2: M/F: 67/79 Part 3[a]: N/A	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): • Monotherapy: 10 mg/kg IV QW or 20 mg/kg IV Q2W, the RDs identified in Part 1 Part 3[a] **(combination therapy)**: •10 mg/kg IV QW, 20 mg/kg IV Q2W, or 30 mg/kg IV Q3W, the RDs identified in Part 1	PK parameters for single (first) dose: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t_{½}$, $AUC_{0-\infty}$, CL, V_z For multiple doses: AUC_{tau} and C_{ave} for Dose 1, C_{max} and C_{min} [trough] for all following doses, accumulation index, fluctuation ratio, C_{ss}, attainment of steady-state

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
ZWI-ZW25-203	Phase 2b, open-label, 2-cohort, single-arm	HER2 gene-amplified, inoperable, and advanced or metastatic BTC, including ICC, ECC, and GBC Cohort 1: HER2 amplification by ISH and HER2 overexpression by IHC 2+ or IHC 3+ M/F: 35/45 Cohort 2: HER2 amplification by ISH and HER2 IHC 0 or IHC 1+ M/F: 5/2	Monotherapy: 20 mg/kg IV Q2W	PK parameters for single (first) dose: C_{max}, t_{max}, AUC_{0-t}, $t_{½}$, $AUC_{0-\infty}$, CL, V_z, C_{trough} For multiple dose: C_{trough}

Abbreviations: $AUC_{0-\infty}$ = area under the curve from time zero to infinity; AUC_{0-t} = area under the curve from time zero to last measurable concentration; AUC_{tau} = area under the curve during the dosing interval; BTC = biliary tract cancer; C_{ave} = average concentration over dosing interval; CL =clearance; C_{max} = maximum concentration; C_{min} = minimum concentration; C_{ss} = concentration at steady-state; C_{trough} = trough concentration DLT = dose-limiting toxicity; ECC = extrahepatic cholangiocarcinoma; F = female; GBC = gallbladder cancer; HER2 = human epidermal growth factor receptor 2; ICC = intrahepatic cholangiocarcinoma; IHC = immunohistochemistry; ISH = in situ hybridization; IV = intravenous; M = male; MTD = maximum tolerated dose; N/A = not applicable; OBD = optimal biologic dose; PK = pharmacokinetic; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; RD = recommended dose; $t_{½}$ = terminal half-life; T_{max} = time of maximum plasma drug concentration; V_z = volume of distribution in the terminal elimination phase; λ_z = terminal elimination rate constant.

[a] Results from Part 3 of Study 101 are not included in this summary.

2.3.2. Clinical pharmacology

2.3.2.1. Pharmacokinetics

The pharmacokinetics of zanidatamab (ZW25) was established from PK data obtained from the phase I study 101 and the phase II study 203. For the Phase I study, the following PK parameters were derived: PK parameters for single (first) dose: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t_{½}$, $AUC_{0-\infty}$, CL, V_z. For multiple doses: AUC_{tau} and C_{ave} for Dose 1, C_{max} and C_{min} [trough] for all following doses, accumulation index, fluctuation ratio, C_{ss}, attainment of steady-state. Dose levels from 5 to 30 mg/kg was tested with either QW, Q2W or Q3W. For the Phase II study 203, the following PK parameters were derived: PK parameters for single (first) dose: C_{max}, t_{max}, AUC_{0-t}, $t_{½}$, $AUC_{0-\infty}$, CL, V_z, $C_{trough.}$ For multiple dose: C_{trough}. The posology in this pivotal study was 20 mg/kg Q2W, which is the posology to be marketed.

Bioanalytical methods

Zanidatamab serum concentrations (PK)

The table below summarizes the zanidatamab serum concentration methods used to support clinical studies.

Table 16 Summary of Bioanalytical Methods for the Assessment of Zanidatamab Serum Concentrations

Validation Report Method Number	Laboratory	Validation Study Title	Clinical Studies Supported
SC-14/343-001 and SC-14/343-001 Addendum 1 GCL-442 (original method)	Eurofins Pharma Bioanalytics Services US Inc., 15 Research Park Drive, St. Charles, MO, 63304, USA	An ELISA for the Determination of ZW25 in Human Serum	ZWI-ZW25-101 (n = 192 participants)
8425-100 and 8425-100 Addendum 1 ELISA-0968	Labcorp Bioanalytical Services LLC, 8211 SciCor Drive, Indianapolis, IN, 46214, USA	Validation of a Method for the Determination of ZW25 in Human Serum Using an Enzyme-Linked Immunosorbent Assay (ELISA)	ZWI-ZW25-203 (n = 63 participants)
8414-357 ICSH-20-014	Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd. Shanghai, China	Validation of a Method for the determination of ZW25 in Human serum using Enzyme-Linked Immunosorbent Assay (ELISA)	ZWI-ZW25-203 (n = 24 participants)

Abbreviations: ELISA = enzyme-linked immunosorbent assay; USA = United States of America; ZW25 = zanidatamab.

An ELISA method for the quantitative determination of zanidatamab in human serum was developed and validated at Eurofins Pharma Bioanalytical Services US Inc (method GCL-442). All PK samples of study 101, as of the data cut-off of 01 November 2021, were analysed at Eurofins Pharma Bioanalytical Services. The ELISA method was then transferred and validated at Labcorp Bioanalytical Services LLC (Indianapolis, US) and at Labcorp Pharmaceutical Research and Development (Shanghai) Co., Ltd. (Shanghai, China) (method ELISA-0968 and method ICSH 20-014, respectively) for analysis of PK samples collected in pivotal Study 203.Validations and cross validation between methods GCL-442 and ELISA-0968 (Labcorp US vs China supporting study 203) were evaluated and met acceptance criteria.

Incurred sample reproducibility (ISR) was confirmed for study 101 (interim) and 203 at both the US and China site of Labcorp.

Immunogenicity

Zanidatamab immunogenicity testing was performed following a 3-tiered approach that included a screening assay (Tier 1), confirmatory assay (Tier 2), and titration (Tier 3). Samples testing positive in the screening assay were tested in a confirmatory assay. Confirmed positive samples were then titrated to determine the titer of antidrug antibody (ADA). Any samples confirmed positive for ADA could be further tested to characterize domain specificity and potentially neutralizing activity (NAb assay).

Of note, limitations of the ADA assay in the presence of soluble HER2 extracellular domain (sHER2-ECD) were observed during method validation and sample analysis, i.e. interference of sHER2-ECD in the ADA assays (low tolerance of approximately 10 to 15 µg/L) producing false positive results.

A combined analysis of positivity of serum samples for ADA against zanidatamab with levels of serum sHER2-ECD was conducted. It was found that positivity correlated with the presence of sHER2-ECD and that ADA positivity decreased during treatment as sHER2-ECD decreased due to treatment.

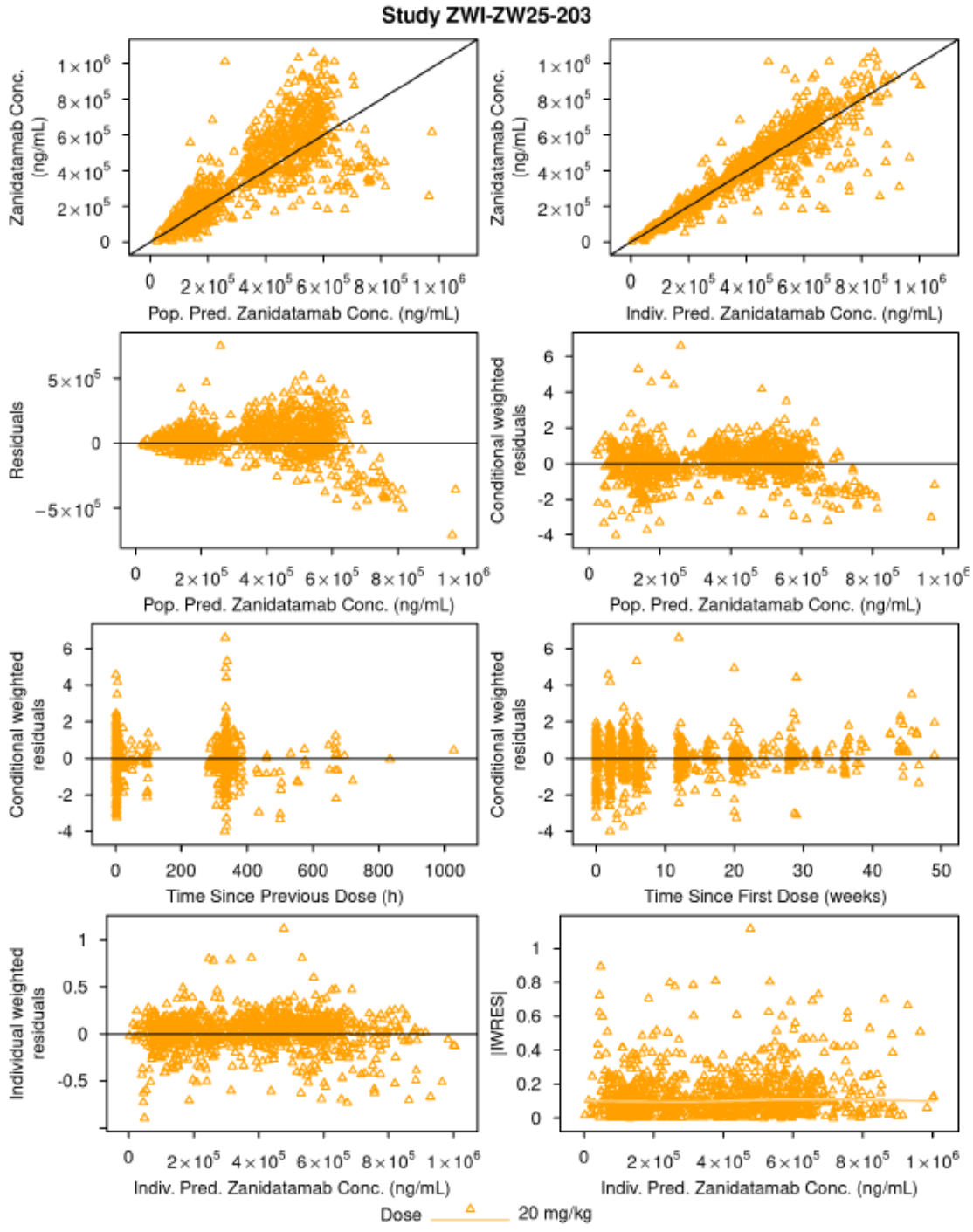
The strategy for interpreting the ADA data was to evaluate if the positive signal of ADA was persistent and if titer was increasing towards the end of the treatment. If this was not the case, the patient was considered negative for ADA.

Population PK model

A Pop PK model for zanidatamab was developed based on data from two clinical studies. Study 101 was a phase I study with multiple dose regimens in patients with various HER2-expressing cancers. Study 203 was a Phase IIb study with 20 mg/kg Q2W dosing on Days 1 and 15 of each 28-d cycles in patients with biliary tract cancer (BTC). Zanidatamab was administered by IV infusion using weight-based dosing defined by the Cycle 1 Day 1 body-weight. The final PK model was a 2-compartment model with zero-order drug input and with parallel linear and nonlinear CL pathways to describe elimination kinetics. Final parameter estimates are shown in in the below table.

Final GoF plots and pcVPCs for study 203 are shown in the below figures.

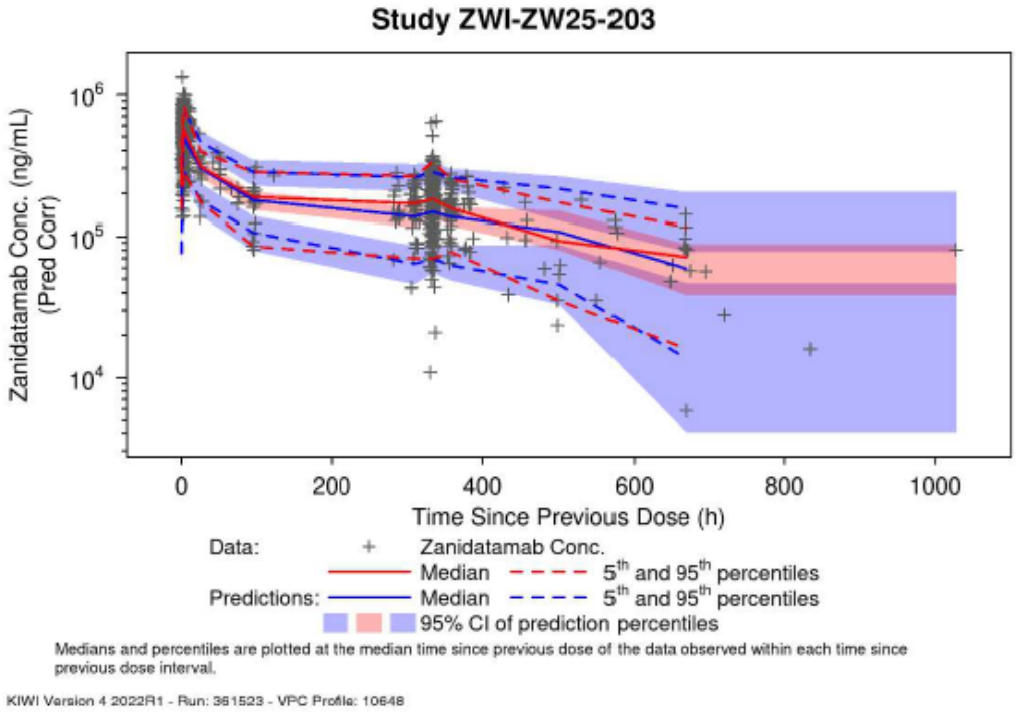
Figure 7 Goodness-of-Fit Plots for the Final Pharmacokinetic Model of Zanidatamab for the Overall Analysis Population, Presented by Study and Stratified by Dose (Continued)



KIWI Version 4 2022R1 - Run: 360224 - GOF Profile: 10621

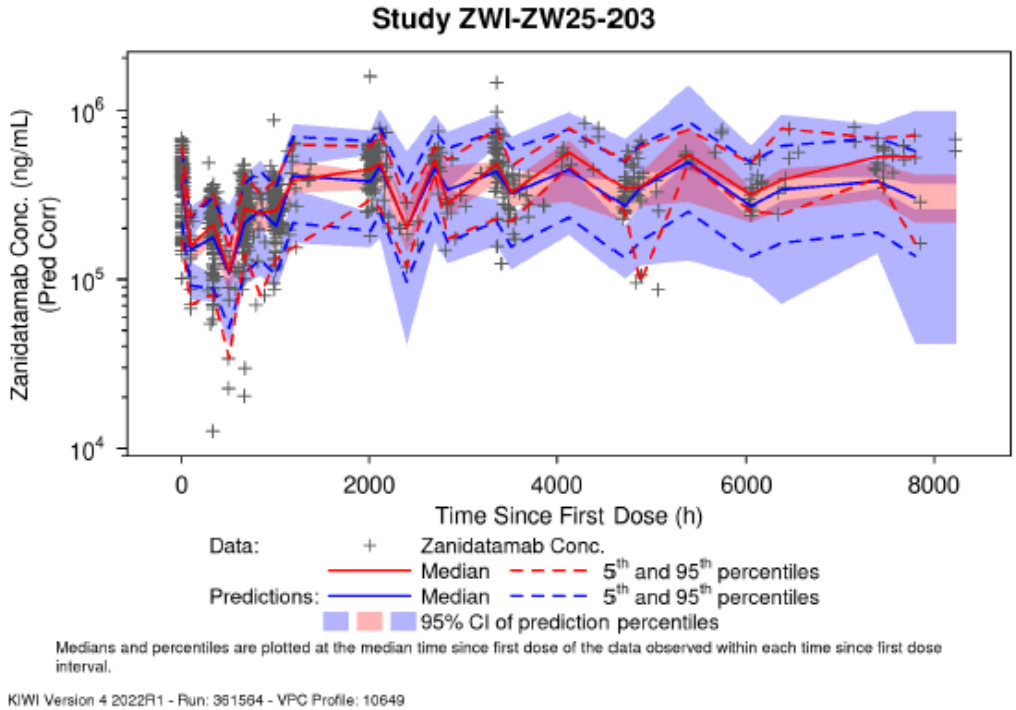
Abbreviations: Conc., concentration; Indiv., individual; |IWRES|, absolute value of the individual weighted residuals; Pop., population; Pred., predicted.

Figure 8 Prediction-Corrected Visual Predictive Check of the Final Pharmacokinetic Model for Study ZWI-ZW25-203 Data



Medians and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose interval.

KIWI Version 4 2022R1 - Run: 361523 - VPC Profile: 10648



Medians and percentiles are plotted at the median time since first dose of the data observed within each time since first dose interval.

KIWI Version 4 2022R1 - Run: 361564 - VPC Profile: 10649

Abbreviations: CI, confidence interval; Conc., concentration; Pred Corr, prediction corrected.

Table 17 Parameter Estimates and Standard Errors for the Final Population Pharmacokinetic 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: ALB, albumin; %CV, coefficient of variation expressed as a percent; GEA, gastroesophageal adenocarcinoma; IIV, interindividual variability; NA, not applicable; NE, not estimated; NLESIONS, number of lesions; %RSE, relative standard error expressed as a percent; 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.

KIWI Run 360224.

A bootstrap resampling technique was used to confirm the stability of the model and precision of parameter estimates across 1000 replicate runs of which 99.1% converged successfully. The mean parameter estimates and the level of variability on parameter estimates were closely reproduced after bootstrap and none of the 95% CI's contained the null. Clinical relevance of statistically significant covariate effects (body weight, ALB, number of lesions, and cancer type) included in the final population PK model was assessed by Forest plots. The figure below shows the impact on AUC,ss.

Figure 9 Forest Plots of Geometric Mean Ratios (90% Confidence Intervals) of Estimated Covariate Effects on Steady-State Zanidatamab Exposures Following Hypothetical 20 mg/kg Q2W Dosing

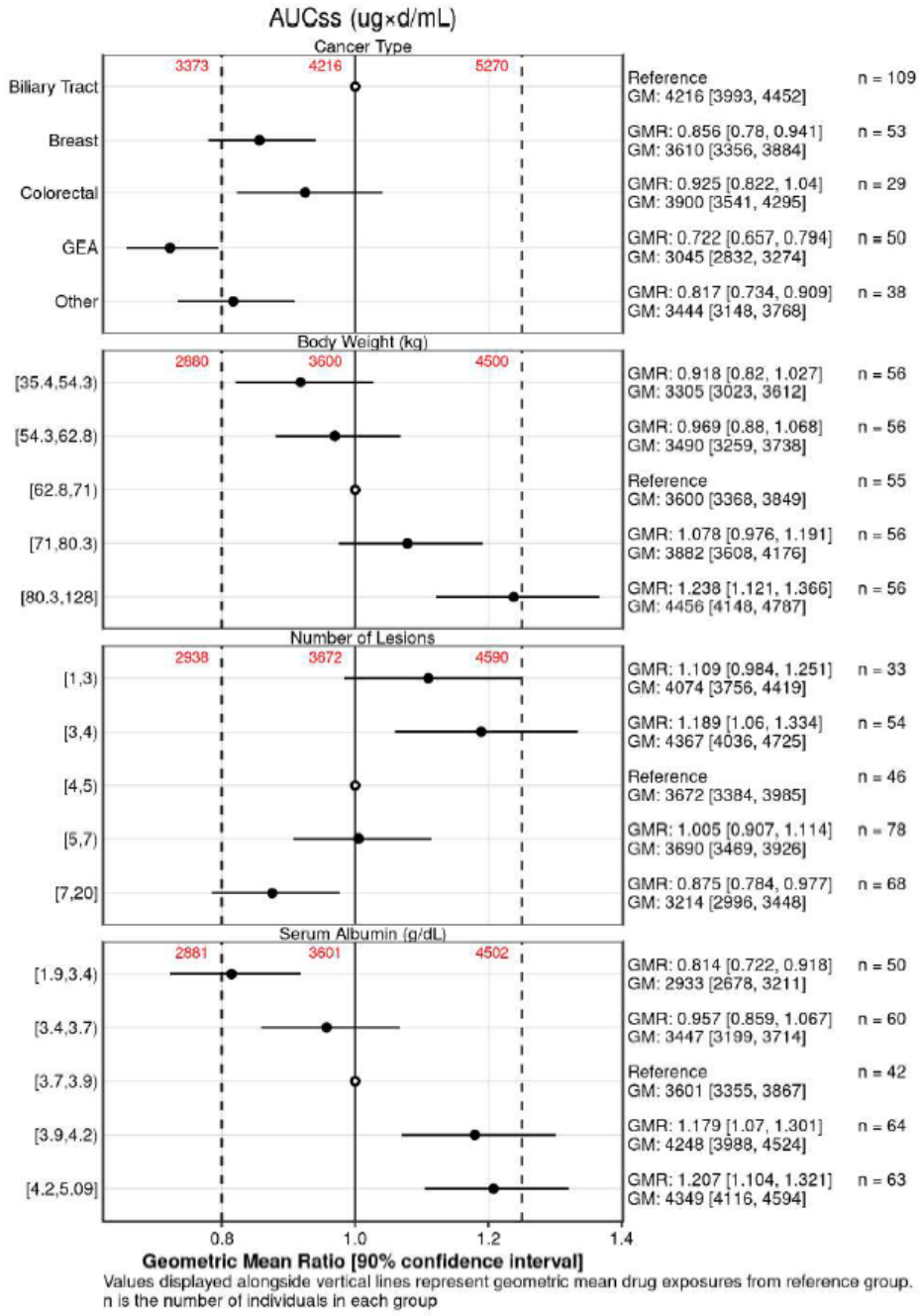
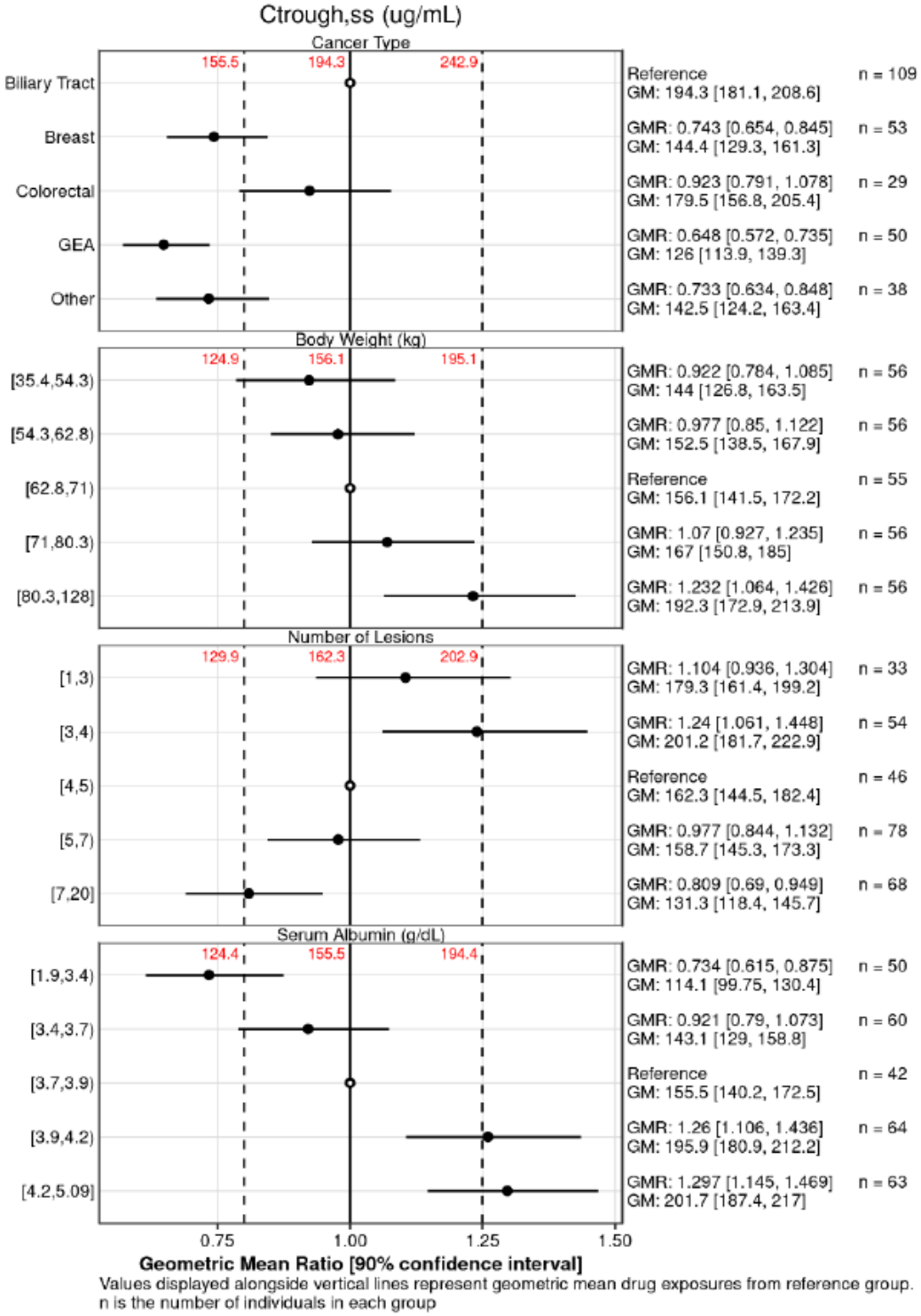


Figure 10 Forest Plots of Geometric Mean Ratios (90% Confidence Intervals) of Estimated Covariate Effects on Steady-State Zanidatamab Exposures Following Hypothetical 20 mg/kg Q2W Dosing

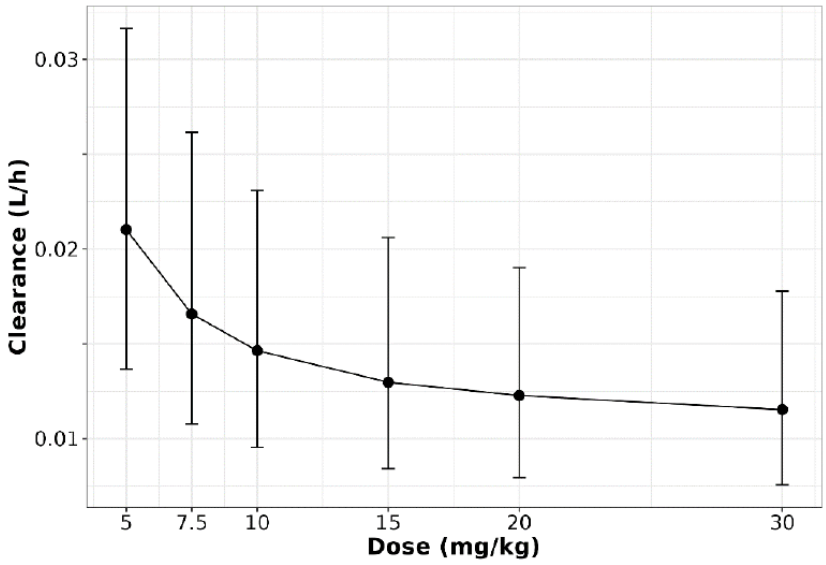


Abbreviations: AUC_{ss} = area under the curve within a dosing interval at steady-state; $C_{avg,ss}$ = average concentration at steady-state; $C_{max,ss}$ = maximum concentration at steady-state; $C_{trough,ss}$ = trough concentration at steady-state; GEA = gastroesophageal adenocarcinoma; GM = geometric mean; GMR = geometric mean ratio; Q2W = once every 2 weeks.

Note: "[or]" indicates the respective endpoint is included in the interval and "(or)" indicates the respective endpoint is not included in the interval.

The final Pop PK model was also used to simulate clearance in BTC patients across different doses (see figure below). The results of simulations indicated the target-mediated elimination pathway was likely saturated at the dose level of 20 mg/kg Q2W.

Figure 11 Predicted Steady-State Zanidatamab Clearance versus Dose Following Different Zanidatamab Q2W Dose Regimens



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: \\datastore\BU\RD\Restricted\PMx\jzp598\simulation\CLss\ClearancevsDoseSS.png

Absorption

Pharmacokinetic parameters of zanidatamab for generation 1 and 2 formulations as used in study 101 and study 203 is presented in the below table.

Table 18 Pharmacokinetic Parameters of Zanidatamab Administered Intravenously at 20 mg/kg Once Every 2 Weeks Following the First Dose

Drug Product Study	Cancer Type	PK Evaluable Participants (N)	Geometric Mean (%CV)					
			C_{max} (µg/mL)	AUC_{0-t} (day*µg/mL)	$AUC_{0-\infty}$ (day*µg/mL)	$t_{½}$ (day)	V_z (mL/kg)	CL (mL/h/kg)
Gen 1 ZWI-ZW25-101 (Parts 1 and 2)	All	32	416 (21.2)	2240 (21.8)	3000 (25.7)	7.12 (26.3)	68.4 (26.6)	0.278 (25.7)
	GEA	8	377 (17.7)	1900 (16.4)	2490 (18.1)	7.02 (13.8)	81.3 (16.5)	0.334 (18.1)
	Non-GEA	24	430 (21.6)	2360 (20.7)	3200 (25.0)	7.15 (29.6)	64.6 (27.0)	0.261 (25.0)
Gen 2 ZWI-ZW25-203	BTC	19	455 (16.3)	2280 (22.7)	2950 (25.9)	6.52 (17.4)	63.6 (20.1)	0.282 (25.9)

Abbreviations: %CV = percent coefficient of variation; AUC_{0-t} = area under the curve from time zero to last measurable concentration; $AUC_{0-\infty}$ = area under the curve from time zero to infinity; BTC = biliary tract cancer; CL = clearance; C_{max} = maximum concentration; GEA = gastroesophageal adenocarcinoma; Gen = generation; PK = pharmacokinetic; $t_{½}$ = terminal half-life; V_z = volume of distribution in the terminal elimination phase.
Note: The number of PK-evaluable participants denotes the lowest number of participants used to calculate the parameters across each row.

The observed zanidatamab exposure and PK parameters following the first administration in the first cycle and steady state, based on the available sampling scheme, are described in the table below.

Table 19 Study 203: Pharmacokinetic parameters (geometric mean [percent coefficient of variation]) of zanidatamab following the first administration of zanidatamab at 20 mg/kg Q2W in cycle 1 and steady-state in BTC patients

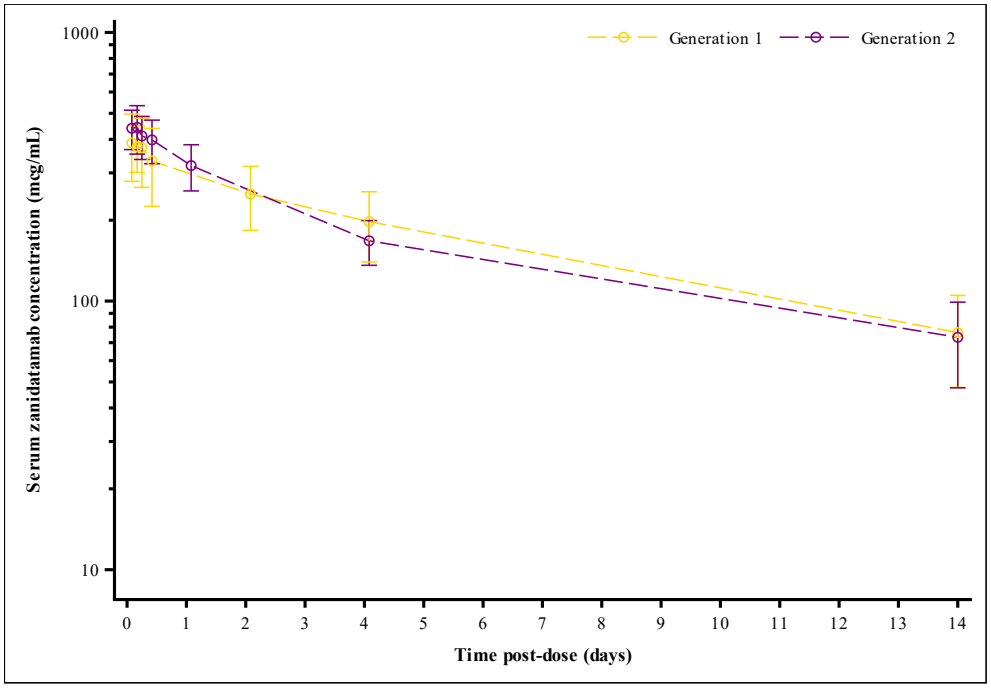
Cycle	**C_{max} (µg/mL)**	**C_{trough} (µg/mL)**	**AUC_{0-tau} (days*µg/mL)**
Cycle 1 N=19	455 (16.3)	68.3 (42.9)	2280 (22.7)
Cycle 4 or later (steady-state) N=8	600 (22.2)	178 (29.6)	3980 (22.5)

Abbreviations: AUC_{0-tau} = area under the curve during the dosing interval; C_{max} = maximum concentration; C_{trough} = trough concentration; Q2W = once every 2 weeks
Note: Cycle 1 and Cycle 4 are referred to as "first dose" and "steady-state", respectively; these terms are interchangeable.

Zanidatamab is by definition fully absorbed into the circulation as it is administered by intravenous infusion, hence bioavailability is 100%. However, two different formulations were used in the clinical trial program:

- Generation 1 formulation of zanidatamab is a liquid formulation utilized in phase 1 supportive study (study 101). In study 101, the PK parameters are presented for patients with and without GEA cancers, as the exposure to zanidatamab appeared to be lower in participants with GEA.
- Generation 2 formulation of zanidatamab is a lyophilized formulation utilized in later-phase clinical development including pivotal phase 2 study (study 203) and is intended to be used in commercialization. No bioequivalence study was performed for the different formulations. The figure below and the table above show similar pharmacokinetics of zanidatamab in the two formulations.

Figure 12 Zanidatamab Mean (± Standard Deviation) Concentration-Time Profiles Following the First Dose of IV 20 mg/kg Q2W of Generation 1 (Solution) and Generation 2 (Lyophilized Powder) Drug Products (PK Analysis Sets)



Abbreviations: GEA = gastroesophageal adenocarcinoma; IV = intravenous; PK = pharmacokinetic; Q2W = once every 2 weeks.
Notes: Symbols and error bars depict the arithmetic mean and standard deviation of zanidatamab serum concentrations. Generation 1 = participants with non-GEA cancers and extensive PK sampling who received Generation 1 (liquid) zanidatamab at 20 mg/kg Q2W in Part 2 of Study 101 (n = 30); Generation 2 = participants with extensive PK sampling who received Generation 2 (lyophilized) zanidatamab at 20 mg/kg Q2W in Study 203 (n = 19).

Distribution

Based on the PopPK analysis (2-compartment model), the typical central volume of distribution was predicted to be Vc = 3.51 L (CV% 21.9) and the typical peripheral volume of distribution was predicted to be Vp = 3.95 L (CV% 66.6) at 20 mg/kg Q2W zanidatamab. The sum of the central and peripheral volume of distribution is 7.46 L.

In pivotal study 203, the geometric mean of Vz (%CV) was 63.6 (20.08) mL/kg from dose levels of 20 mg/kg. Utilizing the median body weight of 68.5 kg, Vz of the noncompartmental analysis (NCA) is then 0.0636 L/kg * 68.5 kg = 4.36 L. Vz amounts to approximately 58% of the combined volumes of the PopPK analysis.

Elimination

Clearance:

The PopPK predicted typical clearance is 0.0115 L/h (CV% 27.9). Zanidatamab is expected to be cleared principally by catabolism. The primary route of clearance is via proteolytic degradation, which is expected to be at least partly target mediated, representing the non-linear saturable clearance pathway.

Half-life:

The PopPK estimated t½ is approximately 21 days for a typical patient with BTC. Based on the t½ estimate, steady-state is reached after approximately 3.5 months (i.e. 5 half-lives) when following multiple-dose administration of zanidatamab.

In the NCA of pivotal study 203, t½ is 6.5 days. The t½ at cycle 4 or later (steady-state) t½ is 13.8 days. The difference to the t½ estimated by the PopPK model is most likely due to the rather few data points on which the t½ is based in the NCA analysis, which is clearly a mixture of distribution and terminal t½. See the 2 figures below for PK profiles for the first dose and at steady state.

Figure 13 Zanidatamab Concentration-time Profiles Following First Dose Pharmacokinetics Analysis Set Semi-Log Scale (Study 203)

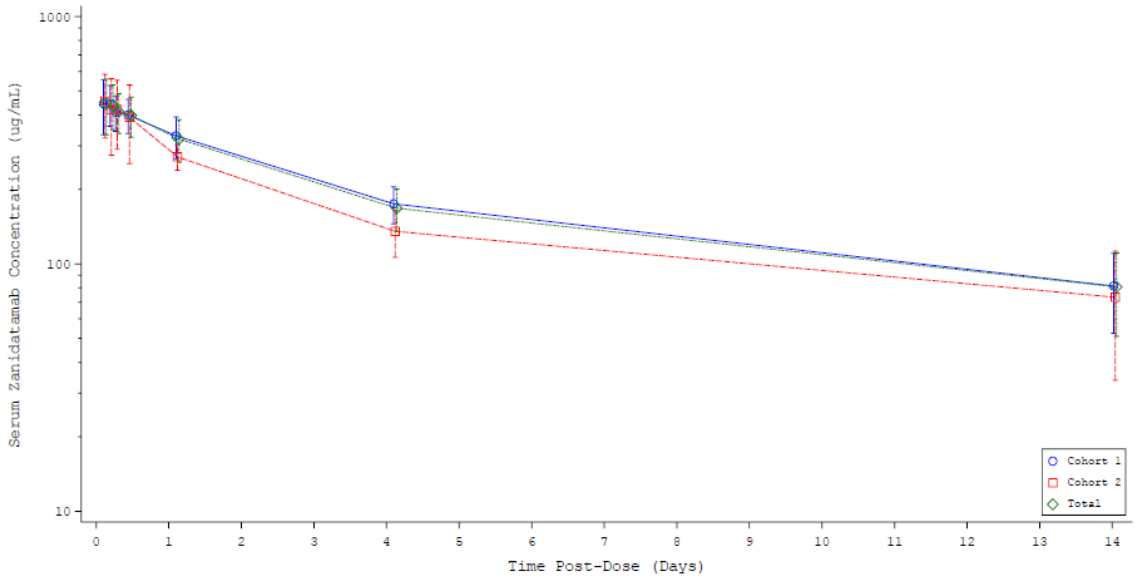
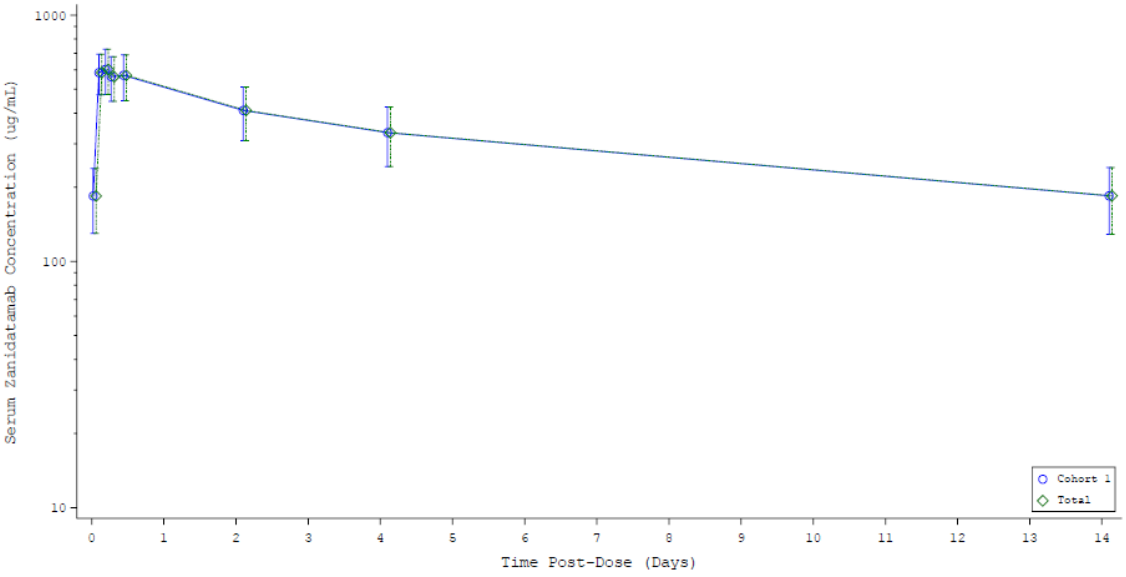


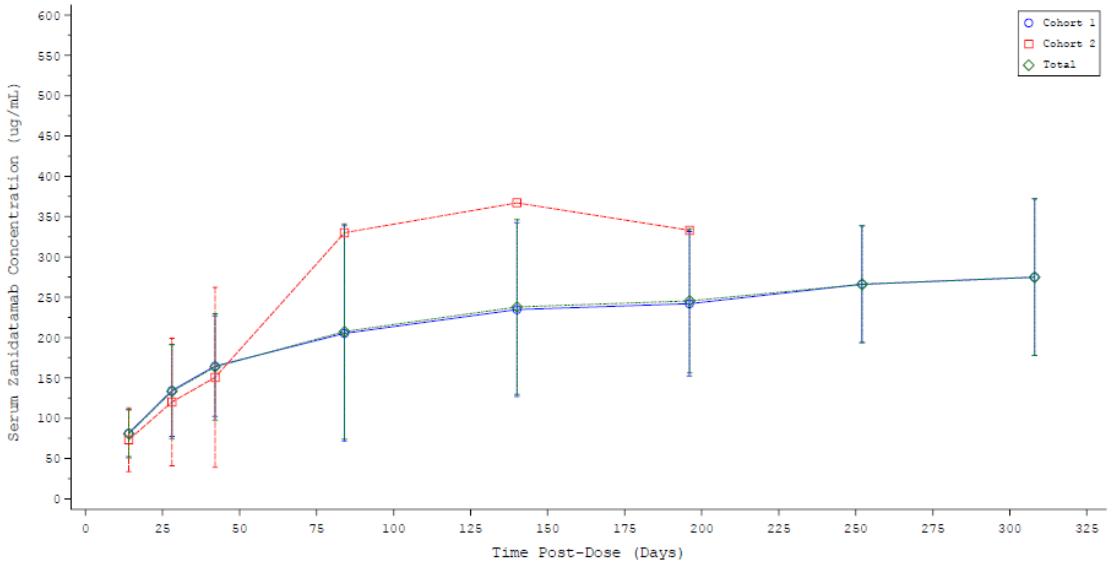
Figure 14 Zanidatamab Concentration-time Profiles in Steady State Pharmacokinetics Analysis Set Semi-Log Scale (Study 203)



Accumulation:

In the NCA, the accumulation index at steady-state was 2.7 for 20 mg/kg zanidatamab Q2W based C_{trough} of study 101. This is reasonably close to the expected accumulation rate of 3 with an estimated $t_{½}$ of 21 days and 14 days between dosing, although NCA data from a few patients in study 203 was more in the vicinity of 2 on AUC_{all}. See also figure below for development of Ctrough over time in study 203.

Figure 15 Zanidatmab Ctrough Over Time by Cohort Pharmacokinetics Analysis Set Linear Scale (Study 203)



Dose proportionality and time dependencies

As expected from monoclonal antibodies with target mediated drug disposition (TMDD), a certain level of non-linearity at the lower dose levels is evident. AUC0-inf of the first dose of QW posology from 5, 10 and 15 mg/kg show higher than dose proportional exposure, whereas AUC0-inf of the first dose of 20, 25 and 30 mg/kg show close to dose proportional increase in exposure. Hence, the recommended dose of 20 mg/kg Q2W is in the linear range, see the two tables below.

Table 20 Study 101 Part 1: Pharmacokinetic Parameters (Geometric Means [%CV]) of Zanidatamab Following the First Dose (PK Analysis Set)

Zanidatamab Dose Regimen	N	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{0-t} (day*µg/mL)	$AUC_{0-\infty}$ (day*µg/mL)	$t_{½}$ (day)	V_z (mL/kg)	CL (mL/h/kg)
5 mg/kg QW	3	105 (6.89)	15.3 (67.9)	348 (9.63)	443 (22.2)	3.64 (32.3)	59.2 (9.66)	0.470 (22.2)
10 mg/kg QW	5	224 (16.9)	73.4 (18.1)	855 (14.7)	1500 (20.6)	6.04 (23.7)	58.0 (18.7)	0.277 (20.6)
15 mg/kg QW	7	276 (35.6)	86.9 (40.1)	1040 (43.8)	1780 (47.3)	5.53 (38.5)	67.4 (47.8)	0.352 (47.3)
20 mg/kg Q2W	6	439 (15.5)	54.3 (40.6)	2180 (20.1)	2730 (20.7)	6.12 (29.4)	64.6 (33.2)	0.305 (20.7)
25 mg/kg Q2W	3	438 (2.40)	74.8 (14.7)	2320 (3.99)	3180 (10.9)	7.60 (29.0)	86.1 (18.5)	0.327 (10.9)
30 mg/kg Q2W	4[a]	542 (13.4)	117 (11.6)	2970 (15.1)	4640 (11.2)	9.59 (18.0)	89.5 (16.0)	0.269 (11.2)
30 mg/kg Q3W	10[b]	630 (19.9)	108 (15.7)	4930 (19.6)	6710 (16.2)	11.1 (14.5)	71.4 (23.1)	0.186 (16.2)

Abbreviations: %CV = percent coefficient of variation; $AUC_{0-\infty}$ = area under the curve from time zero to infinity; AUC_{0-t} = area under curve from time zero to last measurable concentration; CL = clearance; C_{max} = maximum concentration; C_{trough} = trough concentration; PK = pharmacokinetic; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; $t_{½}$ = terminal half-life; V_z = volume of distribution in the terminal elimination phase.
Note: N denotes the lowest number of participants used to calculate the parameters across each row. Values are geometric means (with %CV).
[a] All 4 participants had gastroesophageal adenocarcinoma.

[b] All 10 participants had breast cancer.

Table 21 Study 101 Part 1: Zanidatamab C_{trough} Concentrations (ng/mL) at Cycle 4

Zanidatamab Dose Regimen	n	Mean (StD)	Median	Min, Max	Geometric Mean (%CV)
5 mg/kg QW	1	101	101	101, 101	101
10 mg/kg QW	4	235 (143)	237	94.0, 369	199 (78.0)
15 mg/kg QW	2	293 (23.2)	293	276, 309	292 (7.90)
20 mg/kg Q2W	3	154 (78.1)	168	69.0, 224	138 (67.1)
25 mg/kg Q2W	2	200 (36.9)	200	174, 226	198 (18.7)
30 mg/kg Q2W	4	219 (98.2)	216	122, 322	202 (50.2)
30 mg/kg Q3W	5	172 (39.2)	167	127, 220	169 (23.3)

Abbreviations: %CV = percent coefficient of variation; Max = maximum; Min = minimum; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; StD = standard deviation.

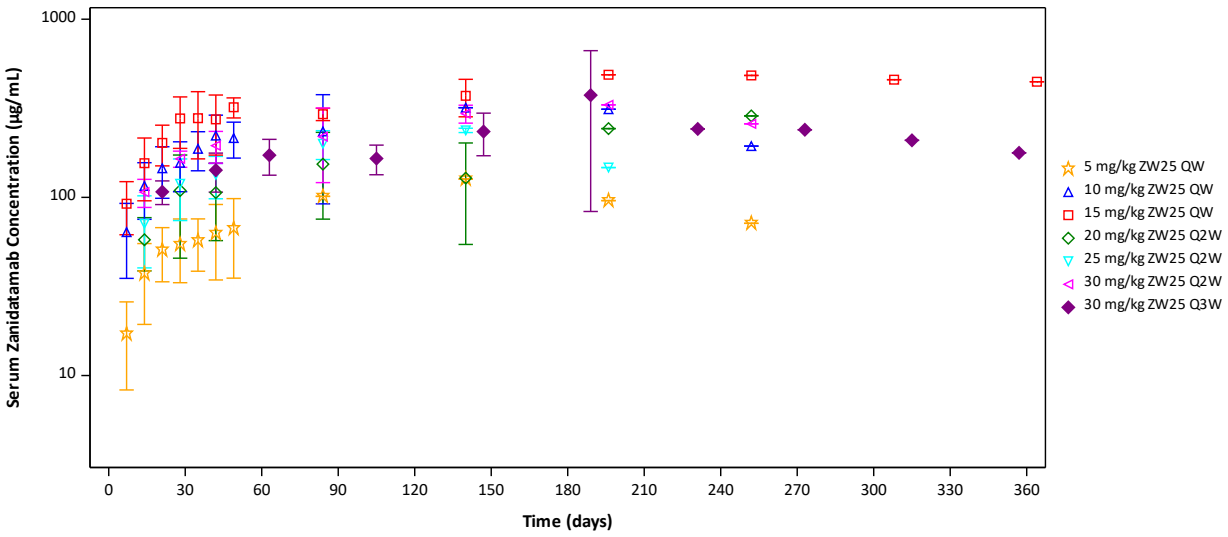
As the half-life is longer than the dosing interval, serum concentrations will increase over time until steady state is reached. This is typically after 4-5 half-lives. The PopPK model estimates the effective half-life to 21 days. Hence, steady state should be reached between 84 and 105 days or 12 and 15 weeks. According to Ctrough serum concentration collected in study 101, the increase in serum concentration levels off after 60 days, but for some posologies plasma concentrations are still increasing after 150 days, also 20 mg/kg Q2W.

Table 22 Study 101 Part 1: Zanidatamab Accumulation Indices (PK Analysis Set)

Zanidatamab Dose Regimen	N	$R_{Ctrough2\_1}$	$R_{Ctrough3\_1}$	$R_{Ctrough6\_1}$
5 mg/kg QW	3	2.2 (16.3)	3.2 (25.0)	3.8 (22.8)
10 mg/kg QW	6	2.0 (34.6)	2.6 (47.0)	3.9 (54.5)
15 mg/kg QW	6	1.6 (14.6)	2.1 (15.3)	2.7 (17.7)
20 mg/kg Q2W	6	1.8 (65.3)	1.8 (58.0)	2.7 (88.5)
25 mg/kg Q2W	3	1.6 (15.8)	1.4 (33.8)	2.2 (60.6)
30 mg/kg Q2W	4	1.5 (10.2)	1.7 (16.2)	1.8 (41.8)
30 mg/kg Q3W	See footnote[a]	1.3 (21.0)	1.5 (24.2)	–

Abbreviations: PK = pharmacokinetic; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; $R_{Ctrough}$ = accumulation index.
Note: N denotes the lowest number of participants used to calculate the parameters across each row. Values are geometric means (with percent coefficient of variation). The accumulation index is calculated as C_{trough} (last dose)/C_{trough} (first dose). [a] N = 10 for $R_{Ctrough2\_1}$; N = 5 for $R_{Ctrough3\_1}$; N = 0 for $R_{Ctrough6\_1}$

Figure 16 Study ZWI-ZW25-101 Part 1: Zanidatamab Mean (StD) C_{trough} Over Time by Dose Regimen (PK Analysis Set)



Abbreviations: C_{trough} = trough concentration; PK = pharmacokinetic; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; StD = standard deviation.

Note: Symbols and error bars depict the arithmetic mean and standard deviation of zanidatamab serum concentrations.

Time dependency due to ADA

The incidence of ADAs observed to date across the clinical studies was 1.5% (4 of 268 evaluable participants) overall. Per study, the incidence of treatment-emergent ADAs was 1.6% (3 of 183 evaluable participants) in study 101 and 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%). When assessing the impact of anti-zanidatamab antibodies on the PK of zanidatamab, C_{trough} for the 1 participant with treatment-emergent ADAs in Study 203 was 75.4 µg/mL on Day 15 of Cycle 1, and geometric mean C_{trough} for the 74 participants in Cohort 1 who did not have treatment-emergent ADAs was 73.7 µg/mL (%CV 58.26). However, 50 days post start of treatment just prior to the fourth dose, the serum concentration of zanidatamab was below lower limit of quantification. See table below.

Table 23 Zanidatamab Serum Concentrations Pharmacokinetics Analysis Set (Study 203)

Cohort/Subject ID/ Cancer Subtype	Visit	Time Point	PK Sample Date: Time(Study Day)	Dose End Date: Time	ZW25 Serum Concentration (ug/mL)	Time Deviation?[a]
1/0306-0096/ Intrahepatic Cholangiocarcinoma	Cycle 1 Day 1	Pre-Dose	07DEC2021:10:30 (1)	07DEC2021:13:45	<0.075	
	Cycle 1 Day 1	End Of Infusion	07DEC2021:13:45 (1)	07DEC2021:13:45	528	
	Cycle 1 Day 15	Pre-Dose	21DEC2021:11:00 (15)	21DEC2021:14:30	75.4	
	Cycle 1 Day 15	End Of Infusion	21DEC2021:14:35 (15)	21DEC2021:14:30	572	
	Cycle 2 Day 1	Pre-Dose	04JAN2022:12:00 (29)	04JAN2022:15:50	65.8	
	Cycle 2 Day 1	End Of Infusion	04JAN2022:15:55 (29)	04JAN2022:15:50	557	
	Cycle 2 Day 15	Pre-Dose	26JAN2022:14:00 (51)	26JAN2022:19:30	<0.075	
	Cycle 2 Day 15	End Of Infusion	26JAN2022:19:45 (51)	26JAN2022:19:30	425	

Special populations

The final PopPK model included the significant parameters baseline body weight, baseline ALB, baseline number of lesions, and cancer type. The clinical relevance was evaluated by Forest plots and none were considered clinically relevant.

Renal impairment

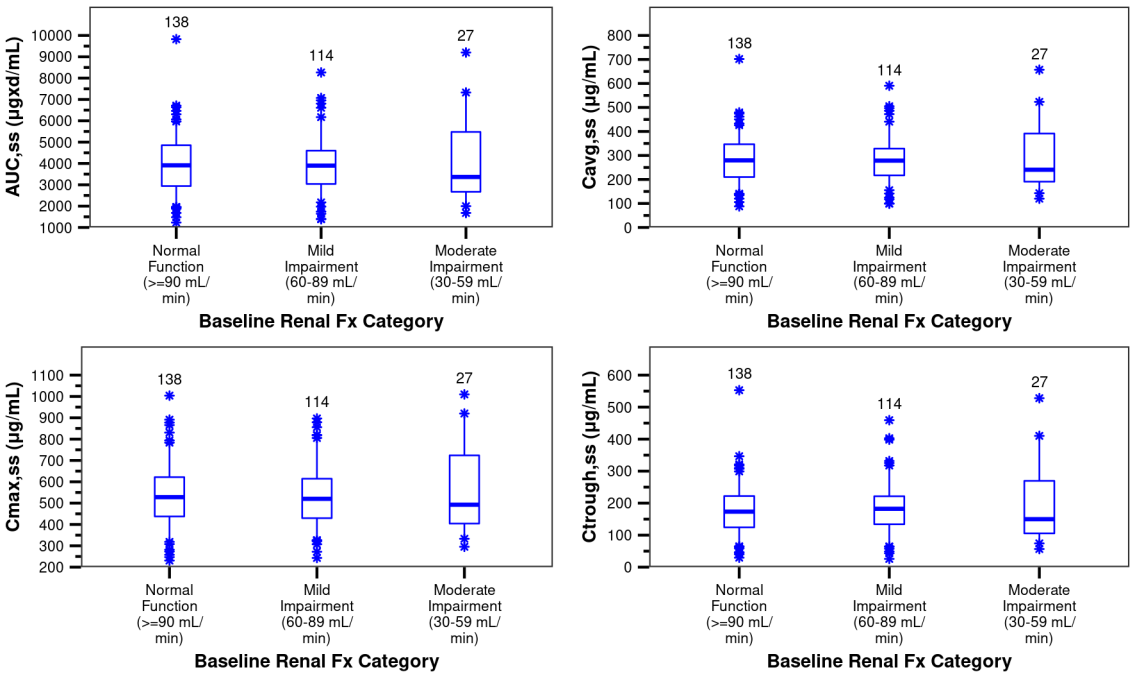
The impact of renal impairment was estimated utilizing PopPK modelling.

The assessment of kidney function is based on the FDA guidance for industry on pharmacokinetics in patients with impaired renal function and classified as normal (eGFR ≥ 90 mL/min), mild impairment (eGFR ≥ 60 mL/min to ≤ 89 mL/min), moderate impairment (eGFR ≥ 30 mL/min to ≤ 59 mL/min), severe impairment (eGFR ≥ 15 mL/min to ≤ 29 mL/min), and end-stage renal disease (eGFR < 15 mL/min or dialysis).

In the PopPK analysis, the renal function groups included were normal, and mild and moderate impairment. No studies were conducted on the impact of severe renal impairment or end-stage renal disease with or without haemodialysis on the PK of zanidatamab, as no such patients were included in the clinical trials.

Based on the PopPK analysis, mild to moderate renal impairment is unlikely to be significantly different from normal renal function (see figure below). Thereby, the renal function covariates were not found to be statistically significant for PK of zanidatamab.

Figure 17 Boxplots of Zanidatamab Exposures at Steady State Following Hypothetical 20 mg/kg Q2W Dosing Versus Renal Function Category (PopPK Total Population)



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

Table 24 Summary Statistics of Categorical Demographic Characteristics and Laboratory Values, Overall and Stratified by Study, for the Pharmacokinetic Analysis Population (Continued)

Variable		Study ZWI-ZW25-101 (N = 192)	Study ZWI-ZW25-203 (N = 87)	Overall (N = 279)
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)
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; Q2W, every 2 weeks; Q3W, every 3 weeks; QW, every week.

Renal or hepatic impairment appeared not to impact PK of zanidatamab. No studies were conducted on the impact of severe hepatic impairment on the PK of zanidatamab. No definitive conclusion could be made for the impact of severe renal impairment or end-stage renal disease with or without haemodialysis on the PK of zanidatamab, as no such patients were included in the clinical trials. There is no expected effect of renal or hepatic impairment on exposure.

Impaired hepatic function

The grading of hepatic impairment follows the National Cancer Institute Organ Dysfunction Working Group Liver Function Classification. The liver dysfunction groups are normal (total bilirubin ≤ ULN and AST ≤ ULN),

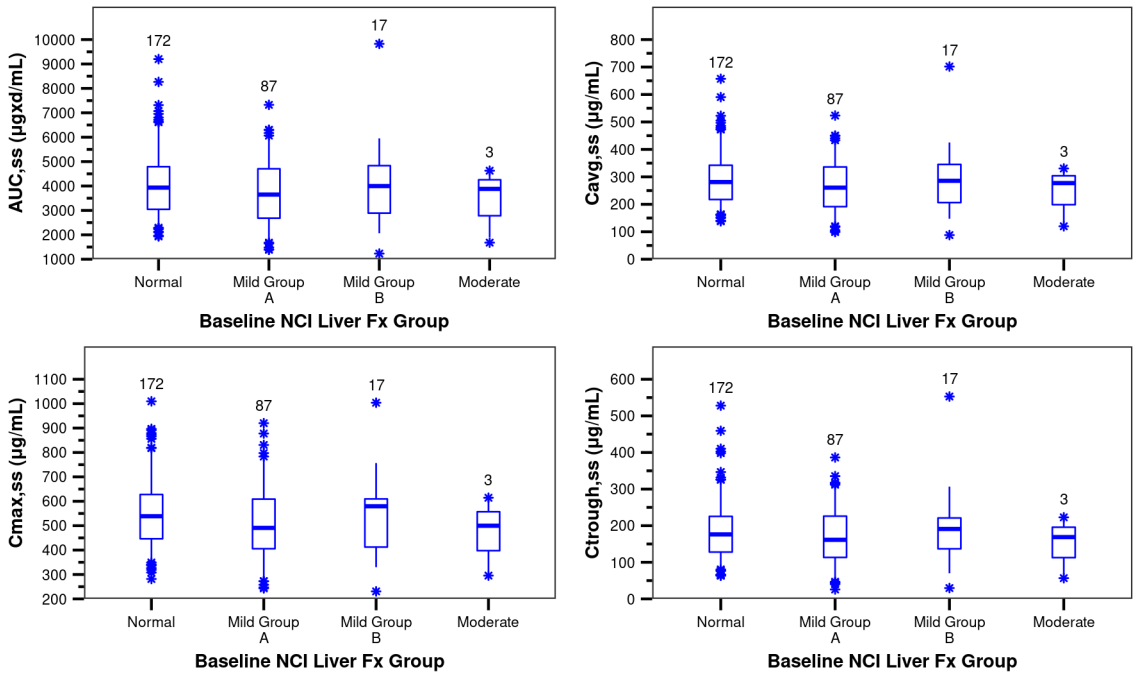
mild; Group A (total bilirubin ≤ ULN and AST > ULN) and Group B (total bilirubin > ULN and ≤ 1.5*ULN, and any AST), moderate (total bilirubin > 1.5 through 3.0*ULN, and any AST), and severe (total bilirubin > 3 through 10*ULN, and any AST).

Based on the PopPK analysis, mild hepatic impairment was not found to be a statistically significant covariate for PK of zanidatamab see figure below).

No definitive conclusion can be made for the impact of moderate hepatic impairment on the PK of zanidatamab due to insufficient available data (N = 1).

No studies were conducted on the impact of severe hepatic impairment on the PK of zanidatamab.

Figure 18 Boxplots of Zanidatamab Exposures at Steady State Following Hypothetical 20 mg/kg Q2W Dosing Versus Liver Function Group (PopPK Total Population)

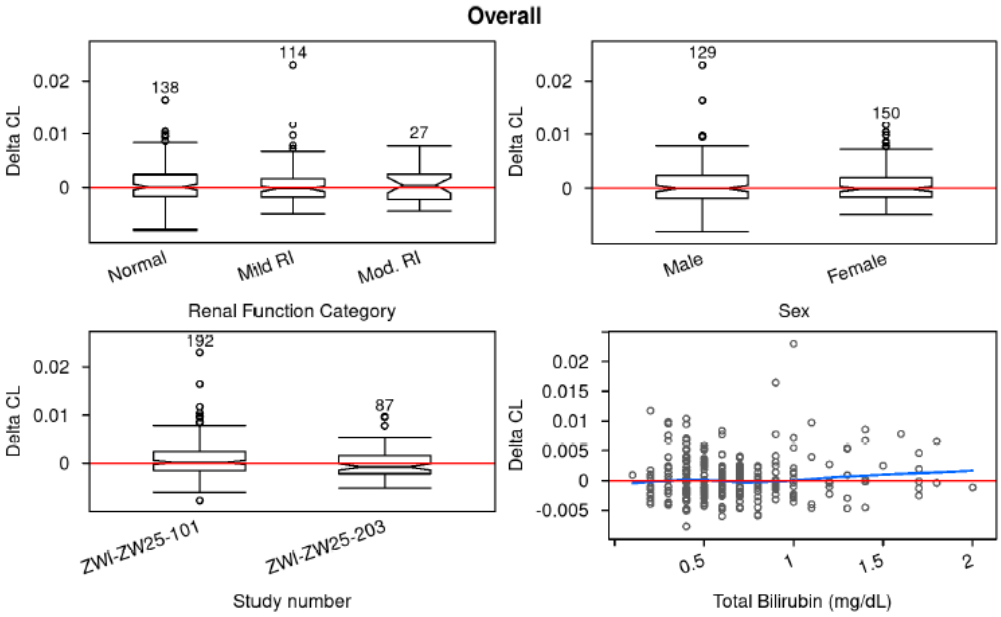


Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles.
Asterisks show data points outside this range. The number of subjects is above each box.

Gender

Based on the PopPK analysis, gender was not found to have a significant impact on the PK of zanidatamab.

Figure 19 Delta Plots of Individual Bayesian Parameter Estimates Minus Typical Value Estimates Versus Covariates for the Pharmacokinetic Model Following Backward Elimination



Boxes represent the 25th and 75th percentiles and lines the median. Notches provide an approximate 95% C.I. about the median. Whiskers extend to the most extreme values within the 1.5 interquartile range. Values outside this range are marked with open circles or subject ID. The numbers of values for each box are displayed in the upper region.

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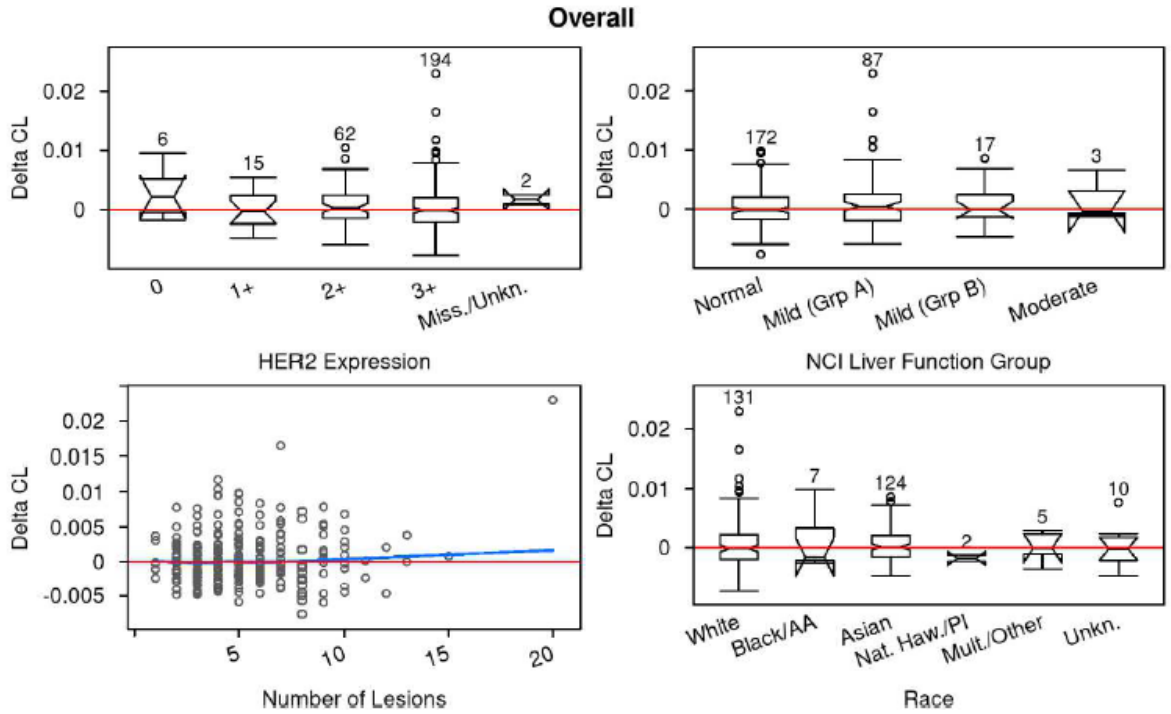
Ethnic factors

The race subgroups were white (N = 131), black/African-American (N = 7), Asian (N = 124), Native Hawaiian/Pacific Islander (N = 2), multiple/other (N = 5), and unknown (N = 10).

As the number of participants is insufficient in the subgroups black/African-American, Native Hawaiian/Pacific Islander, multiple/other, and unknown, these have been regrouped.

Based on the PopPK analysis, race was not found to have a significant impact on the PK of zanidatamab.. It is noted that the regrouping has not been performed in the delta plot. It is likely that the regrouping will not significantly impact the zanidatamab PK exposure.

Figure 20 Delta Plots of Individual Bayesian Parameter Estimates Minus Typical Value Estimates Versus Covariates for the Pharmacokinetic Model Following Backward Elimination



Boxes represent the 25th and 75th percentiles and lines the median. Notches provide an approximate 95% C.I. about the median. Whiskers extend to the most extreme values within the 1.5 interquartile range. Values outside this range are marked with open circles or subject ID. The numbers of values for each box are displayed in the upper region.

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Body weight

Based on the PopPK analysis, baseline body weight (ranging from 35.4 to 128 kg) was found to be a statistically significant covariate. In the investigation of the magnitude of the effect of body weight on the difference in steady-state zanidatamab exposure following 20 mg/kg Q2W dosing, the upper bound of the 90% CI of highest body weight quintile (80.3 kg to 128 kg) exceeds the bound of 1.25 for the parameters AUCss, Cavg,ss, Cmax,ss, and Cthrough,ss. As the GMR values for these parameters do not exceed the bound of 1.25 baseline body weight is not expected to have a clinically relevant impact on the PK of zanidatamab.

Elderly

A dedicated PK analysis in the elderly population was not studied.

The PopPK analysis showed that age, ranging from 24 to 88 years, was not a statistically significant covariate.

The below table defines age ranges studied in the elderly population.

Table 25 Number of patients by age category and study

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials	93 / 279	14 / 279	2 / 279

Abbreviation: PK = pharmacokinetic.

Source: data on file.

Paediatrics

The clinical trials of zanidatamab did not include paediatric participants.

Pharmacokinetic interaction studies

No dedicated clinical studies evaluating the drug interaction potential of zanidatamab have been conducted. Zanidatamab is an antibody that is not expected to impact the cytochrome P450 enzymes. Also, zanidatamab is not known to target mechanisms related to proinflammatory cytokines or any mechanism unrelated to proinflammatory cytokines that may impact the PK of concomitant medicines.

2.3.2.2. Pharmacodynamics

Mechanism of action

Zanidatamab is a humanized, IgG1-like, HER2-targeted bispecific antibody. Zanidatamab is biparatopic, simultaneously binding in trans to 2 distinct sites on HER2 - the juxtamembrane extracellular domain ECD4 and the dimerization domain ECD2. HER2 crosslinking due to trans binding leads to receptor clustering and potent activation of complement-dependent cytotoxicity (CDC). In addition, zanidatamab mediates antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). HER2 crosslinking through zanidatamab also causes a reduction in EGFR, HER2, and HER3 phosphorylation, and downstream intracellular signalling through the mitogen activated protein kinase and phosphatidyl inositol 3-kinase pathways, leading to ligand-dependent and ligand-independent inhibition of tumour cell proliferation. These mechanisms of zanidatamab contribute to the overall effect of tumour growth inhibition and cancer/tumour cell death in vitro and in vivo.

Primary and Secondary pharmacology

No specific PD or biomarker endpoints were defined and reported.

Study 101 was the initial dose-finding study for zanidatamab; it 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 (see figure below).In Part 1, the maximum tolerated dose (MTD) of zanidatamab as monotherapy was not reached. The dose regimen of 5 mg/kg QW was not further evaluated as no response was observed at this dose level. In addition, C_{trough} values following the first dose of 5 mg/kg QW were below the IC_{90} for LDGI, while those following the first dose of 10 mg/kg QW or 20 mg/kg Q2W exceeded the IC_{90} for LDGI associated with zanidatamab in vitro studies. Furthermore, the 10 mg/kg QW and 20 mg/kg Q2W dose regimens demonstrated cORR of 25% (N = 4) and 28.6% (N = 7), respectively. A further increase in dose (i.e. 25 mg/kg Q2W and 30 mg/kg Q2W) did not appear to enhance

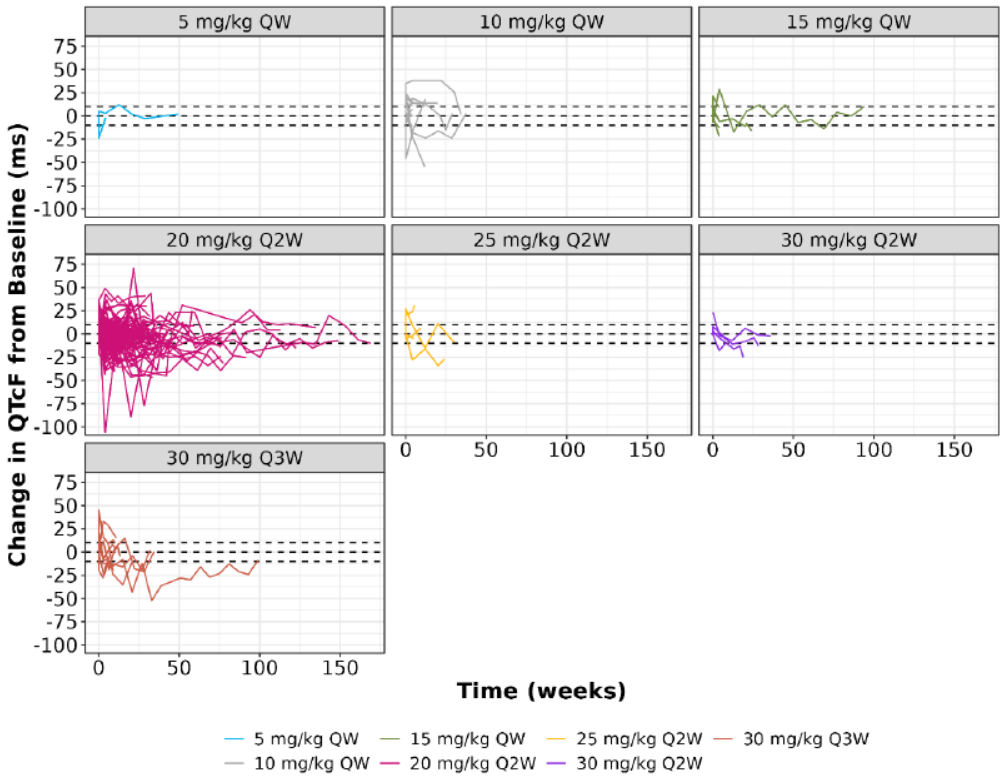
the antitumor activity. In addition, the simulated clearance suggested that the target-mediated elimination pathway was likely saturated at the dose level of 20 mg/kg Q2W at steady-state.

Therefore, the RDs of 10 mg/kg QW and 20 mg/kg Q2W were selected for further evaluation in Part 2 of the study for monotherapy. Since 10 mg/kg QW and 20 mg/kg Q2W have comparable exposures, 20 mg/kg Q2W was selected for evaluation in the pivotal Study 203 to provide a less frequent dosing regimen of zanidatamab.

QTc prolonging effect

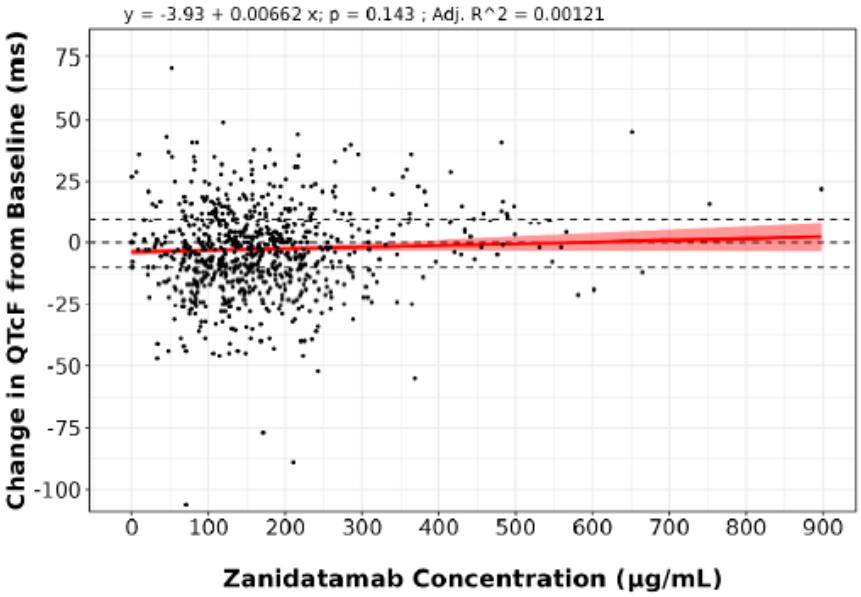
The relationship between time-matched zanidatamab serum concentrations and ΔQTcF measurements was evaluated using linear regression based on data obtained during treatment with zanidatamab from participants in study 101. The c-QT analysis dataset included measurements of QTcF from 179 of 192 participants enrolled in study 101. The zanidatamab serum concentration-QTcF analysis included 948 time-matched zanidatamab concentrations and QTcF measurements. The data represented doses below and above the projected dose regimen of 20 mg/kg Q2W zanidatamab. Individual time profiles of ΔQTcF are shown in the below figure.

Figure 21 Individual Time Profiles of ΔQTcF Stratified by Treatment



Abbreviations: Q2W, every 2 weeks; Q3W, every 3 weeks; QT, interval representing the time of ventricular activity including both depolarization and repolarization; measured from the beginning of the QRS complex to the end of the T wave (repolarization period); QTcF, QT interval corrected for heart rate according to the Fridericia formula; QW, every week. Horizontal dashed lines are drawn at -10, 0, and 10 ms.

Figure 22 Relationship of ΔQTcF versus Observed, Time-Matched Zanidatamab Serum Concentrations



Solid red line shows the estimated linear regression, and the red shaded area is the associated 90% CI. Horizontal dashed lines indicate the range -10 to 10 ms. Black dots represent data of ΔQTcF versus time-matched zanidatamab serum concentrations.

Immunogenicity

Per study, the incidence of treatment-emergent ADAs was 1.6% (3 of 183 evaluable participants) in study 101 and 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%).

Table 26 Summary of Immunogenicity Results for Zanidatamab

Study	Evaluable Participants[a] N	Treatment-Emergent ADA[b] n (%)	Treatment-Boosted ADA[c] n (%)	Treatment-Induced ADA[d] n (%)	Persistent ADA[e] n (%)	Transient ADA[f] n (%)	NAb Positive n (%)[g]
ZWI-ZW25-101	183	3 (1.6)	2 (1.1)	1 (0.5)	0 (0.0)	1 (0.5)	NA
5 mg/kg QW	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
10 mg/kg QW	13	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
15 mg/kg QW	7	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
20 mg/kg Q2W	138	3 (2.2)	2 (1.4)	1 (0.7)	0 (0.0)	1 (0.7)	NA
25 mg/kg Q2W	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
30 mg/kg Q2W	6	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
30 mg/kg Q3W	10	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
ZWI-ZW25-203	85	1 (1.2)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.2)[h]
20 mg/kg Q2W	85	1 (1.2)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.2)[h]
Subtotal of 20 mg/kg Q2W	223	4 (1.8)	2 (0.9)	2 (0.9)	1 (0.4)	1 (0.4)	NA
Total	268	4 (1.5)	2 (0.7)	2 (0.7)	1 (0.4)	1 (0.4)	NA

Abbreviations: ADA = antidrug antibody; NAb = neutralizing antibody; NA = not applicable; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks.

[a] Evaluable participants were those with both a baseline ADA sample and at least 1 ADA sample taken after drug administration during the treatment or follow-up observation period that were appropriate for ADA testing and had reportable results.

[b] The proportion of the study population found to have seroconverted or boosted their pre-existing ADAs during the study period. Participants with ADA incidence were the sum of both treatment-induced and treatment-boosted ADA-positive participants, as a proportion of the evaluable participant population. The term "ADA status" is used interchangeably with "treatment-emergent ADA status."

[c] Defined as pre-existing ADAs that increased to a higher concentration (4-fold or higher level) after administration of a therapeutic protein product.

[d] Defined as ADAs that developed de novo (seroconversion) following administration of therapeutic protein product in a participant who lacked detectable pre-existing ADAs.

[e] Defined as an ADA-positive result detected at the last postbaseline sampling time point or at ≥ 2 time points during treatment where the first and last ADA-positive samples were separated by a period of ≥ 16 weeks, irrespective of any negative samples in between.

[f] Defined as an ADA-positive result detected at only 1 postbaseline sampling time point (excluding the last time point) or at ≥ 2 time points during treatment where the first and last ADA-positive samples were separated by a period of < 16 weeks, irrespective of any negative samples in between.

[g] Note that in Study 101, no NAb analysis was conducted.

[h] Two out of 85 participants tested positive for NAb; however, the 1 participant who tested positive for postbaseline ADA and further tested positive for NAbs to zanidatamab based on the specified bioanalytical rules of NAb evaluation (ie, characterizing NAb for ADA-positive samples based on a screening and confirmatory assay) did not meet the criteria of having treatment-emergent ADA and therefore was not included in this table.

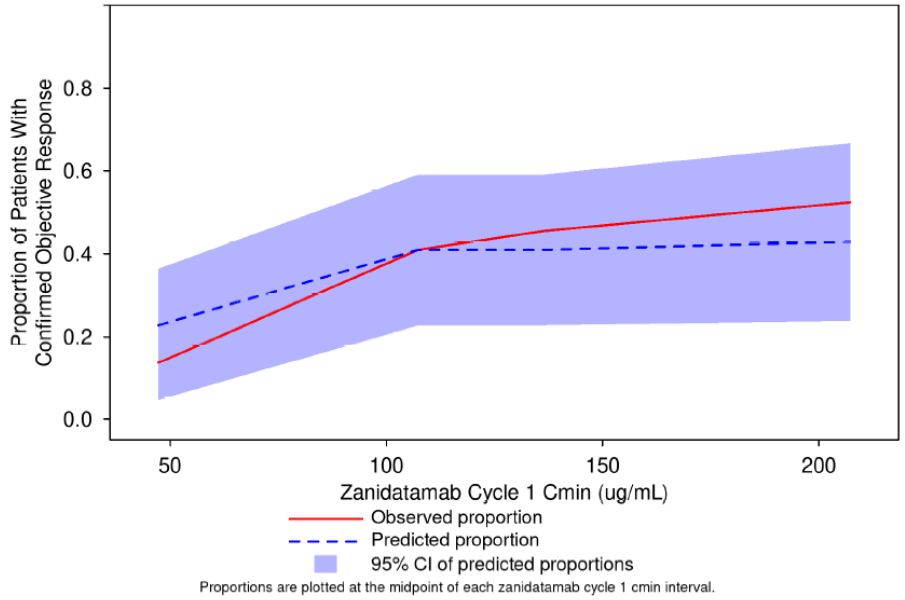
Note: Pooled monotherapy population includes participants from Study 101 and Study 203 (all indications and dose levels).

Exposure-response analyses

Exposure-response relationship for efficacy in patients with BTC

The E-R relationship for the efficacy of zanidatamab was assessed by logistic regression modelling for probability of confirmed OR as assessed by ICR in study 203 with participants who had HER2-amplified BTC (N = 87) and whose exposure metrics were derived using the PopPK model. Among the 87 participants, 0 of 4 (0%) in the HER2 IHC 0, 0 of 3 (0%) in the IHC 1+, 1 of 18 (5.56%) in the IHC 2+, and 32 of 62 (51.6%) in the IHC 3+ were responders. The C_{min} at Cycle 1 was used in the final model. The PK in Cycle 1 was considered to be associated with more biological plausibility since most OR occurred in early cycles (75.8% of confirmed responses occurred by the first postbaseline tumour assessment). A visual predictive check plot for the final OR model is shown in the below figure.

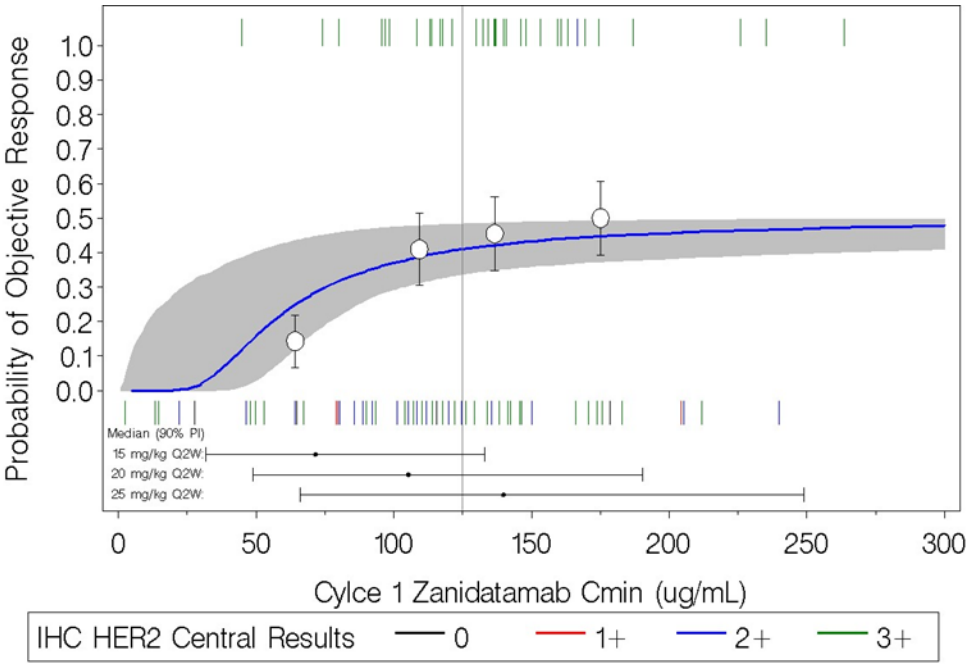
Figure 23 Visual Predictive Check Plot for the Exposure-Response Final Model of the Probability of Confirmed Objective Response Versus Zanidatamab Cycle 1 C_{min}



Abbreviations: Cmin, minimum concentration; CI, confidence interval.

The results are shown in the figure below 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.

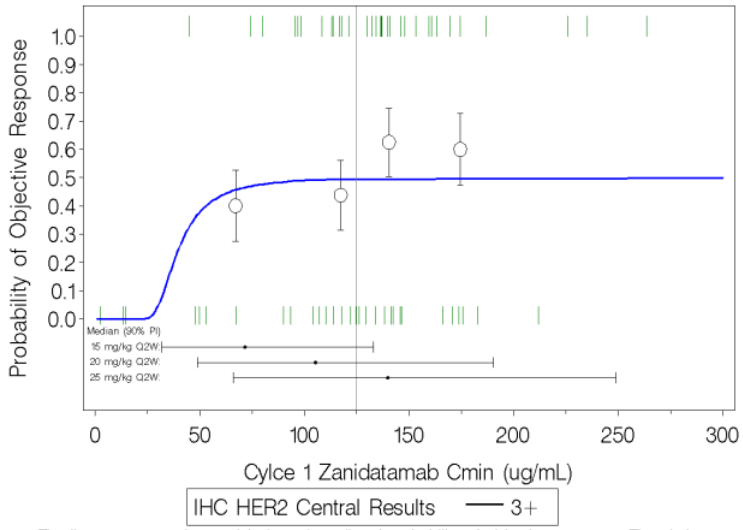
Figure 24 Observed and Model-Predicted Probability of Confirmed Objective Response Versus Zanidatamab Median C_{min} at Cycle 1 for the Exposure-Response Base (Final) Logistic Regression Model



Abbreviations: C_{min} = minimum concentration; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry.
Note: 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 objective response ± 1 standard deviation and are plotted at the median Cycle 1 C_{min} for each quartile. Cycle 1 C_{min} is defined as the minimum exposure level within the cycle. The hash marks at the top and bottom of the figure represent the individual Cycle 1 C_{min} for the objective response yes and no, respectively, color coded by HER2 IHC status. The vertical line represents the median Cycle 1 C_{min}. Horizontal points and error bars at the bottom of the plot show the median and 5th to 95th percentiles of simulated Cycle 1 C_{min} for 1000 simulated patients, administered doses of 15, 20, and 25 mg/kg once every 2 weeks.

When removing the data with HER2 status of 0, 1+, and 2+, the exposure-OR relationship for patients with HER2 status 3+ (N = 62) is depicted in the below figure.

Figure 25 Observed and Model-Predicted Probability of Confirmed Objective Response Versus Cycle 1 Zanidatmab Cmin for the Exposure-Response Logistic Regression Model for Patients with HER2 Status of 3+

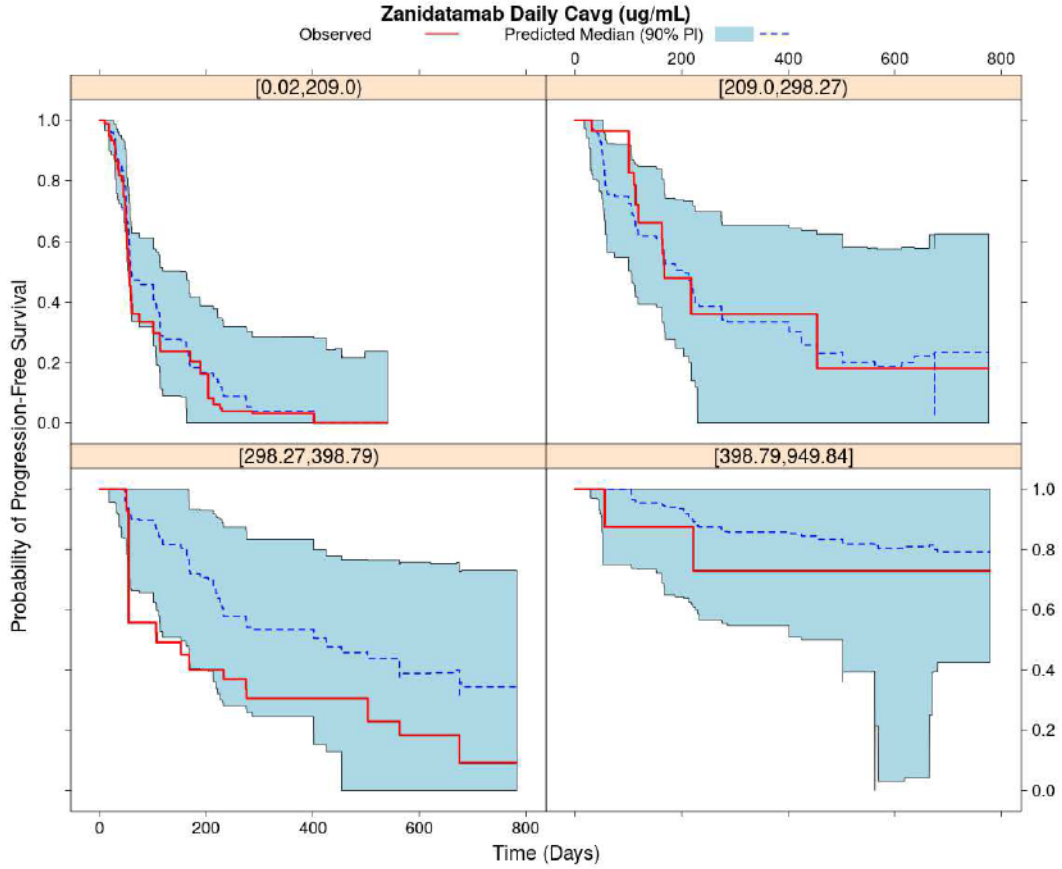


The line represents the model−based predicted probability of objective response. The circles represent observed OR +/− 1 SD and are plotted at the median Cycle 1 Cmin for each quartile. The hash marks at the top and bottom of the figure represent the individual Cycle 1 Cmin for objective response yes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

Abbreviations: Cmin = minimum concentration; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; OR = objective response; SD = standard deviation.
Source: data on file. "M:\zymeworks\zanidatamab\002682\d2er-or\graphs\pnghi\or-lr-5-base-model-anno-rug-v2-std_median90pi-her3.png"

The exposure-efficacy relationship of zanidatamab for **PFS** was analysed in participants with HER2-amplified BTC in the efficacy population from study 203 (N = 87). The final E-R 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). A VPC for the final model is shown in the below figure.

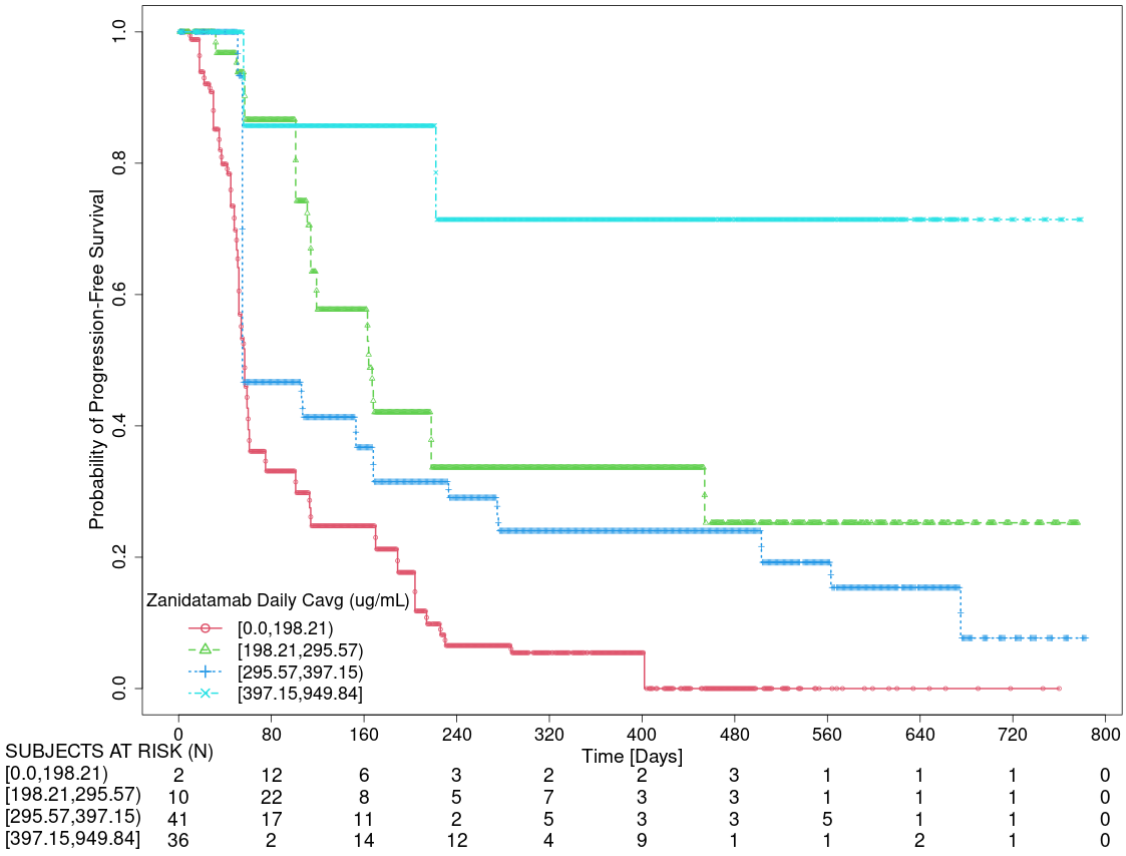
Figure 26 Visual Predictive Check of the Simulated Percentiles of Progression-Free Survival Versus Days With Kaplan-Meier Estimates of the Observed Data Overlaid, by Quartiles of Zanidatamab Daily C_{avg}



Abbreviations: C_{avg}, average concentration; PI, prediction interval.
Note: [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.

Kaplan Meier plot of PFS are shown in the below figure.

Figure 27 Plot of the Simulated Percentiles of Progression Free Survival Versus Days Stratified by Quartiles of Model-Predicted Zanidatamab Daily C_{avg}



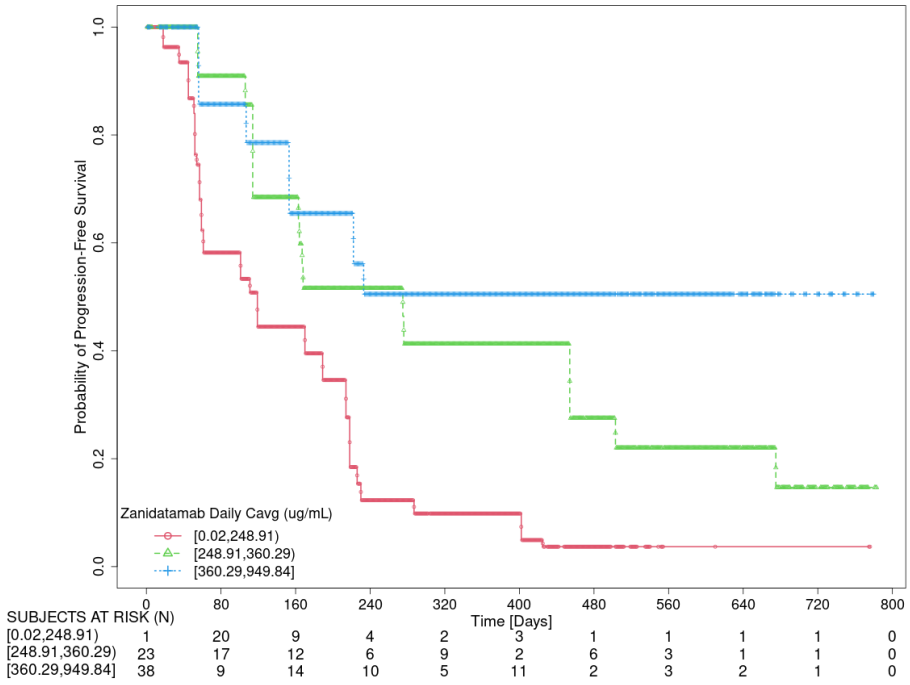
SUBJECTS AT RISK (N)

[0.0,198.21)	2	12	6	3	2	2	3	1	1	1	0
[198.21,295.57)	10	22	8	5	7	3	3	1	1	1	0
[295.57,397.15)	41	17	11	2	5	3	3	5	1	1	0
[397.15,949.84]	36	2	14	12	4	9	1	1	2	1	0

Abbreviations: C_{avg} = average concentration.
Note: [or] indicates respective endpoint is included in the interval, and (or) indicates respective endpoint is not included in the interval.

When removing the data with HER2 status of 0, 1+, and 2+, the exposure-PFS relationship for patients with HER2 status 3+ (N = 62) is depicted in the below figure.

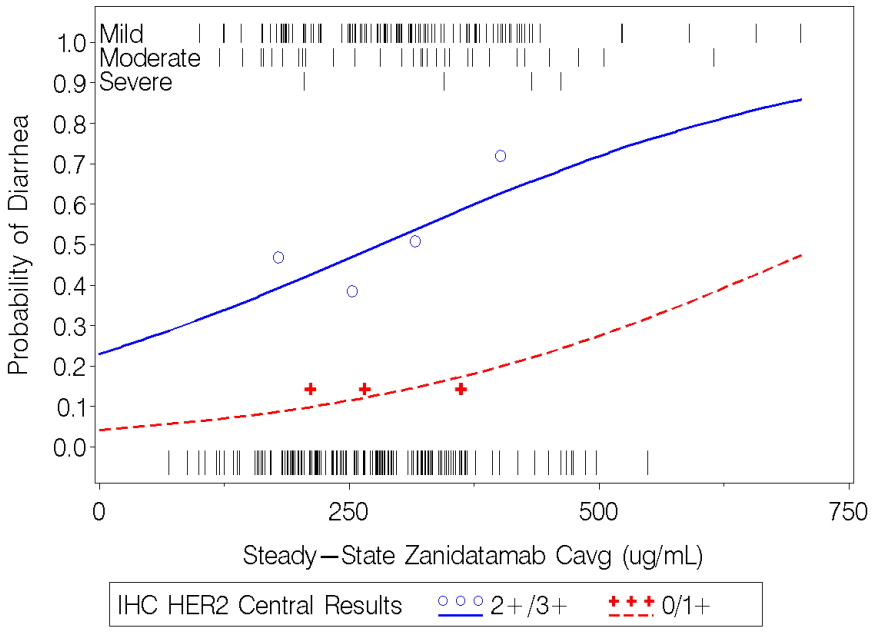
Figure 28 Kaplan-Meier Plot of Progression-Free Survival Versus Time, by Tertiles of Exposure Measures, for Patients With HER2 Status of 3+.



Exposure-safety analyses

Data from study 101 in participants with HER2-expressing cancers and from study 203 in participants with HER2-amplified BTC were used for the E-R safety analyses (N = 279). The exposure-safety relationship for adverse events of diarrhoea, Grade ≥ 3 diarrhoea, Grade ≥ 3 TEAEs, IRRs, Grade ≥ 3 IRRs, and SAEs were evaluated. No statistically significant exposure-safety relationship was found for any of the safety endpoints examined (including Grade ≥ 3 diarrhoea and Grade ≥ 3 TEAEs or IRRs), except for diarrhoea, for which higher zanidatamab exposure was associated with an increased probability of diarrhoea (see below figure). The probability of diarrhoea was modelled using logistic regression. HER2 IHC status was a significant covariate, as participants with HER2 IHC 0 or 1+ had a lower probability of diarrhoea relative to those with IHC 2+ or 3+. Despite the apparent E-R trend for the probability of diarrhoea, there was no statistically significant E-R relationship for Grade ≥ 3 diarrhoea. Limited participants had SAE events that were related to zanidatamab (n = 10 of 85 total participants with SAEs); hence, no analyses were summarized.

Figure 29 Observed and Model-Predicted Probability of Diarrhoea Versus Zanidatamab Steady-State C_{avg} for the Final Exposure-Response Model for the Occurrence of Diarrhoea in Study 101 and Study 203



Abbreviations: C_{avg} = average concentration; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry.
Note: The line represents the model-based predicted probability of diarrhoea based on HER2 category. The symbols represent the median steady-state C_{avg} values and associated observed probabilities. The hash marks at the bottom of the figure represent the individual steady-state C_{avg} for participants with no diarrhoea. The hash marks at the top of the figure represent the individual steady-state C_{avg} for participants with diarrhoea by Standard Toxicity Grade.

2.3.3. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

Methods for PK samples were sufficiently validated and demonstrated reproducibility in the clinical studies.

Overall, the immunogenicity assay technologies used and the validation of ADA assays are considered state of the art and sufficient, except for the evaluation of drug tolerance in the screening assay.

In study 101, it was observed that ADA positivity correlated with the presence of sHER2-ECD and that ADA positivity decreased during treatment as sHER2-ECD decreased due to treatment. Therefore, sHER2-ECD is interfering with all the ADA assays.

In study 203, 31 out of 80 subjects were positive for sHER2-ECD in at least one occasion. Hence, many pre-dose ADA samples fell out positive, even all the way to Nab assay. The applicant's strategy for interpreting the ADA data was to evaluate, if the positive signal of ADA was persistent and titer increasing towards end of treatment. If this was not the case, the patient was considered negative for ADA. This is considered acceptable.

Specifically, one subject was not considered a true positive for ADA towards zanidatamab, as the titer was lower at safety follow-up as compared to pre-dose, whereas another subject was considered positive (also for Nab), since this patient was negative at pre-dose and positive, although with a low titer, at safety follow-up,

which is 30 days post last dose. Of note; the first patient referred to above had relatively high concentration of sHER2-ECD (Day 1: 260.5 ng/mL vs 80.7 ng/mL at EOT), whereas the second patient referred to above had low concentration (Day: 8.2 ng/mL vs 5.2 ng/mL at EOT).

Bioanalytical data from one subject showed serum concentration below LLOQ at pre-dose of cycle 2, Day 15, approximately 7 weeks after the first dose. Hence, only one true case of Nab interfering with pharmacokinetics was identified. Only two other patients showed decreasing pre-dose concentration over time. It is therefore agreed that ADA/NAb are most likely not interfering with PK of zanidatamab, except on rare occasions.

Due to the suboptimal drug tolerance of the ADA assay, approximately 20% of the samples collected for assessment of ADA may not detect ADA even if it is present, because the concentration of zanidatamab is too high. The applicant highlighted that an assay with better drug tolerance is under development. Since a relatively low proportion of samples have too high concentration of zanidatamab, this is considered acceptable.

Pharmacokinetic data analysis

The pharmacokinetics of zanidatamab following intravenous infusion in participants with HER2 expressing cancers was evaluated in a population pharmacokinetic model analysis from 279 participants pooling data from 1 phase I study (ZWI-ZW25-101) and 1 phase IIb study (ZWI-ZW25-203). Participants from study ZWI-ZW25-101 included patients with breast cancer, gastroesophageal adenocarcinoma (GEA), ovarian cancer, colorectal cancer (CRC), non-small cell lung cancer, biliary tract cancer (BTC), or "Other" type cancers. All participants in study ZWI-ZW25-203 were patients with BTC. Zanidatamab was administered by intravenous (IV) infusion, generally over a duration of 120 to 150 minutes. All dosages of zanidatamab were weight-based. The PK sampling strategies employed in each study were dependent on the specific dosing regimen. In both studies, a combination of extensive and sparse PK sampling strategies was employed.

Zanidatamab PK exhibited non-linear kinetics with more rapid clearance (CL) at low doses ranging from 5 to 30 mg/kg. Following the first dose, the geometric mean zanidatamab C_{max} was dose proportional with increasing doses, while total systemic exposure ($AUC_{0-\infty}$) was greater than dose proportional with increasing doses. The geometric mean accumulation indices based on C_{trough} at steady state was approximately 2.7 for the 20 mg/kg once every 2 weeks zanidatamab dose level. Zanidatamab PK could be therefore described by a 2-compartment Pop PK model with a zero-order infusion input and with parallel linear and non-linear elimination as described by Michaelis Menten kinetics.

The main study 203 utilised the projected treatment regimen of 20 mg/kg Q2W given as IV infusions and included only patients with biliary tract cancer (BTC). None of the included significant covariates (body weight, ALB, number of lesions, and cancer type) had clinically relevant effect on exposure. Forest plots showed that exposure increased with body weight despite a weight-based dose regimen and that BTC patients had higher zanidatamab exposure than patients with the other HER2+ cancer types. HER2 amplification was eliminated as a significant covariate in Pop PK analysis. Simulations indicated the target-mediated elimination pathway was likely saturated at the dose level of 20 mg/kg Q2W. The exposure metrics based on individual Empirical Bayes Estimates (EBEs) are considered acceptable for evaluation of exposure-response relations due to the richly informed PK data set.

Absorption

Bioavailability of zanidatamab is by definition 100% as it is administered by intravenous infusion.

Generation 1 formulation of zanidatamab is a liquid formulation utilized in phase 1 supportive study (study 101). In study 101, the PK parameters are presented for patients with and without GEA cancers, as the exposure to zanidatamab appeared to be lower in participants with GEA. Generation 2 formulation of zanidatamab is a lyophilized formulation utilized in later-phase clinical development including pivotal phase 2 study (study 203) and is intended to be used in commercialization.

No bioequivalence study was performed for the different formulations. This is considered acceptable, as the formulation utilized for the pivotal phase 2 study (study 203) is the formulation intended to be used in commercialization and the PK parameters for the two formulations are comparable.

Distribution

Following intravenous dosing, zanidatamab undergoes biphasic elimination from the circulation. Based on population pharmacokinetic analysis, participants with HER2 amplified BTC were predicted to have a typical Vc of 3.51 L and a typical Vp of 3.95 L.

Elimination

From NCA, clearance and half-life increase with time. This is due to accumulation with repeated dosing with dosing intervals being less than the half-life and hence saturation of target mediated clearance.

T½ derived from NCA at steady state in individual studies is shorter than t½ estimated in the PopPK model using all data. The sampling times are not optimal for NCA capturing the elimination phase, due to the relatively frequent dosing schedules of QW, Q2W or Q3W compared to the classical half-life of IgG1s (21 days), and insufficient number of sampling points after time for maximal serum concentration for estimating clearance and half-life.

Although the CV% on the PopPK derived estimate on clearance is high, the estimate is spot on the typical half-life of an IgG1. Hence, the PK parameters obtained with the PopPK model should be used to describe the pharmacokinetics of zanidatamab in the SmPC.

Based on population pharmacokinetic analysis, participants with BTC were predicted to have a typical CL of 0.0115 L/h and an estimated t1/2 of approximately 21 days for zanidatamab administered at 20 mg/kg every 2 weeks at steady-state.

Dose proportionality and time dependency

As expected for a monoclonal antibody, zanidatamab show non-linear kinetics in the lower dosing rangei.e. the half-life and clearance of zanidatamab increase with an increasing dose. The most likely reason for this increase is the target-mediated drug disposition (TMDD), which may play a significant role at the lower dosing levels. At high mAb concentrations, the clearance approaches a first-order process where the FcRn-mediated pathway is dominant, and the nonlinear pathway (TMDD) becomes negligible. Dose proportionality was only assessed for a single dose. Due to non-linear kinetics, exposure (AUC) to zanidatamab is not dose proportional. The PopPK predicted clearance decreased with increasing dose and was predicted to still decrease even at 30 mg/kg.

As mentioned above, in study 203, only one patient showed decrease in C_{trough}, which could be ascribed to neutralising antibodies.

Therapeutic window

Interindividual variability is considered moderate as assessed in the PopPK model and by NCA. Intra-individual variability was not addressed by the applicant in this application, however since the incidence of ADA is low and C_{trough} is decreasing over time in very few patients, this is considered acceptable and not further pursued.

The proposed posology of 20 mg/kg every 2 weeks is supported by patient data from both the proposed posology, lower (-50%) and higher dose levels (+50%). Lower exposure lead to decreased or lack of efficacy (-50%). However, no discussion of a suggested maximal exposure in terms of safety was provided by the applicant in this application. As no covariate was identified to impact exposure beyond the 80-125%, except albumin on C_{trough}, this is considered acceptable.

Otherwise, section 4.2 of the SmPC provides recommendations for treatment modifications in cases of left ventricular dysfunction and infusion related reactions. Hence, possibilities for individual posology based on level of known potential adverse effects is already included.

The exposure in the target population is supported by sufficient relevant pharmacokinetic data. Section 4.2 of the SmPC is not advising regarding posology modifications in populations with clinically relevant reduced or increased exposure as no such populations were identified. Instead, recommendations for dose modifications are provided based on adverse effect observations (left ventricular dysfunction and infusion related reactions). This is considered acceptable.

Special populations

Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of zanidatamab were observed based on age (24 to 88 years), sex, race (White, Black, Asian), and body weight (35.4 kg to 128 kg).

No dose adjustment is required in patients aged 65 years and over.

Children under the age of 18 were not included in the clinical trials. Hence, the safety, efficacy and pharmacokinetics of Ziihera have not been established in this population.

Renal impairment

Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of zanidatamab were observed based on mild and moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI). The pharmacokinetics of zanidatamab in patients with severe renal impairment and end-stage renal disease with or without hemodialysis is unknown. However, as IgG monoclonal antibodies are not primarily cleared via renal pathways, a change in renal function is not expected to influence zanidatamab exposure.

Dose adjustments are not required for patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min estimated using the CKD-EPI). Ziihera has not been evaluated in patients with severe renal impairment and patients with end-stage renal disease with or without dialysis. However, due to minor involvement of renal processes in the clearance of zanidatamab, no dose adjustment of Ziihera is recommended for patients with renal impairment as no difference in exposure is expected.

Hepatic impairment

Based on population pharmacokinetics analysis, no clinically significant differences in the pharmacokinetics of zanidatamab were observed based on 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). The pharmacokinetics of zanidatamab in patients with moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) or severe hepatic impairment (total bilirubin >3 ULN and any AST) is unknown. However, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence zanidatamab exposure.

Dose adjustments are not required for patients with 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). Ziihera has not been evaluated in patients with moderate (total bilirubin > 1.5 to ≤ 3 ULN and any AST) to severe (total bilirubin > 3 ULN and any AST) hepatic impairment. However, due to minor involvement of hepatic processes in the clearance of zanidatamab, no dose adjustment of Ziihera is recommended for patients with hepatic impairment as no difference in exposure is expected.

Pharmacodynamics

Mechanism of action

Zanidatamab is a dual HER2-targeted bispecific antibody that simultaneously binds extracellular domains 2 and 4 on separate HER2 monomers (binding in trans). Binding of zanidatamab with HER2 results in internalization leading to a reduction of the receptor on the cell surface. Zanidatamab induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumour growth inhibition and tumour cell death. Study 101 was an early dose finding study in patients with a locally advanced (unresectable) and/or metastatic HER2-expressing cancer. Patients received zanidatamab monotherapy at doses ranging from 5 mg/kg to 15 mg/kg QW, 20 mg/kg to 30 mg/kg Q2W, and 30 mg/kg Q3W. Based on the chosen IC90 value for LDGI, the range of doses tested is considered adequate for the selection of the recommended dose used in the pivotal study. Compared with the other tested doses, the dose of 5 mg/kg QW did not reach the IC90 value for LDGI of 25 ug/mL. For the evaluation of the dose range tested, it is important to have a dose not reaching the chosen IC90 value for LDGI.

No specific PD or biomarker endpoints were defined and reported in studies 101 and 203. In study 203, the probability of OR was described by a logistic regression model including an intercept and a power function of Cycle 1 Cmin. PFS was described by a Cox Proportional Hazard model with daily Cavg include as a linear function and effect of HER2 status as a covariate. The model suffered from overestimation of PFS at higher exposure quartiles thus the results should be interpreted with caution.

Cardiac electrophysiology

The relationship between time-matched zanidatamab serum concentrations and ΔQTcF measurements was evaluated based on data obtained during treatment with zanidatamab from participants in study 101. The C-QT analysis dataset included measurements of QTcF from 179 out of the 192 participants enrolled in study 101. Zanidatamab has no effect on QTc interval and there was no relationship between zanidatamab exposure and change in QTc interval.

Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the studies described below with incidence of ADA in other studies.

ADA were rarely detected. Zanidatamab is categorised 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 ADAs observed to date across the clinical studies (1.6% [3 of 183 evaluable participants] and 1.2% [1 of 85 evaluable participants] in study 101 and study 203, respectively). No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed, however, data are still limited.

Exposure-response analyses

For evaluation of exposure-safety relations, patients who did not experience any AE were included in the final safety data set. Probability of diarrhoea was described by a logistic regression model with an additive shift of HER2 status (0/+1 versus 2+/3+) included on the intercept and the slope of drug effect described by a linear function of zanidatamab Cavg,ss. The predicted probability of diarrhoea was in concordance with observed for patients with HER2 2+/3+. No further E-R safety modelling was performed as no relation was found between zanidatamab exposure and any other evaluated safety endpoint.

No PD drug-drug interactions are expected.

As for exposure-efficacy, the logistic regression of exposure-OR and the Kaplan-Meier exposure-PFS analyses both indicate a trend of increasing PFS and OR with higher exposure quartiles. However, no firm conclusion can be made at this point.

As for exposure-safety, no statistically significant ER relationship was found for any of the safety endpoints examined, except for diarrhoea, where HER2 status was a significant covariate.

The overall evaluation of exposure-response (PKPD relationship), anti-tumour activity, and safety, associated with different doses of zanidatamab, seems to justify the proposed dose regimen. Dose modifications are not considered necessary in special populations.

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of zanidatamab is similar to other monoclonal antibodies showing target dependent disposition. The SmPC recommended 20 mg/kg dose, administered as an intravenous infusion every 2 weeks, is supported by the data collected in clinical studies 101 and 2023. The PK and PD data collected in these two trials can be considered valid and only minor inconsistencies were found. E-R analysis showed patients with HER2 status 3+ is a distinct subgroup, with distinct pharmacological response, and the statistical analysis now focus on this BTC subgroup.

2.3.5. Clinical efficacy

Table 27 Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
ZWI-ZW25-203	Study ongoing September 2020 Cohort 1: 80 Cohort 2: 7 Enrollment complete DCO	Open-label, 2-cohort, single-arm	Monotherapy 20 mg/kg IV Q2W	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+
ZWI-ZW25-101	Study ongoing September 2016 Part 1: 46 Part 2: 146 Enrollment complete DCO for cohort 5a (n=22): 14 January 2022	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	**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	Locally advanced (unresectable) and/or metastatic HER2 expressing cancers **Part 2 BTC Cohort:** HER2 expression of IHC 3+ or IHC 2+ and ISH+

Abbreviations: BTC = biliary tract cancer; DLT = dose-limiting toxicity; HER2 = human epidermal growth factor receptor 2; ID = identification; IHC = immunohistochemistry; IV = intravenous; ISH = in situ hybridization; MTD = maximum tolerated dose; OBD = optimal biologic dose; QW = once a week; Q2W = every 2 weeks; Q3W = every 3 weeks; RD = recommended dose.

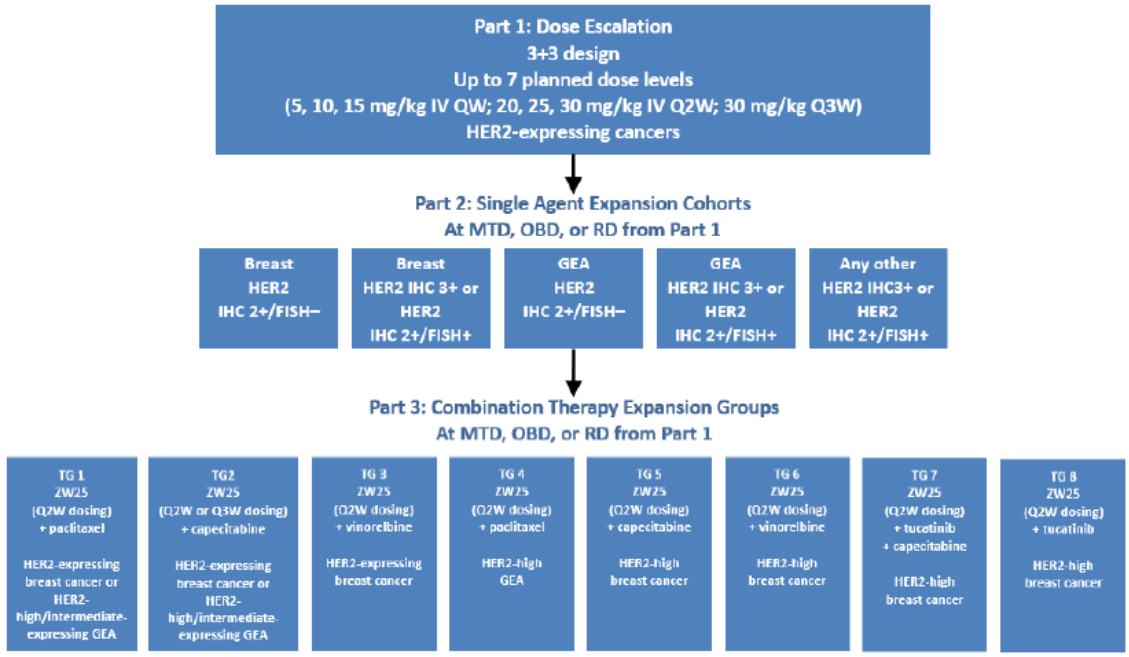
2.3.5.1. Dose response study

Study 101, the initial dose-finding study for zanidatamab, was a first-in-human, multicentre, global, phase I, open-label, 3-part study designed to investigate the safety, tolerability, PK, and preliminary anti-tumour activity of zanidatamab monotherapy (Parts 1 and 2) and zanidatamab in combination with selected anticancer agents (Part 3) in participants with locally advanced (unresectable) and/or metastatic HER2-expressing cancer. It 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 (see table above).

The study design is summarized in the figure below. An interim CSR has been provided with a clinical data cut-off date of 14 January 2022.

Figure 30 Overall Study Design for study 101



FISH = fluorescence in situ hybridization; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IV = intravenously; MTD = maximum tolerated dose; OBD = optimum biological dose; QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; RD = recommended dose; TG = treatment group; ZW25 = zanidatamab.
Note: HER2 high-expressing = IHC 3+ or IHC 2+/FISH+; HER2 intermediate-expressing = IHC 2+/FISH–.

Part 1: Dose Escalation

A conventional algorithm (3+3 subjects per dose level) was used to identify the RDs for further evaluation in Parts 2 and 3 of the study. Escalation to a higher dose level was to occur if 0/3 or 1/6 dose-limiting toxicities were observed in subjects enrolled at the current dose level being tested. De-escalation to a lower dose level was to occur if 2 or more DLTs were observed in subjects at a current dose level. The following dose levels of zanidatamab were prespecified for evaluation: 5 mg/kg IV weekly (QW), 10 mg/kg IV QW, 15 mg/kg IV QW, 20 mg/kg IV once every 2 weeks (Q2W), 25 mg/kg IV Q2W, 30 mg/kg IV Q2W, and/or 30 mg/kg IV once every 3 weeks (Q3W).

Cohort advancement or dose de-escalation was based on safety data during the first 3- or 4-week treatment cycle from cohorts of up to 6 evaluable subjects. Safety data from subjects receiving additional treatment cycles of zanidatamab were also taken into consideration.

The MTD was predefined as the highest dose level at which no more than 1 of 6 evaluable subjects experienced a DLT during the DLT evaluation period. The OBD was predefined as the dose of zanidatamab that resulted in a serum concentration of zanidatamab at trough (7 days postdose) that is at least 10-fold above the maximum binding capacity of zanidatamab on a cell line representing the HER2-3+ tumor histology. The RD was predefined as any dose and schedule of zanidatamab that did not exceed the MTD.

Based upon safety and PK data, the Safety Monitoring Committee (SMC) was to recommend a dose and schedule(s) for further study in Part 2. This could have been the MTD, OBD, or an RD identified in Part 1. A minimum of 6 evaluable subjects had to be treated at that or a higher dose level for that dose to be declared the MTD, OBD, or an RD.

After a dose had been determined to either not have exceeded the MTD or to be the MTD, OBD, or an RD as defined by the SMC, any subject remaining on the study and being treated with a lower dose of zanidatamab could, at the discretion of the investigator and agreement of the sponsor, be offered treatment at that higher dose.

Methods

- **Study participants**

Main inclusion criteria:

For inclusion into the trial, subjects were required to fulfil each of the following criteria:

1. HER2-expressing cancer as follows:

Part 1:

- Cohorts 1–3:
    - Any locally advanced (unresectable) and/or metastatic HER2-expressing (HER2 1+, 2+, or 3+ by IHC) cancer (including but not limited to breast, gastric, ovarian, colorectal and NSCLC) that has progressed after receipt of all therapies known to confer clinical benefit
- Cohort 4:
    - HER2 IHC 2+ /FISH– breast cancer or GEA
    - HER2 IHC 3+ or HER2 IHC 2+/FISH+ breast cancer or GEA
    - Any other HER2 IHC 3+ or FISH+ cancer:
        - HER2-overexpressing (3+ by IHC) or HER2-2+ and FISH+ breast cancer must have progressed after prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1)
        - HER2-overexpressing (3+ by IHC) or HER2-2+ and FISH+ GEA must have progressed after prior treatment with trastuzumab
        - Subjects with CRC must be Kirsten rat sarcoma (KRAS) wild type
        - Subjects with NSCLC must have anaplastic lymphoma kinase (ALK) wild type, EGFR wild type, and receptor tyrosine kinase (ROS1) fusion negative as determined by standard methods
- Cohorts 5 and 6:

- HER2 IHC 3+ or HER2 IHC 2+/FISH+ GEA must have progressed after prior treatment with trastuzumab

- Cohort 7 (only at selected sites):
  - HER2 IHC 3+ or HER2 IHC 2+/FISH+ breast cancer

2. Male or female, ≥ 18 years of age at the time of signing informed consent.

3. ECOG performance status 0 or 1.

Main exclusion Criteria

Any of the following was regarded as a criterion for exclusion from the trial:

1. Treatment with experimental therapies within 4 weeks before first zanidatamab dosing

2. Treatment with other cancer therapy not otherwise specified within 4 weeks before zanidatamab dosing

3. Treatment with anthracyclines within 90 days before first zanidatamab dosing or total lifetime dose exceeding 300 mg/m2 Adriamycin® or equivalent

4. Treatment with trastuzumab, pertuzumab, lapatinib, or T-DM1 within 3 weeks before first zanidatamab dosing

5. Subjects in Part 3 TG 4 must not have received prior taxanes

6. Subjects in Part 3 TG 5 must not have received prior capecitabine for metastatic disease or received any prior fam-trastuzumab deruxtecan-nxki (DS-8201a)

7. With the exception of Part 3 TGs 7 and 8, untreated brain metastases (subjects with treated brain metastases who are off steroids and are stable for at least 1 month at the time of Screening are eligible). All breast cancer subjects (including those in TGs 7 and 8) should undergo screening prior to starting treatment. Those subjects found to have untreated brain metastases may be rescreened following appropriate therapy.

8. Clinically assessed leptomeningeal disease (LMD). If LMD has been reported radiographically on baseline MRI but is not suspected clinically by the investigator, the subject is eligible if he or she is free of neurological symptoms of LMD as documented by the investigator.

9. Major surgery or radiotherapy within 3 weeks before first zanidatamab dosing. Brain lesions requiring surgical resection within 4 weeks before first zanidatamab dosing.

10. Pregnant or breastfeeding women

- **Treatments**

All parts of this study were open-label and no randomization to cohorts or treatment groups occurred. In Part 1, subjects were allocated to a dose level based on their time of enrollment.

- **Dose selection**

In Part 1, the starting dose and schedule for zanidatamab was 5 mg/kg administered IV QW. This dose and schedule were determined based on GLP toxicology and PK studies conducted in cynomolgus monkeys using 2 methods: the no observed adverse effect level (NOAEL) with allometric scaling of cynomolgus monkey zanidatamab exposure to predicted human exposure and the highest non severely toxic dose (HNSTD) with

scaling by weight. The predicted human exposure suggests that zanidatamab levels at the NOAEL of 150 mg/kg for the cynomolgus monkey (GLP toxicology study) provide a safety margin of at least 20-fold based on area under the serum concentration versus time curve from time zero through 168 hours (AUC0-168h) and of at least 30-fold based on area under the serum concentration versus time curve from time 0 to the last quantifiable concentration (AUCTlast), relative to the clinical starting dose of 5 mg/kg.

Alternatively, based on 1/6 of the HNSTD proposed in the ICH guideline S9, a safe starting dose would be 25 mg/kg. The 5 mg/kg starting dose is 5-fold less than the estimate based on the HNSTD.

After the starting dose of 5 mg/kg, the next planned dose levels for Part 1 were 10 mg/kg and 15 mg/kg administered QW. Additional planned doses were 20, 25, or 30 mg/kg administered Q2W and 30 mg/kg Q3W.

- **Sample size**

Table 28 Part 1 and 2: Sample Sizes

Study Part	Cohorts		
	Indication	Number	Sample Size
1	Locally advanced (unresectable) and/or metastatic HER2-expressing cancers	1	3 – 6
		2	3 – 6
		3	3 – 6
		4	3 – 6
		5	3 – 6
		6	3 – 6
	Breast cancer–- HER2 high or intermediate	7	3 – 15
2	Breast cancer – HER2 intermediate	1	6 – 15
	Breast cancer–- HER2 high	2	6 – 25
	GEA – HER2 intermediate	3	6 – 15
	GEA – HER2 high	4	6 – 46
	GI cancers other than GEA – HER2 high	5a	6 – 85
	Any other solid tumor types that were not breast or GI cancers–- HER2 high	5b	6 – 35

GEA = gastroesophageal adenocarcinoma; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2.

- **Blinding**

This was an open-label study.

- **Primary Efficacy Variable(s)**

There were no primary efficacy endpoints for any part of this trial.

The following were evaluated as secondary endpoints for Parts 1, 2, and 3:

- ORR assessed using RECIST v1.1
- DCR, defined as the percentage of subjects with CR, PR, or SD per RECIST v1.1
- PFS

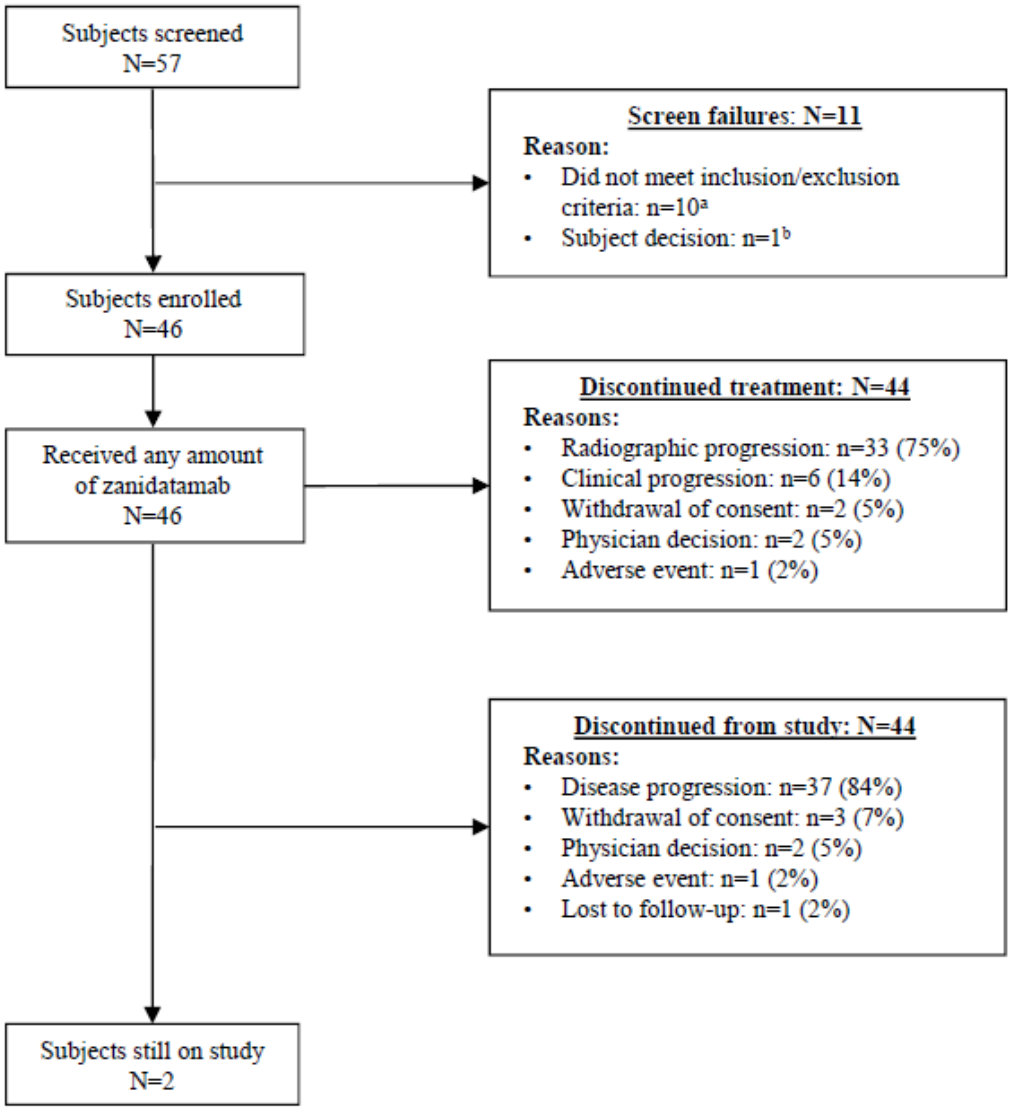
- Drug Concentration Measurements

Concentrations of zanidatamab were measured in serum using a validated assay. Samples were collected for subjects receiving QW, Q2W, and Q3W dosing. A minimum of 12 and up to 15 subjects were also to be assigned to a steady-state extensive PK sampling schedule that was employed to collect additional samples at Cycle 4.

Results

- **Participant flow**

Figure 31 Part1: Subject Disposition



a One subject's screen failure was recorded in the database as not meeting the inclusion/exclusion criterion for signed informed consent prior to any study procedures. This subject signed informed consent prior to study procedures but later withdrew consent before starting study treatment in order to pursue standard-of-care treatment. The database required entry of a reason for screen failure, and withdrawal of consent was not an option; this criterion was the only entry possible.
b One subject met all inclusion/exclusion criteria but chose not to wait for a spot in the trial to become available.

- **Conduct of the study**

Protocol amendments

No subjects were enrolled under the original protocol (Version 1), dated 15 June 2016. The protocol was subsequently amended 9 times. The first subject was screened on 06 September 2016 and subsequently enrolled on 14 September 2016 under Amendment 1 of the protocol, dated 25 July 2016.

Changes to the Planned Analyses

Version 1 of the SAP was finalized on 29 October 2019; the SAP was subsequently revised twice.

Changes to the planned analyses included:

- Exploratory analyses to evaluate the effect of zanidatamab on tumour volume for Part 1 of the study were not conducted because data were available for a limited number of subjects and no meaningful conclusions could be made.
- The PK parameter tmax was not assessed because it is not a meaningful parameter with IV antibodies where the time of maximum concentration will always be at the time of infusion.
- Formal by-subject listings of laboratory results by assessment timepoint were not generated. However, these individual subject-level data are available in the Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM) datasets.

- **Baseline data**

Table 29 Part 1: Subject Disposition (Safety Analysis Set)

Reason for Discontinuation	5 mg/kg ZW25 QW (N=3)	10 mg/kg ZW25 QW (N=6)	15 mg/kg ZW25 QW (N=7)	20 mg/kg ZW25 Q2W (N=7)	25 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q3W (N=11)	Total (N=46)
Subjects with treatment ongoing, n (%)	0	0	0	0	0	1 (17)	1 (9)	2 (4)
Subjects who have discontinued treatment [a], n (%)	3 (100)	6 (100)	7 (100)	7 (100)	6 (100)	5 (83)	10 (91)	44 (96)
Radiographic progression	3/3 (100)	6/6 (100)	4/7 (57)	4/7 (57)	4/6 (67)	4/5 (80)	8/10 (80)	33/44 (75)
Clinical progression	0/3	0/6	0/7	2/7 (29)	2/6 (33)	1/5 (20)	1/10 (10)	6/44 (14)
Physician decision	0/3	0/6	1/7 (14)	1/7 (14)	0/6	0/5	0/10	2/44 (5)
Withdrawal of consent	0/3	0/6	1/7 (14)	0/7	0/6	0/5	1/10 (10)	2/44 (5)
Adverse event	0/3	0/6	1/7 (14)	0/7	0/6	0/5	0/10	1/44 (2)
Subjects who have discontinued the study [a], n (%)	3 (100)	6 (100)	7 (100)	7 (100)	6 (100)	5 (83)	10 (91)	44 (96)
Disease progression [b]	3/3 (100)	6/6 (100)	4/7 (57)	6/7 (86)	5/6 (83)	4/5 (80)	9/10 (90)	37/44 (84)
Withdrawal of consent	0/3	0/6	1/7 (14)	0/7	1/6 (17)	0/5	1/10 (10)	3/44 (7)
Physician decision	0/3	0/6	1/7 (14)	1/7 (14)	0/6	0/5	0/10	2/44 (5)
Adverse event	0/3	0/6	1/7 (14)	0/7	0/6	0/5	0/10	1/44 (2)
Lost to follow-up	0/3	0/6	0/7	0/7	0/6	1/5 (20)	0/10	1/44 (2)

QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; ZW25 = zanidatamab.

a Incidences in the subcategories that follow are subject count per reason over the number of subjects who have discontinued treatment or discontinued the study in each dose-regimen cohort, as applicable.

b Includes both radiographic and clinical progression.

Table 30 Part 1: Subject Demographics (Safety Analysis Set)

Parameter	5 mg/kg ZW25 QW (N=3)	10 mg/kg ZW25 QW (N=6)	15 mg/kg ZW25 QW (N=7)	20 mg/kg ZW25 Q2W (N=7)	25 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q3W (N=11)	Total (N=46)
Age at informed consent (yrs)								
Median	61.0	64.5	52.0	70.0	59.0	59.5	61.0	61.5
Min, Max	58, 64	31, 73	36, 70	27, 75	43, 73	52, 72	50, 88	27, 88
Age category, n (%)								
< 65 years	3 (100)	3 (50)	5 (71)	3 (43)	3 (50)	3 (50)	7 (64)	27 (59)
≥ 65 years	0	3 (50)	2 (29)	4 (57)	3 (50)	3 (50)	4 (36)	19 (41)
Sex, n (%)								
Female	2 (67)	2 (33)	4 (57)	5 (71)	0	0	11 (100)	24 (52)
Male	1 (33)	4 (67)	3 (43)	2 (29)	6 (100)	6 (100)	0	22 (48)
Ethnicity, n (%)								
Hispanic or Latino	0	2 (33)	2 (29)	1 (14)	0	0	2 (18)	7 (15)
Not Hispanic or Latino	3 (100)	4 (67)	5 (71)	6 (86)	6 (100)	5 (83)	9 (82)	38 (83)
Unknown	0	0	0	0	0	1 (17)	0	1 (2)
Race [a], n (%)								
Asian	0	1 (17)	1 (14)	0	1 (17)	2 (33)	0	5 (11)
Black or African American	0	1 (17)	0	1 (14)	0	0	0	2 (4)
Native Hawaiian or Other Pacific Islander	0	1 (17)	0	0	0	0	1 (9)	2 (4)
White	3 (100)	3 (50)	6 (86)	6 (86)	5 (83)	3 (50)	10 (91)	36 (78)
Other	0	0	0	0	0	1 (17)	0	1 (2)
Baseline ECOG PS, n (%)								
0	1 (33)	2 (33)	3 (43)	0	2 (33)	3 (50)	7 (64)	18 (39)
1	2 (67)	4 (67)	4 (57)	7 (100)	4 (67)	3 (50)	4 (36)	28 (61)

ECOG PS = Eastern Cooperative Oncology Group performance status; Max = maximum; Min = minimum; QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; ZW25 = zanidatamab.

a Subjects may select more than one race category.

Table 31 Part 1: Enrolment by Dose-regimen Cohort

Indication	Cohort Number	Zanidatamab Dose	Cancer Group	Treated (N=46) n (%)
Locally advanced (unresectable) and/or metastatic HER2-expressing cancer	1	5 mg/kg QW	Breast	2 (4)
			GEA	1 (2)
			Total	**3 (7)**
Locally advanced (unresectable) and/or metastatic HER2-expressing cancer	2	10 mg/kg QW	Breast	2 (4)
			GEA	3 (7)
			All Other [a]	1 (2)
			Total	**6 (13)**
Locally advanced (unresectable) and/or metastatic HER2-expressing cancer	3	15 mg/kg QW	Breast	4 (9)
			GEA	2 (4)
			CRC	1 (2)
			Total	**7 (15)**
Breast cancer / GEA (HER2 IHC 2+ /FISH–) Breast cancer / GEA (HER2 IHC 3+ or HER2 IHC 2+ /FISH+) Any other cancer (HER2 IHC 3+ or FISH+)	4	20 mg/kg Q2W	Breast	3 (7)
			GEA	3 (7)
			All Other [b]	1 (2)
			Total	**7 (15)**
GEA (HER2 IHC 3+ or HER2 IHC 2+ /FISH+)	5	25 mg/kg Q2W	GEA	6 (13)
GEA (HER2 IHC 3+ or HER2 IHC 2+ /FISH+)	6	30 mg/kg Q2W	GEA	6 (13)
Breast cancer (HER2 IHC 3+, HER2 IHC 2+ /FISH+, or HER2 IHC 2+ /FISH–)	7	30 mg/kg Q3W	Breast	11 (24)

CRC = colorectal cancer; FISH = fluorescence in situ hybridization; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks.

a Skin cancer.

b Cervical cancer.

Table 32 Part 1: Baseline Disease Characteristics and Disease History (Safety Analysis Set)

Characteristic	5 mg/kg ZW25 QW (N=3)	10 mg/kg ZW25 QW (N=6)	15 mg/kg ZW25 QW (N=7)	20 mg/kg ZW25 Q2W (N=7)	25 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q3W (N=11)	Total (N=46)
Primary diagnosis, n (%)								
Breast	2 (67)	2 (33)	4 (57)	3 (43)	0	0	11 (100)	22 (48)
GEA	1 (33)	3 (50)	2 (29)	3 (43)	6 (100)	6 (100)	0	21 (46)
CRC	0	0	1 (14)	0	0	0	0	1 (2)
All other [a]	0	1 (17)	0	1 (14)	0	0	0	2 (4)
Stage at initial diagnosis, n (%)								
I	0	0	0	0	0	0	1 (9)	1 (2)
II, IIA, IIB	0	3 (50)	2 (29)	3 (43)	0	0	1 (9)	9 (20)
III, IIIB	1 (33)	2 (33)	3 (43)	2 (29)	1 (17)	1 (17)	3 (27)	13 (28)
IV, IVB	2 (67)	1 (17)	2 (29)	2 (29)	5 (83)	5 (83)	4 (36)	21 (46)
Unknown	0	0	0	0	0	0	2 (18)	2 (4)
Time from initial diagnosis to metastatic disease [b] (years)								
n	3	6	7	6	5	6	9	42
Median	1.0	1.0	4.0	1.5	0.0	0.0	1.0	1.0
Min, Max	0.0, 7.0	1.0, 3.0	0.0, 6.0	0.0, 2.0	0.0, 0.0	0.0, 5.0	0.0, 9.0	0.0, 9.0
HER2 status: IHC 3+ or IHC 2+/FISH+, n (%)								
Yes	3 (100)	5 (83)	5 (71)	5 (71)	3 (50)	5 (83)	8 (73)	34 (74)
No [c]	0	1 (17)	2 (29)	2 (29)	3 (50)	1 (17)	3 (27)	12 (26)
Brain metastases at screening, n (%)								
Yes	0	0	0	0	0	1 (17)	0	1 (2)
No	3 (100)	6 (100)	7 (100)	7 (100)	6 (100)	5 (83)	11 (100)	45 (98)

CRC = colorectal cancer; FISH = fluorescence in situ hybridization; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; Max = maximum; Min = minimum; QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; ZW25 = zanidatamab.

a All other includes 1 subject with skin cancer (10 mg/kg QW) and 1 subject with cervical cancer (20 mg/kg Q2W).

b Based on central laboratory results and if not available then based on local laboratory results. Subjects that were Stage IV, IVA, or IVB at initial diagnosis and had no time to metastatic disease indicated are assumed to have a value of 0 years.

c Subjects who were not IHC 3+ or IHC 2+/FISH+.

- **Outcomes and estimation**

Disease response analyses in this section are presented for the measurable-disease analysis set (N = 42), and do not include 4 subjects with non measurable disease. Progression-free survival was analysed using the safety analysis set (N = 46).

Select efficacy analyses were also performed on the response-evaluable analysis set (N = 40).

Two subjects in the measurable-disease analysis set did not have postbaseline disease assessments prior to discontinuation of their study participation.

ORR

Table 33 Part1: Disease Response Endpoints per Investigator Assessment Using RECIST v1.1 (Measurable Disease Analysis Set)

Endpoint	5 mg/kg ZW25 QW (N=3)	10 mg/kg ZW25 QW (N=4)	15 mg/kg ZW25 QW (N=5)	20 mg/kg ZW25 Q2W (N=7)	25 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q2W (N=6)	30 mg/kg ZW25 Q3W (N=11)	Total (N=42)
Confirmed BOR [a,b], n (%)								
Partial response (PR)	0	1 (25.0)	1 (20.0)	2 (28.6)	1 (16.7)	0	1 (9.1)	6 (14.3)
Stable disease (SD)	1 (33.3)	2 (50.0)	0	2 (28.6)	2 (33.3)	4 (66.7)	5 (45.5)	16 (38.1)
Progressive disease (PD)	2 (66.7)	1 (25.0)	3 (60.0)	3 (42.9)	3 (50.0)	2 (33.3)	4 (36.4)	18 (42.9)
Radiographic progression	2 (66.7)	1 (25.0)	3 (60.0)	2 (28.6)	3 (50.0)	2 (33.3)	4 (36.4)	17 (40.5)
Clinical progression	0	0	0	1 (14.3)	0	0	0	1 (2.4)
Not Evaluable (NE)	0	0	1 (20.0)	0	0	0	1 (9.1)	2 (4.8)
Confirmed ORR [b]								
n (%)	0	1 (25.0)	1 (20.0)	2 (28.6)	1 (16.7)	0	1 (9.1)	6 (14.3)
95% CI	(0.0, 70.8)	(0.6, 80.6)	(0.5, 71.6)	(3.7, 71.0)	(0.4, 64.1)	(0.0, 45.9)	(0.2, 41.3)	(5.4, 28.5)
ORR								
n (%)	1 (33.3)	2 (50.0)	1 (20.0)	3 (42.9)	1 (16.7)	1 (16.7)	1 (9.1)	10 (23.8)
95% CI	(0.8, 90.6)	(6.8, 93.2)	(0.5, 71.6)	(9.9, 81.6)	(0.4, 64.1)	(0.4, 64.1)	(0.2, 41.3)	(12.1, 39.5)
CBR [c]								
n (%)	1 (33.3)	2 (50.0)	1 (20.0)	3 (42.9)	2 (33.3)	2 (33.3)	3 (27.3)	14 (33.3)
95% CI	(0.8, 90.6)	(6.8, 93.2)	(0.5, 71.6)	(9.9, 81.6)	(4.3, 77.7)	(4.3, 77.7)	(6.0, 61.0)	(19.6, 49.5)
DCR [d]								
n (%)	1 (33.3)	3 (75.0)	1 (20.0)	4 (57.1)	3 (50.0)	4 (66.7)	6 (54.5)	22 (52.4)
95% CI	(0.8, 90.6)	(19.4, 99.4)	(0.5, 71.6)	(18.4, 90.1)	(11.8, 88.2)	(22.3, 95.7)	(23.4, 83.3)	(36.4, 68.0)

BOR = best overall response; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCR = disease control rate; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors v1.1; SD = stable disease; ZW25 = zanidatamab.

a By RECIST v1.1 or clinical progression.

b Only CR and PR are confirmed.

c SD ≥ 24 weeks or confirmed BOR of CR or PR.

d Best overall response of CR, PR, or SD.

Note: Subjects who died or who had clinical progression before radiographic progression was observed are imputed as PD.

Duration of Response

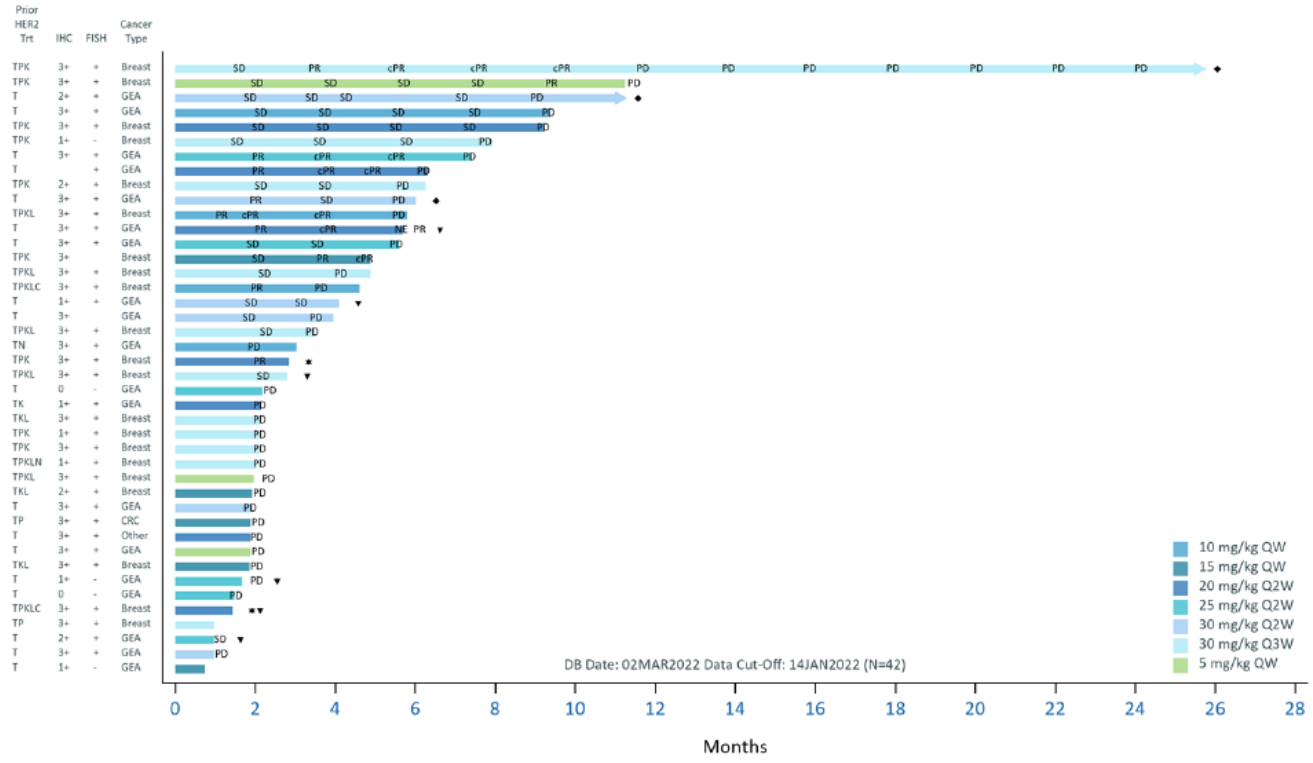
For the 6 subjects with confirmed objective response (all 6 with cPR by investigator assessment), the median DOR was 4.7 months (range, 1.1 to 8.2 months). One subject was censored, and 5 subjects had either radiographic progression by RECIST v1.1 or clinical progression.

Duration of Treatment

Of the 6 subjects who achieved a confirmed objective response, 1 subject with breast cancer and 3 subjects with GEA achieved confirmed response by the second postbaseline assessment (range, 1.9 to 3.8 months after C1D1), and 2 subjects with breast cancer achieved response by the third postbaseline assessment (4.7 and 5.5 months after C1D1).

Seven subjects had received 10 or more cycles of treatment at the data cut-off; of these, 1 subject achieved an objective response (30 mg/kg Q3W; breast cancer). The remaining 6 subjects achieved only best response of SD before disease progression, including a subject (15 mg/kg QW; breast cancer) with non measurable disease who reached Cycle 25 of treatment (22.6 months on study treatment) and a subject with low (IHC 1+/FISH–) HER2-expressing breast cancer in the 30 mg/kg Q3W dose-regimen cohort who reached Cycle 11 (7.2 months on study treatment).

Table 34 Part 1: Treatment Duration (Measurable Disease Analysis Set, N= 42)



CRC = colorectal; C = tucatinib; cPR = confirmed partial response; FISH = fluorescence in situ hybridization; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; K = T-DM1; L = lapatinib; N = neratinib; NE = not evaluable; Other = other cancer type, cervical; P = pertuzumab; PD = progressive disease; PR = partial response; QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; SD = stable disease; T = trastuzumab; Trt = treatment.

Notes: ▼ Clinical progression, ✱ Death, ◆ Continued study treatment beyond PD based on investigator determination of clinical benefit.

Decreases in tumour size were observed with zanidatamab monotherapy in all dose regimens evaluated, including 5 mg/kg QW, the lowest dose exposure evaluated in Part 1. At the time of the data cut-off, the median study follow-up time was 2.9 months.

- cORR was 14.3% (95% CI: 5.4, 28.5), with 6 of 42 subjects in the measurable disease analysis set achieving cPR (per investigator assessment). Median DOR was 4.7 months (range, 1.1 to 8.2 months).
- Overall CBR was 33.3%, and DCR was 52.4%.
- Of the 6 subjects who achieved cPR, 4 subjects did so by the second postbaseline response assessment (range, 1.9 to 3.8 months after C1D1), and 2 subjects by the third (4.7 and 5.5 months after C1D1).
- Median PFS based on investigator assessment was 2.4 months (95% CI: 1.9, 4.1).
- Seven subjects (7/46; 15%) were able to receive 10 or more cycles of zanidatamab treatment.
- At the data cutoff, 2 subjects were still receiving zanidatamab beyond progression for clinical benefit and were at Cycle 12 and Cycle 37 of treatment.

Only the 10 mg/kg QW and the 20 mg/kg Q2W dose regimens were evaluated in Part 2 of this study.

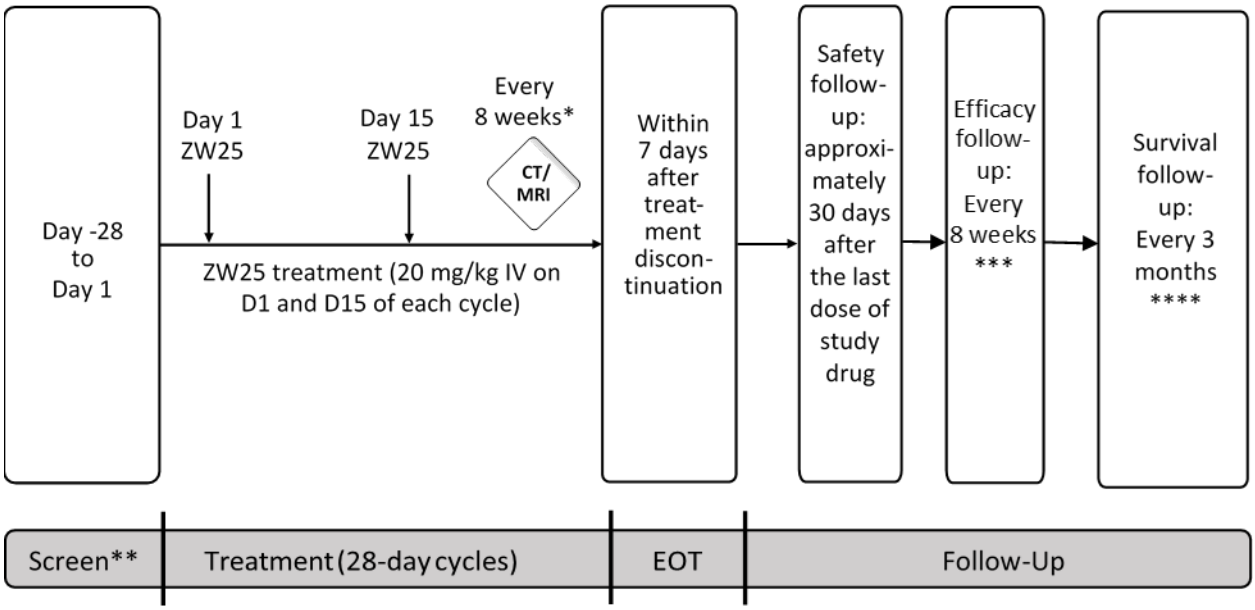
For additional information on study 101, please also refer to section 2.6.5.6 Supportive studies.

2.3.5.2. Main study

ZWI-ZW25-203: A Phase IIb, Open-label, Single-arm Study of Zanidatamab (ZW25) Monotherapy in Participants with Advanced or Metastatic HER2-amplified Biliary Tract Cancers

Methods

Figure 32 Study Schema



Abbreviations: CT = computed tomography; D = day; EOT = end of treatment; HER2 =human epidermal growth factor receptor 2; IV = intravenous; MRI = magnetic resonance imaging; ZW25 = zanidatamab (also known as JZP598)
* Timed from Cycle 1 Day 1
** Participants may be tested for HER2 status any time after diagnosis of advanced or metastatic disease and before study enrollment. Participants who elect to be prescreened for HER2 status must sign a separate informed consent for collection, storage, and analysis of the tumour tissue.
*** Every 8 weeks until disease progression or start of subsequent anticancer therapy.
**** Every 3 months until death, lost to follow up, withdrawal of consent, study completion, or study termination by sponsor

- **Study participants**

Participants were enrolled at 32 investigative sites in a total of 9 counties in North America (Canada and the US), South America (Chile), Europe (France, Great Britain, Italy, and Spain) and Asia (China and South Korea).

Inclusion criteria

1. Histologically or cytologically confirmed BTC, including ICC, ECC, or GBC.

2. Locally advanced or metastatic BTC and not eligible for curative resection, transplantation, or ablative therapies.

3. Received at least 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, and experienced disease progression after or developed intolerance to the most recent prior therapy. For participants who received gemcitabine in prior adjuvant or neoadjuvant treatment, if progression occurred < 6 months from the latter of primary surgical resection or completion of gemcitabine-containing adjuvant therapy, they were considered as having received 1 prior line of therapy for advanced disease.

4. Participants must have at least 1 measurable target lesion by RECIST v1.1. Participants who had received prior local therapy (embolization, chemoembolization, radiofrequency ablation, or radiation therapy) were eligible provided measurable disease fell outside of the treatment field or was within the treatment field and had shown ≥ 20% growth in size since post-treatment assessments.

5. Participants must have tested positive for HER2 amplification by ISH assay at a central laboratory on a new biopsy or archival tissue. Note that fine needle aspirates (FNAs; cytology samples) and biopsies from sites of bone metastases were not acceptable. Testing could have occurred at any time after diagnosis of advanced or metastatic disease and before study enrolment.

6. Male or female, ≥ 18 years of age (or the legal age of adulthood per country-specific regulations).

7. ECOG PS ≤ 1.

8. Adequate hematologic function, defined as ANC ≥ 1.5 × 109/L, platelet count ≥ 75 × 109/L (not requiring transfusion support), and haemoglobin ≥ 9 g/dL (participants with chronic anaemia that was supported by intermittent RBC transfusions were eligible).

9. Liver function: serum bilirubin ≤ 1.5 × the ULN or ≤ 3 × ULN for participants with Gilbert's disease, AST ≤ 3 × ULN, and ALT ≤ 3 × ULN. For participants with liver involvement, AST, and ALT ≤ 5.0 × ULN was acceptable.

10. Adequate cardiac function, as defined by LVEF ≥ 50%.

11. Kidney function: GFR ≥ 30 mL/min as estimated by the Modification of Diet in Renal Disease equation.

12. Females of childbearing potential must have had a negative serum or urine β-hCG pregnancy test result within 3 days prior to the first dose of zanidatamab. Females with false positive urine test results could be enrolled if subsequent serum testing was negative.

13. For female participants of childbearing potential and for male participants with a partner of childbearing potential, willingness for the couple to use 2 methods of birth control with a failure rate of less than 1% per year during the study and for 12 months after the last dose of zanidatamab.

14. Male participants must have agreed to not donate sperm and female participants must have agreed to not donate oocytes starting at screening and throughout the study period, and for at least 12 months after the last dose of zanidatamab.

15. The participant or participant's legally acceptable representative must have provided written informed consent. Participants who elected to be prescreened for HER2 status must have signed a separate written informed consent for collection, storage, and analysis of the tumour tissue.

Exclusion criteria

1. Received systemic anticancer therapy within 3 weeks of the first dose of zanidatamab. Received radiotherapy within 2 weeks of the first dose of zanidatamab.

2. Had major surgery within 4 weeks of the first dose of zanidatamab.

3. Prior treatment with HER2-targeted agents.

4. Untreated CNS metastases, symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks of start of study treatment. Stable, treated brain metastases were allowed (defined as participants who were off steroids and anticonvulsants and were neurologically stable with no evidence of radiographic progression for at least 4 weeks at the time of screening).

5. Known LMD. If LMD had been reported radiographically on baseline MRI, but was not suspected clinically by the investigator, the participant must be free of neurological symptoms of LMD.

6. Concurrent uncontrolled or active hepatobiliary disorders or untreated or ongoing complications after laparoscopic procedures or stent placement, including but not limited to active cholangitis, unresolved biliary obstruction, infected biloma, or abscess. Any complications must have been resolved more than 2 weeks prior to the first dose of zanidatamab.

7. Prior or concurrent malignancy whose natural history or treatment had, in the opinion of the investigator or medical monitor, the potential to interfere with the safety or efficacy assessment of the investigational regimen.

8. Significant acute infection or chronic infections that had not stabilized with treatment.

9. Active hepatitis, including the following criteria:

a. Acute or chronic hepatitis B (Exception: participants who were hepatitis B surface antigen positive were eligible if they had HBV DNA less than 500 IU/mL)

b. Infection with hepatitis C (Exception [i] participants who had no history of curative viral treatment and were documented to be viral load negative were eligible; [ii] participants who had completed curative viral therapy ≥ 12 weeks prior to enrolment, and viral load was negative were eligible).

10. Infection with HIV-1 or HIV-2 (Exception: participants with well-controlled HIV [e.g., CD4 > 350/mm3 and undetectable viral load] were eligible).

11. Females who were breastfeeding or pregnant, and females and males planning a pregnancy.

12. History of life-threatening hypersensitivity to monoclonal antibodies or to recombinant proteins or excipients in the drug formulation of zanidatamab.

13. Treatment with anthracyclines within 90 days before first dose of zanidatamab and/or total lifetime load exceeding 360 mg/m2 Adriamycin® or equivalent.

14. Use of corticosteroids administered at doses equivalent to > 15 mg per day of prednisone within 2 weeks of first zanidatamab dosing unless otherwise approved by the medical monitor. Topical, ocular, intra-articular, intranasal, and/or inhalational corticosteroids were permitted.

15. Ongoing, clinically significant toxicity (Grade 2 or higher) associated with prior cancer therapies, with the following exceptions:

a. Alopecia

b. CHF, which must have been ≤ Grade 1 at the time of occurrence and which must have completely resolved

c. Grade 2 peripheral sensory neuropathy.

16. QTcF > 470 ms.

17. History of myocardial infarction or unstable angina within 6 months prior to enrolment, troponin levels consistent with myocardial infarction, or clinically significant cardiac disease, such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic CHF.

18. Acute or chronic uncontrolled pancreatitis or Child-Pugh Class C liver disease.

19. Any other medical, social, or psychosocial factors that, in the opinion of the investigator, could have impacted safety or compliance with study procedures.

- **Treatments**

All participants received zanidatamab IV at 20 mg/kg every 2 weeks on Days 1 and 15 of each 28-day cycle. Participants received zanidatamab treatment until unacceptable toxicity, disease progression (either radiographic progression per RECIST v1.1 or unequivocal clinical progression), death, loss to follow-up, pregnancy, physician decision, or withdrawal of consent.

- **Objectives/endpoints**

Primary objective

The primary efficacy endpoint was confirmed ORR by RECIST version 1.1 assessed by ICR. This was a single-arm, open-label study. No statistical hypotheses were tested.

The primary efficacy endpoint was confirmed ORR by RECIST version 1.1 assessed by ICR.

Table 35: Estimand for primary objective

Population	**Participants with central lab confirmed HER2 gene amplified (HER2 expression of IHC 2+ or 3+ and ISH+), inoperable, and advanced or metastatic BTC, who were previously treated (participants have 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, or have progressed less than 6 months after this treatment in the adjuvant setting)**
Treatment condition	Z*anidatamab 20 mg/kg IV was given every 2 weeks in 28 days cycles (Q2W)*
Endpoint (variable)	Confirmed ORR by RECIST version 1.1 assessed by ICR
Population-level summary	Percentage of patients with cORR
Intercurrent events and strategy to handle them	
Initiation of new anticancer therapy	A while-on-treatment strategy is planned for this type of intercurrent event: use data collected prior to the intercurrent event to determine whether a confirmed response has occurred.
Disease progression	A while-on-treatment strategy is planned for this intercurrent event: use data collected prior to the intercurrent event to determine whether a confirmed response has occurred.
Early discontinuation from the study due to withdrawal of consent	A while-on-treatment strategy is planned for this intercurrent event: use data collected prior to the intercurrent event to determine whether a confirmed response has occurred.
Early discontinuation from the study intervention for any other reason	A treatment-policy strategy is planned for this type of intercurrent event: use all data to determine whether a confirmed response has occurred.

Abbreviations: BTC = biliary tract cancer; cORR = confirmed objective response rate; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; ISH = in situ hybridization; IV = intravenous; ORR = objective response rate; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors.

IV = intravenous; ORR = objective response rate; Q2W = every 2 weeks; RECIST = Response Evaluation Criteria in Solid Tumors.

Secondary objective

The secondary efficacy endpoints were DOR, DCR, CBR, PFS by RECIST version 1.1 assessed by both ICR and investigator, OS, and ORR assessed by investigator. This was a single-arm, open-label study. No statistical hypotheses were tested.

Efficacy population (cohort 1): Patients with HER2 gene-amplified (HER2 expression of IHC 2+ or 3+ and ISH+), inoperable, and advanced or metastatic BTC. Patients are previously treated (patients have 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, or have progressed less than 6 months after this treatment in the adjuvant setting).

Treatment: zanidatamab 20 mg/kg IV was given every 2 weeks in 28 days cycles (Q2W).

Endpoint (most important): Duration of response (DOR). DOR is defined as the time from the first confirmed objective response (CR or PR) to documented PD per RECIST 1.1 or death from any cause.

Population summary measure: Kaplan-Meier plot of DOR and Kaplan-Meier estimates of the quartiles (median, 25th and 75th) will be computed.

Intercurrent events: A table of censoring rules for PFS is given due to the fact that DOR is treated the same way with date of first dose replaced by date of first response.

Table 36 Censoring and Event Scheme for PFS

Scenario	Progression/Censor Date	Outcome
No baseline or no post-baseline response assessments and no death	Date of first dose	Censored
No disease progression (PD)	Date of last CR, PR, SD, or non-CR/non-PD	Censored
New anti-cancer treatment started before first PD	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of new anti-cancer treatment	Censored
Progressive disease (PD)	Date of PD, if response assessment prior to PD was either CR, PR, SD, or non-CR/non-PD	Progressed
	Date of last CR, PR, SD, or non-CR/non-PD, if PD occurred after 2 or more consecutive missed and/or NE overall response assessments*	Censored
Death	Death date, if last response assessment prior to death was CR, PR, SD, or non-CR/non-PD and death occurred ≤18 weeks from the last response assessment	Progressed
	Death date, if there are no baseline or no post-baseline response assessments and death occurred ≤18 weeks from the first dose.	Progressed
	Date of last CR, PR, SD, or non-CR/non-PD, if death occurred after 2 or more consecutive missed and/or NE overall response assessments*	Censored
	Date of first dose, if there are no baseline or no post-baseline response assessments and death occurred >18 weeks from the first dose	Censored

Note: * Two consecutive post-baseline tumor assessments refers to the next two protocol scheduled tumor assessments. Time is measured from the last adequate response assessment date. Subject will be considered to have missed two consecutive scheduled visits if no scans, scheduled or unscheduled, have occurred within the protocol-mandated disease assessment schedule; this will be within 2*(8 + 1) = 18 weeks. Note: The scanning schedule is every 8 weeks.

Here is a short summary of DOR-censoring rules that are deemed critical:

- If patients initiate new cancer therapy before PD they are censored.
- If PD or death occurred after 2 or more consecutive missed and/or NE overall response assessments they are censored.

Of note, the above censoring rules are examined in sensitivity analysis for PFS, but not for DOR.

- **Sample size**

This study was projected to enrol approximately 100 participants: approximately 75 participants in Cohort 1 and approximately 25 participants in Cohort 2. No formal sample size calculations were performed.

- **Randomisation and blinding (masking)**

Study 203 was a single-arm, open label study, so no randomisation nor blinding of participants or investigators occurred.

- **Statistical methods**

Planned analyses

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 postbaseline 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 2-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 2-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 tumour 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 tumour assessments were considered to have had PD on the date of the first missed visit.

The proportion of subjects with a DOR≥16 weeks and the corresponding two-sided, exact Clopper Pearson binomial 95% CI will also be calculated. In addition, the Kaplan-Meier probability and corresponding 2-sided 95% CI at Week 16 will be calculated.

Planned subgroup analyses

The following subgroups were evaluated for efficacy:

- Disease subtype (GBC, ICC, ECC)
- Intolerance to the most recent prior therapy (yes, no [progressed on the most recent regimen])
- Number of prior regimens for treatment of metastatic disease (< 2, ≥ 2)
- HER2 expression
    - Cohort 1: IHC 3+, IHC 2+
    - Cohort 2: IHC 1+, IHC 0
- Geographic region (North America, Asia, other)
- Sex (female, male)
- Age (< 65 years, ≥ 65 years, < 75 years, ≥ 75 years)
- Baseline ECOG PS (0, 1)
- Disease stage at baseline (study entry) (Stage IIB and Stage III, Stage IV)
- Race (Asian, non-Asian).

Changes from Protocol-specified analyses

The SAP (v2.0) was finalized prior to database lock for the primary analysis. There were no changes to the planned analyses described in the SAP for the primary analysis or the subsequent analysis.

There were no statistical hypotheses as the trial was single-arm.

Multiplicity control was not addressed.

Data quality assurance

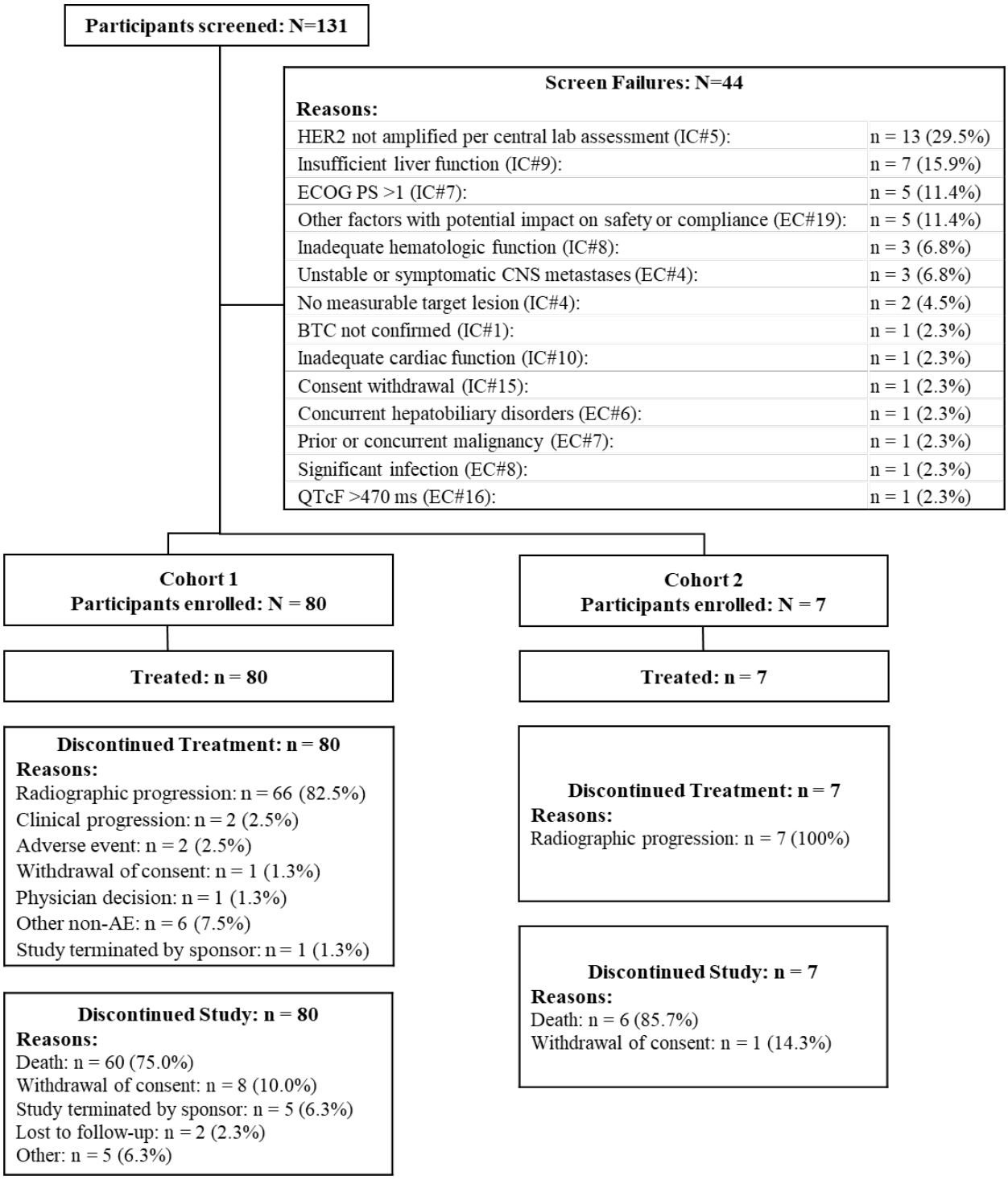
The sponsors or their designated clinical and medical personnel or delegate conducted initiation visits with the investigators and clinic staff prior to enrolment of participants at the sites. These initiation visits included, but were not limited to, review and explanation of the protocol, eCRFs, AE reporting procedures, and discussion of the responsibilities of the investigator for record keeping, investigational product accountability, and GCP. Sponsor representative(s) or their delegate(s) made periodic site visits to review study progress and source documentation. Data in the eCRFs were source data verified, deviations from the protocol were noted, and incoming data were monitored to detect and resolve discrepancies or inconsistencies.

The Clinical Quality Assurance group provided independent quality assurance support for this trial. Audits of the systems and suppliers that support the preparation, conduct, and reporting of this trial form part of the ongoing quality oversight activities.

Results

- **Participant flow**

Figure 33 Participant Flow



Abbreviations: BTC = biliary tract cancer; CNS = central nervous system; EC = exclusion criterion; ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2; IC = inclusion criterion, QTcF = QT with Fridericia correction.

- **Recruitment**

The first participant was enrolled on 15 September 2020 and received first treatment on 01 October 2020. The last participant was enrolled on 16 March 2022 and received first treatment on 25 March 2022. The median duration of study follow-up as of 28 July 2023 was 33.4 months.

- **Conduct of the study**

The original protocol was dated 13 February 2020.The protocol was subsequently amended 3 times, and a summary of the changes implemented under each amendment is provided in the table below.

Table 37 Protocol amendments

Amendment	Date	Description of substantive changes	Number of participants enrolled
1	26 April 2020	• Updated pain assessment questionnaire to BPI short form and updated the timeframe over which opioid use was to be analysed to align with the use of BPI for pain assessment. • Removed EORTC QLQ-C30 and QLQ-BIL21 quality-of-life questionnaires. • Clarified that absolute decreases of ≥ 10 percentage points below baseline LVEF were to be considered an AESI. • Clarified instructions for zanidatamab IV infusion. • Specified that there must be a minimum of 12 days between doses and clarified how to handle missed doses. • Clarified the procedure for reporting infusion-related reactions.	38
1 (China specific)	23 July 2020	Included a requirement for extensive PK in the first 10 participants enrolled in China. Updated IDMC schedule to include additional IDMC meetings for safety in these participants.	21
2	21 Apr 2021	**1. Clarified Inclusion Criterion #3 pertaining to prior gemcitabine-containing chemotherapy regimens.** 2. Revised description of women of childbearing potential in Inclusion Criterion #13 to make it consistent with Inclusion Criterion #12. 3. Revised Exclusion Criterion #6 to specify exclusion of participants with infected biloma rather than any biloma. 4. Revised Exclusion Criterion #7 to apply to any malignancy, not just invasive malignancy.	28

Amendment	Date	Description of substantive changes	Number of participants enrolled
		5. Revised Exclusion Criterion #15 so that participants with Grade 2 peripheral sensory neuropathy could be enrolled. 6. Extended radiographic efficacy assessments to continue every 8 weeks after treatment discontinuation until disease progression or start of subsequent anticancer therapy. 7. Added option for screening brain scan by CT if MRI was not feasible and specified that participants with history or clinical suspicion of brain metastases should have repeat scan at the time of tumour restaging. 8. Clarified that ECHO/MUGA should be performed every 3 cycles, within 7 days prior to treatment. 9. Increased number of participants to undergo initial extensive PK sampling from 16 to 30. 10. Added extensive PK sampling at steady state to enable collection of additional extensive PK data in participants who had received at least 4 cycles of zanidatamab treatment. 11. Removed option for a 60-minute infusion and added option for an infusion duration of < 90 minutes provided the maximum infusion rate was not exceeded. 12. Revised AESIs to include: infusion-related reactions, noninfectious pulmonary toxicities, and cardiac events of absolute decrease in LVEF ≥ 10 percentage points from pretreatment baseline and absolute value < 50% and/or Grade ≥ 2 heart failure. 13. Revised guidance for management of the following: 13.1. Potential zanidatamab-associated toxicities, including dose modifications for nausea/vomiting, diarrhoea, rash, and other toxicities 13.2. LVEF dysfunction and infusion-related reactions 14. Added that any alternative premedication regimen must be approved by the sponsor before use. 15. Added requirement for male participants with partners of childbearing potential to confirm their partner was not pregnant. 16. Added guidance for management of pulmonary toxicity. 17. Added option for next-generation sequencing and sharing of those results (not applicable in China).	

Amendment	Date	Description of substantive changes	Number of participants enrolled
		18. Provided guidelines to assist sites in conducting the study during the COVID-19 pandemic. 19. Updated safety reporting: 19.1. In the original protocol, progression of underlying malignancy was not to be reported as an AE or SAE. This was changed so that clinical manifestations of disease progression that met the criteria for an SAE were to be reported as such. 19.2. Follow-up reporting procedures were aligned for all AEs. 19.3. Safety reporting period - from the start of study drug dosing to 30 days after the last dose of study drug. Updated to be regardless of subsequent anticancer therapy. 19.4. Collect only protocol-related SAEs during the screening period (from the time of signing the prescreening or main informed consent form), rather than collect all protocol-related AEs. 19.5. Removed the time requirement of ≥ 24 hours of hospitalization for an AE to be classified as an SAE. 20. Added post-treatment HER2 tumour status as a biomarker assessment. 21. Added option for next-generation sequencing and sharing of those results if additional tissue slides were provided.	
3[a]	08 Sep 2023	• Administrative updates to reflect the current sponsor, medical monitor, investigational product synonym, and EU CT number	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus 2019; CT = computerized tomography; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EU CT = European Union clinical trial; HER2 = human epidermal growth factor receptor 2; IDMC = independent data monitoring committee; IV = intravenous; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PK = pharmacokinetics; QLQ = quality-of-life questionnaire; SAE = serious adverse event.

[a] Protocol amendment was approved after the DCO and before finalization of this report; provided for completeness.

Changes to study conduct that were not described in a protocol amendment are as follows:

- The protocol specified that approximately 25 participants would be enrolled in Cohort 2 based on the expectation that IHC 0/1+ would be observed in 25% of HER2-amplified BTC and IHC 2+/3+ would be observed in 75%. Enrolment in this cohort was stopped at the same time as enrolment to Cohort 2 with a lower rate of IHC 0 and IHC 1+ than estimated based on historical data. Actual enrolment in Cohort 2 was 7 participants.
- The protocol specified that steady state PK would be performed on 30 participants; however, it was only performed on 8 participants.

- The protocol specified that exploratory biomarkers of response could have been assessed, but these assessments were not performed.

Changes in planned analyses in the SAP

Table 38 Changes in the SAP planned analyses

Change	Reason for change
Definition of treatment emergent adverse event (TEAE). Protocol definition: "TEAEs are defined as events with an onset during or after receipt of the first dose of zanidatamab and up to and including 30 days after the last dose but prior to the start of a new anti-cancer therapy."	The new definition in the SAP is more conservative than the definition in the study protocol.
SAP definition: "TEAEs are defined as AEs with an onset during or after receipt of the first dose of zanidatamab and up to and including 30 days after the last dose."	

- **Baseline data**

Table 39 Demographics (Safety Analysis Set)

	Cohort 1 (N = 80)	Cohort 2 (N = 7)	Total (N = 87)
Age at informed consent (years)			
n	80	7	87
Mean (StD)	62.5 (9.56)	65.4 (8.75)	62.7 (9.48)
Median	64.0	62.0	64.0
Min, Max	32, 79	56, 77	32, 79
Age category, n (%)			
< 65 years	41 (51.3)	4 (57.1)	45 (51.7)
65-74 years	37 (46.3)	1 (14.3)	38 (43.7)
≥ 65 years	39 (48.8)	3 (42.9)	42 (48.3)
< 75 years	78 (97.5)	5 (71.4)	83 (95.4)
≥ 75 years	2 (2.5)	2 (28.6)	4 (4.6)
Sex, n (%)			
Female	45 (56.3)	2 (28.6)	47 (54.0)
Male	35 (43.8)	5 (71.4)	40 (46.0)
Ethnicity, n (%)			
Hispanic or Latino	5 (6.3)	1 (14.3)	6 (6.9)
Not Hispanic or Latino	72 (90.0)	6 (85.7)	78 (89.7)
Not reported	2 (2.5)	0	2 (2.3)
Unknown	1 (1.3)	0	1 (1.1)
Race[a], n (%)			
American Indian or Alaska native	1 (1.3)	0	1 (1.1)
Asian	52 (65.0)	5 (71.4)	57 (65.5)
White	23 (28.8)	2 (28.6)	25 (28.7)
Not reportable[b]	2 (2.5)	0	2 (2.3)
Unknown	2 (2.5)	0	2 (2.3)
Race[a], n (%)			
Asian	52 (65.0)	5 (71.4)	57 (65.5)
Non-Asian	28 (35.0)	2 (28.6)	30 (34.5)
Geographic region, n (%)			
North America	18 (22.5)	0	18 (20.7)
Asia	50 (62.5)	5 (71.4)	55 (63.2)
Other	12 (15.0)	2 (28.6)	14 (16.1)
ECOG performance status, n (%)			
0	22 (27.5)	1 (14.3)	23 (26.4)
1	58 (72.5)	6 (85.7)	64 (73.6)

ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; StD = standard deviation.

[a] Participants may select more than 1 race category.

[b] Not reportable: Collection and/or reporting of this information is prohibited by local and/or regional laws or regulations.

Table 40 Baseline Disease Characteristics and Disease History (Safety Analysis Set)

Characteristic	Cohort 1 (N = 80)	Cohort 2 (N = 7)	Total (N = 87)
Disease subtype, n (%)			
Gallbladder cancer	41 (51.3)	4 (57.1)	45 (51.7)
Intrahepatic cholangiocarcinoma	23 (28.8)	3 (42.9)	26 (29.9)
Extrahepatic cholangiocarcinoma	16 (20.0)	0	16 (18.4)
Perihilar	8 (10.0)	0	8 (9.2)
Distal	8 (10.0)	0	8 (9.2)
Stage at initial diagnosis, n (%)			

Characteristic	Cohort 1 (N = 80)	Cohort 2 (N = 7)	Total (N = 87)
I	2 (2.5)	0	2 (2.3)
II	9 (11.3)	2 (28.6)	11 (12.6)
III	23 (28.8)	2 (28.6)	25 (28.7)
IV	44 (55.0)	3 (42.9)	47 (54.0)
Unknown	2 (2.5)	0	2 (2.3)
Stage at study entry,[a] n (%)			
IIIA	1 (1.3)	0	1 (1.1)
IIIB	8 (10.0)	1 (14.3)	9 (10.3)
IV	27 (33.8)	2 (28.6)	29 (33.3)
IVB	44 (55.0)	4 (57.1)	48 (55.2)
Baseline hepatic impairment,[b] n (%)			
None	44 (55.0)	3 (42.9)	47 (54.0)
Mild	35 (43.8)	4 (57.1)	39 (44.8)
Moderate	1 (1.3)	0	1 (1.1)
Severe	0	0	0
Baseline renal impairment,[c] n (%)			
Normal	27 (33.8)	1 (14.3)	28 (32.2)
Mild to moderate	53 (66.3)	6 (85.7)	59 (67.8)
Outcome to most recent prior therapy, n (%)			
Progressed	72 (90.0)	6 (85.7)	78 (89.7)
Intolerant	8 (10.0)	1 (14.3)	9 (10.3)
Time from initial diagnosis to metastatic or locally advanced (months)			
Mean (StD)	4.68 (9.764)	4.57 (6.044)	4.67 (9.493)
Median	0.00	0.00	0.00
Min, Max	0, 72.0	0, 13.3	0, 72.0
Prior history of brain metastases, n (%)			
Yes	1 (1.3)	0	1 (1.1)
No	79 (98.8)	7 (100)	86 (98.9)
IHC result,[d,e] n (%)			
3+	62 (77.5)	0	62 (71.3)
2+	18 (22.5)	0	18 (20.7)
1+	0	3 (42.9)	3 (3.4)
0	0	4 (57.1)	4 (4.6)
Baseline sum of diameters (mm)f			
Independent central review			
n	80	5	85
Mean (StD)	78.8 (46.46)	59.0 (28.38)	77.7 (45.72)
Median	68.0	49.0	68.0
Min, Max	13, 183	23, 88	13, 183
Investigator			
n	80	7	87
Mean (StD)	83.8 (49.95)	85.4 (67.93)	83.9 (51.13)
Median	67.5	43.0	67.0
Min, Max	14, 205	13, 178	13, 205

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] Baseline renal impairment 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, September 2020.

[d] Based on a central laboratory companion diagnostic testing.

[e] All participants enrolled in the study were ISH+ at screening, based on a central laboratory companion diagnostic test.

[f] Sum of diameters of target lesions selected for disease response assessment per RECIST v1.1 tumor assessment.

Table 41 Prior Anticancer Therapies (Safety Analysis Set)

	Cohort 1 (N = 80)	Cohort 2 (N = 7)	Total (N = 87)
Prior systemic cancer therapy, n (%)			
Yes	80 (100)	7 (100)	87 (100)
Number of regimens			
n	80	7	87
Mean (StD)	1.8 (1.18)	1.7 (0.76)	1.8 (1.15)
Median	1.0	2.0	1.0
Min, Max	1, 8	1, 3	1, 8
Prior therapy for metastatic or locally advanced disease, n (%)[a]			
Yes	80 (100)	7 (100)	87 (100)
Number of regimens[b]			
n	80	7	87
Mean (StD)	1.7 (1.06)	1.7 (0.76)	1.7 (1.04)
Median	1.0	2.0	1.0
Min, Max	1, 7	1, 3	1, 7
Number of regimens[b]			
Less than 2	47 (58.8)	3 (42.9)	50 (57.5)
2 or more	33 (41.3)	4 (57.1)	37 (42.5)
Received gemcitabine			
Yes	80 (100)	7 (100)	87 (100)
Regimen received[c]			
Gemcitabin/oxaliplatin	12 (15.0)	3 (42.9)	15 (17.2)
Gemcitabine/cisplatin	61 (76.3)	4 (57.1)	65 (74.7)
Gemcitabine/fluoropyrimidine	5 (6.3)	0	5 (5.7)
Gemcitabine/other	2 (2.5)	0	2 (2.3)
Gemcitabine monotherapy	4 (5.0)	0	4 (4.6)
Fluoropyrimidine based[d]	27 (33.8)	4 (57.1)	31 (35.6)
PD1/PDL1 inhibitor	21 (26.3)	1 (14.3)	22 (25.3)
Prior radiotherapy, n (%)			
Yes	13 (16.3)	1 (14.3)	14 (16.1)
No	67 (83.8)	6 (85.7)	73 (83.9)
Prior surgeries with curative intent, n (%)			
Yes	25 (31.3)	2 (28.6)	27 (31.0)
No	55 (68.8)	5 (71.4)	60 (69.0)

Max = maximum; Min = minimum; PD1 = programmed cell death protein 1; PDL1 = programmed death ligand 1; StD = standard deviation.
[a] Includes gemcitabine-based therapies received in the adjuvant/neoadjuvant setting if progression occurred within 6 months of completion or surgery.
[b] Total regimens as designated by the investigator.
[c] Participants were counted at most once under each regimen type received and could be counted in multiple categories.
[d] Excludes regimens in combination with gemcitabine.

In the IHC3+ subgroup (N=62) in study 203, the median age was 64 years (range: 38 to 79 years), 47% of patients were age 65 or older; 55% were female; 61% were Asian, 31% were White. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (32%) or 1 (68%). Fifty-three percent of patients had gallbladder cancer, 27% had intrahepatic cholangiocarcinoma, and 19% had extrahepatic cholangiocarcinoma. Forty percent of patients had received more than one prior line of therapy for metastatic or locally advanced disease. The most commonly received prior treatments, other than gemcitabine, included: cisplatin (76%), oxaliplatin (16%), 5-fluoruracil (39%), and PD-1 or PD-L1 inhibitor (26%).

- **Numbers analysed**

Table 42 Participant Disposition (Safety Analysis Sets)

	ZWI-ZW25-203	ZWI-ZW25-101
	Cohort 1 (N = 80)	**BTC (N = 22)**
Participants treated, n (%)	80 (100)	22 (100)
Participants on study at DCO, n (%)	0	0
Participants on study treatment at DCO, n (%)	0	0
Participants who discontinued study treatment, n (%)	80 (100)	22 (100)
Disease progression – radiographic	66 (82.5)	18 (82)
Disease progression – clinical	2 (2.5)	1 (5)
Death	1 (1.3)	1 (5)
Adverse event	2 (2.5)	0
Physician decision	1 (1.3)	1 (5)
Withdrawal of consent	1 (1.3)	1 (5)
Other Non-AE	6 (7.5)	0
Participants in survival follow-up at DCO[a, n (%)]	0	Not applicable
Participants who discontinued the study, n (%)	80 (100)	22 (100)
Death	60 (75.0)	1 (5)
Withdrawal of consent	8 (10.0)	4 (18)
Study terminated by sponsor	5 (6.3)	0
Lost To Follow-up	2 (2.5)	0
Other	5 (6.3)	0
Progressive disease	0	16 (73)
Physician decision	0	1 (5)
Duration of study follow-up (months)[b]		
Median	33.4	3.7
Min, Max	28, 45	0.2, 28.2

Abbreviations: BTC = biliary tract cancer; DCO = data cutoff; Max = maximum; Min = minimum.

Error! Reference source not found. In Study 203, participants who discontinued treatment remained on study until death or withdrawal of consent for survival follow-up. In Study 101, participants were only followed for 30 days after the last study treatment.

[b] Duration of study follow-up for each participant is defined as the time between the date of first dose and date of last contact or death (in Study 101), or DCO (in Study 203).

- **Outcomes and estimation**

Primary endpoint: Confirmed ORR by ICR

Table 43 Disease Response as Assessed by ICR Using RECIST v1.1. (Efficacy Analysis Set)

Endpoint	Cohort 1 (N = 80)	Cohort 2 (N = 7)	Total (N = 87)
Confirmed ORR[a]			
n (%)	33 (41.3)	0	33 (37.9)
95% CI	(30.4, 52.8)	(0.0, 41.0)	(27.7, 49.0)
Confirmed BOR[a], n (%)			
CR	3 (3.8)	0	3 (3.4)
PR	30 (37.5)	0	30 (34.5)
SD	22 (27.5)	1 (14.3)	23 (26.4)
Non-CR/non-PD	0	2 (28.6)[b]	2 (2.3)
PD	24 (30.0)	3 (42.9)	27 (31.0)
NE[c]	1 (1.3)	1 (14.3)	2 (2.3)
Death	1 (1.3)[d]	0	1 (1.1)
Unevaluable scans	0	1 (14.3)[e]	1 (1.1)
CBR[f]			
n (%)	38 (47.5)	1 (14.3)	39 (44.8)
95% CI	(36.2, 59.0)	(0.4, 57.9)	(34.1, 55.9)
DCR[g]			
n (%)	55 (68.8)	3 (42.9)	58 (66.7)
95% CI	(57.4, 78.7)	(9.9, 81.6)	(55.7, 76.4)

BOR = Best overall response; CBR = clinical benefit rate; CI = Clopper-Pearson binomial confidence interval; CR = complete response; DCR = disease control rate; ICR = independent central review; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] Includes only confirmed CRs and PRs.

[b] Participants did not have measurable disease by ICR assessment.

[c] No evaluable post-baseline response assessments.

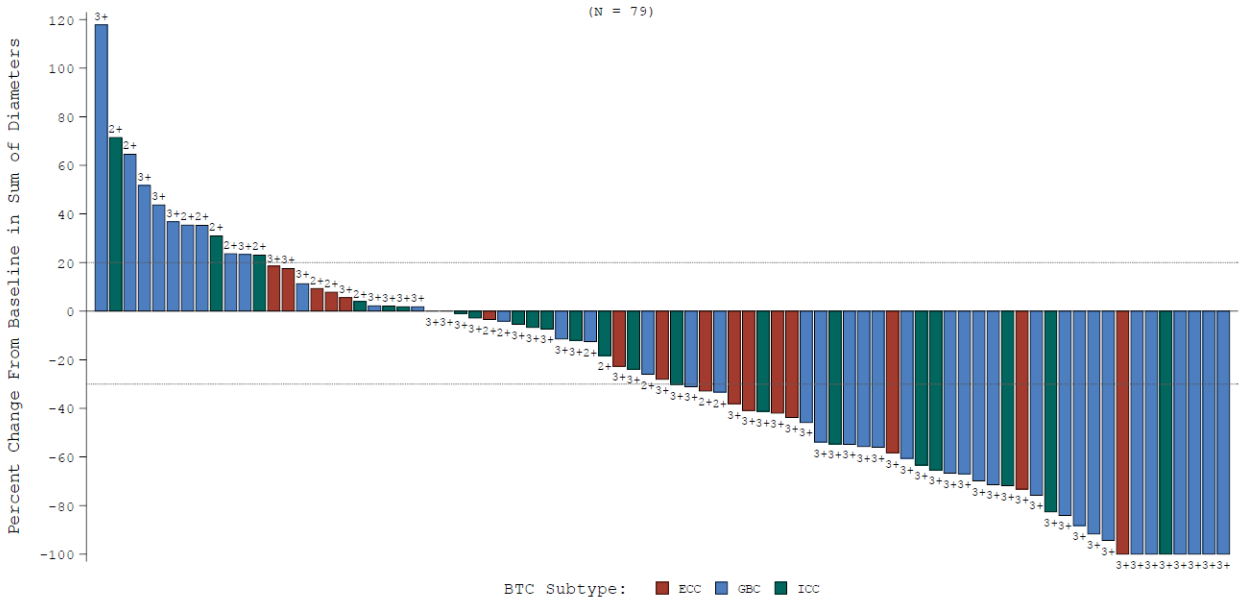
[d] Participant died prior to first post-baseline tumor assessment.

[e] First scan was not evaluable and participant died prior to second scan.

[f] SD or non-CR/non-PD ≥ 24 weeks or confirmed BOR of CR or PR.

[g] BOR of SD, non-CR/non-PD, or confirmed CR or PR.

Figure 34 Target Lesion Reduction by ICR



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 participant (2+ or 3+) is displayed above the individual bars.
Only participants with measurable disease at baseline and at least 1 postbaseline assessment are included in the figure.

Table 44 Concordance of Confirmed Objective Response per ICR and Investigator Assessment (Efficacy Analysis Set)

				Cohort 1	Cohort 2	Total
		ICR	Investigator	(N=80)	(N=7)	(N=87)
Concordance	By confirmed OR	Responder	Responder	30 (37.5)	0	30 (34.5)
		Nonresponder	Nonresponder	43 (53.8)	7 (100)	50 (57.5)
	Total			73 (91.3)	7 (100)	80 (92.0)
Discordance	By confirmed OR	Responder	Nonresponder	3 (3.8)	0	3 (3.4)
		Nonresponder	Responder	4 (5.0)	0	4 (4.6)
	Total			7 (8.8)	0	7 (8.0)

BOR = best overall response; CR = complete response; ICR = independent central review; OR = objective response; PR = partial response.
Note: Confirmed OR is defined as confirmed BOR of CR or PR.

Secondary endpoints: DoR by ICR, DCR by ICR, PFS by ICR, OS

Table 45 Duration of Response by ICR and Investigator Assessments (Response Evaluable Data Sets)

Endpoint	ICR Assessment	Investigator Assessment	
	ZWI-ZW25-203	ZWI-ZW25-203	ZWI-ZW25-101
	Cohort 1 (N = 33)	Cohort 1 (N = 34)	BTC (N = 8)
Had event, n (%)	18 (54.5)	24 (70.6)	6 (75.0)
Radiographic progression	16 (48.5)	24 (70.6)	6 (75.0)
Clinical progression	0	0	0
Death	2 (6.1)	0	0
Censored, n (%)	15 (45.5)	10 (29.4)	2 (25.0)
Ongoing radiographic follow-up	0	9 (26.5)	0
Subsequent anticancer therapy initiated	8 (24.2)	1 (2.9)	0
Two missed/unevaluable consecutive response assessments	2 (6.1)	0	0
Off treatment	NA	NA	2 (25.0)
Duration of Response (months)			
Min, Max	1.5, 20.6	1.9, 24.2	3.2, 22.1
Median (95% CI)	14.92 (7.39, 23.98)	11.10 (7.46, 16.53)	8.5 (3.2, NE)

Abbreviations: BTC = biliary tract cancer; CI = confidence interval; ICR = independent central review; Max = maximum; Min = minimum; NA = not applicable; NE = not evaluable.
Note: Duration of response defined as time from first objective response (complete response or partial response) that is subsequently confirmed, until disease progression or death. Only participants who had a confirmed objective response included in the analysis.

Table 46 Duration of Response as Assessed by ICR Using RECIST v1.1 (Response Evaluable Set per ICR-Participants with Confirmed Response)

	Cohort 1 (N=34)	Cohort 2 (N=0)	Total (N=34)
Had event, n (%)	27 (79.4)	–	27 (79.4)
Radiographic progression	25 (73.5)	–	25 (73.5)
Death	2 (5.9)	–	2 (5.9)
Censored, n (%)	7 (20.6)	–	7 (20.6)
Ongoing radiographic follow-up	0	–	0
Withdrawal of consent	6 (17.6)	–	6 (17.6)
Subsequent anticancer therapy initiated	1 (2.9)	–	1 (2.9)
2 or more consecutive missed/unevaluable response assessments	0	–	0
Total, n (%)	34 (100)	–	34 (100)
Duration of response[a] (months)			
Min, Max	1.9, 32.9	–	1.9, 32.9
Median (95% CI)	11.10 (7.46, 14.06)	–	11.10 (7.46, 14.06)
Kaplan-Meier estimate at Week 16			
Probability (95% CI)[b]	88.24 (71.63, 95.41)	–	88.24 (71.63, 95.41)
Participants with DOR ≥ 16 weeks			
n (%)	31 (91.2)	–	31 (91.2)
95% CI[c]	(76.3, 98.1)	–	(76.3, 98.1)

CI = confidence interval; CR = complete response; DOR = duration of response; Max = maximum; Min = minimum; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Estimates per Kaplan-Meier method; CIs based on the Brookmeyer and Crowley method with log-log transformation.

[b] CI based on Greenwood method.

[c] Clopper-Pearson, exact, binomial confidence interval.

Note: DOR is defined as time from the first confirmed objective response (CR or PR) to documented PD (per RECIST version 1.1) or death from any cause. Only participants with a confirmed objective response are included.

Table 47 Time to First Confirmed Objective Response as Assessed by ICR Using RECIST v1.1 (Response Evaluable Set per ICR)

First Confirmed Response[a,b]	Cohort 1 (N = 79)	Cohort 2 (N = 7)	Total (N = 86)
Time observed (week)			
n	33	0	33
Median	7.71	–	7.71
Min, Max	7.1, 24.1	–	7.1, 24.1
Percentage of participants responding by time point[c], n (%)			
Week 9	25 (75.8)	0	25 (75.8)
Week 17	30 (90.9)	0	30 (90.9)
Week 25	33 (100)	0	33 (100)
Week 33	33 (100)	0	33 (100)
Week 41	33 (100)	0	33 (100)
> Week 41	33 (100)	0	33 (100)

CR = complete response; ICR = independent central review; Max = maximum; Min = minimum; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Confirmed best overall response of PR or CR.

[b] Per the study protocol, radiographic scans occurred within ± 7-day window every 8 weeks from Cycle 1 Day 1.

[c] Cumulative percentage of participants whose first confirmed response occurred on or before the time point (week).

Table 48 Progression-Free Survival as Assessed by ICR Using RECIST v1.1 (Efficacy Analysis Set)

	Cohort 1 (N = 80)	Cohort 2 (N = 7)	Total (N = 87)
Events, n (%)	61 (76.3)	6 (85.7)	67 (77.0)
Radiographic progression	56 (70.0)	4 (57.1)	60 (69.0)
Death	5 (6.3)	2 (28.6)	7 (8.0)
Censored, n (%)	19 (23.8)	1 (14.3)	20 (23.0)
Ongoing radiographic follow-up	0	0	0
Withdrawal of consent	5 (6.3)	0	5 (5.7)
Subsequent anticancer therapy initiated	11 (13.8)	1 (14.3)	12 (13.8)
2 or more consecutive missed/unevaluable response assessments	3 (3.8)	0	3 (3.4)
No post-baseline response assessments	0	0	0
Total, n (%)	80 (100)	7 (100)	87 (100)
PFS time (months)[a]			
Min, Max	0.3, 35.1	1.2, 18.5	0.3, 35.1
Median (95% CI)	5.49 (3.65, 7.29)	1.87 (1.22, NE)	5.39 (3.48, 7.03)
Kaplan-Meier probabilities (95% CI)[b]			
3 months	67.2 (55.7, 76.4)	17.9 (0.8, 53.8)	63.9 (52.7, 73.0)
6 months	45.3 (33.8, 56.1)	17.9 (0.8, 53.8)	43.4 (32.5, 53.9)
9 months	33.4 (22.8, 44.3)	17.9 (0.8, 53.8)	32.4 (22.3, 42.9)
12 months	28.8 (18.8, 39.6)	17.9 (0.8, 53.8)	28.2 (18.6, 38.5)
Duration of PFS follow-up (months)[c]			
Min, Max	0.3, 35.1	1.2, 18.5	0.3, 35.1
Median	4.34	1.77	3.75

CI = confidence interval; ICR = independent central review; Max = maximum; Min = minimum; NE = not estimable; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.
[a] Estimates per the Kaplan-Meier method; CIs based on the Brookmeyer and Crowley method with log-log transformation.
[b] Confidence intervals based on the Greenwood method.
[c] Defined as time (months) from first dose of zanidatamab to PFS event or PFS censoring.
Note: PFS is defined as the time from first dose of study treatment to the date of documented disease progression (per RECIST version 1.1) or death from any cause, whichever occurred first.

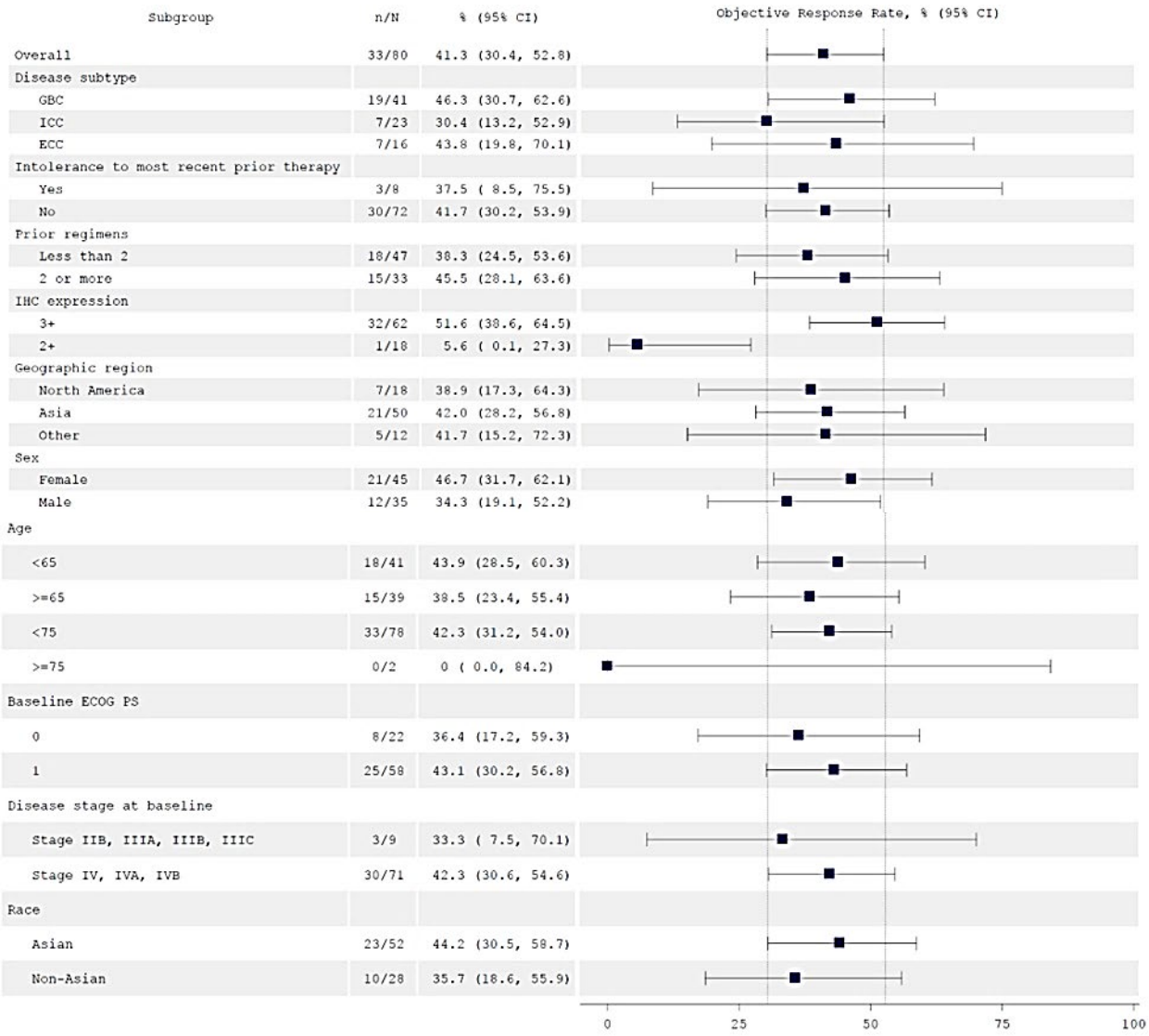
Table 49 Overall Survival (Efficacy Analysis Set)

	Cohort 1 (N=80)	Cohort 2 (N=7)	Total (N=87)
Events[a], n (%)	60 (75.0)	6 (85.7)	66 (75.9)
Censored, n (%)	20 (25.0)	1 (14.3)	21 (24.1)
Death after LPLV	0	0	0
Alive as of LPLV	10 (12.5)	0	10 (11.5)
Lost to follow-up	2 (2.5)	0	2 (2.3)
Withdrawal of consent	8 (10.0)	1 (14.3)	9 (10.3)
Total, n (%)	80 (100)	7 (100)	87 (100)
OS Time (months)[b]			
Min, Max	1.0, 38.1	1.2, 20.5	1.0, 38.1
Median (95% CI)	15.54 (10.38, 18.66)	5.52 (1.22, NE)	13.31 (10.22, 18.07)
Kaplan-Meier probabilities (95% CI)[c]			
3 months	93.6 (85.4, 97.3)	68.6 (21.3, 91.2)	91.8 (83.5, 96.0)
6 months	80.3 (69.4, 87.6)	34.3 (4.8, 68.5)	76.9 (66.2, 84.6)
9 months	69.6 (57.9, 78.6)	34.3 (4.8, 68.5)	67.0 (55.6, 76.0)
12 months	56.2 (44.3, 66.5)	17.1 (0.8, 52.6)	53.3 (41.9, 63.5)
Duration of OS follow-up			
Min, Max	1.0, 38.1	1.2, 20.5	1.0, 38.1
Median (95% CI)	12.76	5.52	11.24

CI = confidence interval; LPLV = last participant last visit; Max = maximum; Min = minimum; OS = overall survival.
[a] All-cause mortalities.
[b] Estimates per the Kaplan-Meier method; confidence intervals based on the Brookmeyer and Crowley method with log-log transformation.
[c] Confidence intervals based on the Greenwood method.
Note: OS is defined as the time from first dose of study treatment to the date of death.

- **Ancillary analyses**

Figure 35 Confirmed Objective Response Rate in Cohort 1 as Assessed by ICR by Subgroups (Efficacy Analysis Set)



Abbreviations: CI = confidence interval; ECC = extrahepatic cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status; GBC = gallbladder cancer; ICC = intrahepatic cholangiocarcinoma; ICR = independent central review; IHC = immunohistochemistry.
Note: The category of disease stage at baseline was prespecified to include Stage IIB; however, no participants at that stage were enrolled.

Table 50 Duration of Response per Independent Central Review using RECIST 1.1 ICR Response Evaluable Analysis Set – Subjects with Confirmed Response *(All Subjects)*

All Subjects

		IHC 3+ Cohort 1 ZW25 20 mg/kg (N=32)	IHC 2+ Cohort 1 ZW25 20 mg/kg (N=1)	Overall Cohort 1 ZW25 20 mg/kg (N=33)
Subjects Included in Analysis, n (%)	Events	15 (46.9)	0	15 (45.5)
	Radiographic Progression	15 (46.9)	0	15 (45.5)
	Death	0	0	0
	Censored	17 (53.1)	1 (100)	18 (54.5)
	Ongoing Radiographic Follow-up	8 (25.0)	0	8 (24.2)
	Withdrawal of Consent	0	0	0
	Subsequent Anti-Cancer Therapy Initiated	8 (25.0)	1 (100)	9 (27.3)
	2 or More Missed/Unevaluable Response Assessments[b]	1 (3.1)	0	1 (3.0)
	Total	32 (100)	1 (100)	33 (100)
Duration of Response (months)[a]	Min, Max	1.5, 20.6	7.5, 7.5	1.5, 20.6
	25th Percentile (95% CI)	5.75 (3.68, 12.22)	NE (NE , NE)	5.95 (3.71, 12.22)
	Median (95% CI)	14.92 (7.39, NE)	NE (NE , NE)	14.92 (7.39, NE)
	75th Percentile (95% CI)	20.57 (14.92, NE)	NE (NE , NE)	20.57 (14.92, NE)

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Table 51 Duration of Response per Independent Central Review using RECIST 1.1. ICR Response Evaluable Analysis Set – Subjects with Confirmed Response (Disease Subtype: Gallbladder cancer)

Disease Subtype: Gallbladder Cancer

		IHC 3+ Cohort 1 ZW25 20 mg/kg (N=19)	IHC 2+ Cohort 1 ZW25 20 mg/kg (N=0)	Overall Cohort 1 ZW25 20 mg/kg (N=19)
Subjects Included in Analysis, n (%)	Events	11 (57.9)		11 (57.9)
	Radiographic Progression	11 (57.9)		11 (57.9)
	Death	0		0
	Censored	8 (42.1)		8 (42.1)
	Ongoing Radiographic Follow-up	5 (26.3)		5 (26.3)
	Withdrawal of Consent	0		0
	Subsequent Anti-Cancer Therapy Initiated	3 (15.8)		3 (15.8)
	2 or More Missed/Unevaluable Response Assessments[b]	0		0
	Total	19 (100)		19 (100)
Duration of Response (months)[a]	Min, Max	3.3, 20.3		3.3, 20.3
	25th Percentile (95% CI)	3.91 (3.29, 11.24)		3.91 (3.29, 11.24)
	Median (95% CI)	12.91 (3.91, NE)		12.91 (3.91, NE)
	75th Percentile (95% CI)	NE (12.91, NE)		NE (12.91, NE)
Kaplan-Meier Estimate at Week 16	Probability (95% CI)[c]	89.47 (64.08, 97.26)		89.47 (64.08, 97.26)
Subjects with DOR >= 16 weeks	n (%)	18 (94.7)		18 (94.7)
	95% CI[d]	(74.0, 99.9)		(74.0, 99.9)

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Table 52 Duration of Response per Independent Central Review using RECIST 1.1. ICR Response Evaluable Analysis Set – Subjects with Confirmed Response (Disease Subtype: Intrahepatic Cholangiocarcinoma)

Disease Subtype: Intrahepatic Cholangiocarcinoma

		IHC 3+ Cohort 1 ZW25 20 mg/kg (N=7)	IHC 2+ Cohort 1 ZW25 20 mg/kg (N=0)	Overall Cohort 1 ZW25 20 mg/kg (N=7)
Subjects Included in Analysis, n (%)	Events	2 (28.6)		2 (28.6)
	Radiographic Progression	2 (28.6)		2 (28.6)
	Death	0		0
	Censored	5 (71.4)		5 (71.4)
	Ongoing Radiographic Follow-up	2 (28.6)		2 (28.6)
	Withdrawal of Consent	0		0
	Subsequent Anti-Cancer Therapy Initiated 2 or More Missed/Unevaluable Response Assessments[b]	3 (42.9)		3 (42.9)
	Total	0		0
		7 (100)		7 (100)
Duration of Response (months)[a]	Min, Max	1.9, 18.8		1.9, 18.8
	25th Percentile (95% CI)	12.22 (5.55, NE)		12.22 (5.55, NE)
	Median (95% CI)	NE (5.55, NE)		NE (5.55, NE)
	75th Percentile (95% CI)	NE (12.22, NE)		NE (12.22, NE)
Kaplan-Meier Estimate at Week 16	Probability (95% CI)[c]	100 (100 , 100)		100 (100 , 100)
Subjects with DOR >= 16 weeks	n (%)	6 (85.7)		6 (85.7)
	95% CI[d]	(42.1, 99.6)		(42.1, 99.6)

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Table 53 Duration of Response per Independent Central Review using RECIST 1.1. ICR Response Evaluable Analysis Set – Subjects with Confirmed Response (Disease Subtype: Extrahepatic Cholangiocarcinoma)

Disease Subtype: Extrahepatic Cholangiocarcinoma

		IHC 3+ Cohort 1 ZW25 20 mg/kg (N=6)	IHC 2+ Cohort 1 ZW25 20 mg/kg (N=1)	Overall Cohort 1 ZW25 20 mg/kg (N=7)
Subjects Included in Analysis, n (%)	Events	2 (33.3)	0	2 (28.6)
	Radiographic Progression	2 (33.3)	0	2 (28.6)
	Death	0	0	0
	Censored	4 (66.7)	1 (100)	5 (71.4)
	Ongoing Radiographic Follow-up	1 (16.7)	0	1 (14.3)
	Withdrawal of Consent	0	0	0
	Subsequent Anti-Cancer Therapy Initiated 2 or More Missed/Unevaluable Response Assessments[b]	2 (33.3)	1 (100)	3 (42.9)
	Total	1 (16.7)	0	1 (14.3)
		6 (100)	1 (100)	7 (100)
Duration of Response (months)[a]	Min, Max	1.5, 20.6	7.5, 7.5	1.5, 20.6
	25th Percentile (95% CI)	7.39 (7.39, NE)	NE (NE , NE)	13.98 (7.39, NE)
	Median (95% CI)	20.57 (7.39, NE)	NE (NE , NE)	20.57 (7.39, NE)
	75th Percentile (95% CI)	20.57 (7.39, NE)	NE (NE , NE)	20.57 (7.39, NE)
Kaplan-Meier Estimate at Week 16	Probability (95% CI)[c]	100 (100 , 100)	100 (100 , 100)	100 (100 , 100)
Subjects with DOR >= 16 weeks	n (%)	3 (50.0)	1 (100)	4 (57.1)
	95% CI[d]	(11.8, 88.2)	(2.5, 100)	(18.4, 90.1)

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Table 54 Duration of Response per Independent Central Review using RECIST 1.1. ICR Response Evaluable Analysis Set – Subjects with Confirmed Response (Baseline ECOG: 0)

Baseline ECOG: 0

		IHC 3+ Cohort 1 ZW25 20 mg/kg (N=8)	IHC 2+ Cohort 1 ZW25 20 mg/kg (N=0)	Overall Cohort 1 ZW25 20 mg/kg (N=8)
Subjects Included in Analysis, n (%)	Events	6 (75.0)		6 (75.0)
	Radiographic Progression	6 (75.0)		6 (75.0)
	Death	0		0
	Censored	2 (25.0)		2 (25.0)
	Ongoing Radiographic Follow-up	0		0
	Withdrawal of Consent	0		0
	Subsequent Anti-Cancer Therapy Initiated	2 (25.0)		2 (25.0)
	2 or More Missed/Unevaluable Response Assessments[b]	0		0
	Total	8 (100)		8 (100)
Duration of Response (months)[a]	Min, Max	3.3, 20.6		3.3, 20.6
	25th Percentile (95% CI)	4.16 (3.29, 12.91)		4.16 (3.29, 12.91)
	Median (95% CI)	12.57 (3.29, NE)		12.57 (3.29, NE)
	75th Percentile (95% CI)	20.57 (4.40, NE)		20.57 (4.40, NE)
Kaplan-Meier Estimate at Week 16	Probability (95% CI)[c]	87.50 (38.70, 98.14)		87.50 (38.70, 98.14)
Subjects with DOR >= 16 weeks	n (%)	7 (87.5)		7 (87.5)
	95% CI[d]	(47.3, 99.7)		(47.3, 99.7)

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Table 55 Duration of Response per Independent Central Review using RECIST 1.1. ICR Response Evaluable Analysis Set – Subjects with Confirmed Response (Baseline ECOG: 1)

Baseline ECOG: 1

		IHC 3+ Cohort 1 ZW25 20 mg/kg (N=24)	IHC 2+ Cohort 1 ZW25 20 mg/kg (N=1)	Overall Cohort 1 ZW25 20 mg/kg (N=25)
Subjects Included in Analysis, n (%)	Events	9 (37.5)	0	9 (36.0)
	Radiographic Progression	9 (37.5)	0	9 (36.0)
	Death	0	0	0
	Censored	15 (62.5)	1 (100)	16 (64.0)
	Ongoing Radiographic Follow-up	8 (33.3)	0	8 (32.0)
	Withdrawal of Consent	0	0	0
	Subsequent Anti-Cancer Therapy Initiated	6 (25.0)	1 (100)	7 (28.0)
	2 or More Missed/Unevaluable Response Assessments[b]	1 (4.2)	0	1 (4.0)
	Total	24 (100)	1 (100)	25 (100)
Duration of Response (months)[a]	Min, Max	1.5, 20.3	7.5, 7.5	1.5, 20.3
	25th Percentile (95% CI)	5.95 (3.68, 14.92)	NE (NE , NE)	7.39 (3.68, 14.92)
	Median (95% CI)	14.92 (5.95, NE)	NE (NE , NE)	14.92 (7.39, NE)
	75th Percentile (95% CI)	NE (14.92, NE)	NE (NE , NE)	NE (14.92, NE)
Kaplan-Meier Estimate at Week 16	Probability (95% CI)[c]	95.00 (69.47, 99.28)	100 (100 , 100)	95.24 (70.72, 99.32)
Subjects with DOR >= 16 weeks	n (%)	20 (83.3)	1 (100)	21 (84.0)
	95% CI[d]	(62.6, 95.3)	(2.5, 100)	(63.9, 95.5)

Duration of Response (DOR) is defined as time from the first confirmed objective response (CR or PR) to documented PD (per RECIST 1.1) or death from any cause. Only subjects who had a confirmed objective response included in the analysis.

[a] Estimates per the Kaplan-Meier method, confidence intervals based on the Brookmeyer and Crowley method with log-log transformation.

[b] 2 or more consecutive missing or unevaluable assessments prior to event.

[c] CI based on the Greenwood method.

[d] CI = Clopper-Pearson, exact, binomial confidence interval.

Program: t-km-tte.sas Date/Time of Run: 27NOV2023:09:42, Data cut-off: 28JUL2023

IHC 3+ subgroup

Table 56 Efficacy results in Study 203

Efficacy parameter*	**N=62**
Confirmed objective response rate (cORR)	
n % (95% CI)	32 51.6 (38.6, 64.5)
Complete response, n (%)	3 (4.8)
Partial response, n (%)	29 (46.8)
Duration of response (DOR)	**N=32**
Median †, months (95% CI)	14.9 (7.4, 24.0)

*Assessed by independent central review
†Based on Kaplan-Meier estimate

The median duration of study follow-up in the IHC3+ population was 34.0 months. The median overall survival (OS) in the IHC3+ population was 18.1 months (95% CI: 12.2, 22.9).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 57 Summary of efficacy for trial ZWI-ZW25-203

Title: A Phase 2b, Open-label, Single-arm Study of Zanidatamab (ZW25) Monotherapy in Participants with Advanced or Metastatic HER2-amplified Biliary Tract Cancers			
Study identifier	ZWI-ZW25-203 (HERIZON-BTC-01) EudraCT: 2020-000459-11 Clinicaltrials.gov: NCT04466891		
Design	Multicenter, open-label, single-arm trial to evaluate the anti-tumour activity of zanidatamab monotherapy in participants with HER2-amplified advanced or metastatic BTC not eligible for curative resection, including ICC, ECC, and GBC. Two cohorts of participants were enrolled: • Cohort 1: participants with HER2 amplification by ISH and HER2 overexpression by IHC; ie, IHC 2+ or IHC 3+ • Cohort 2: participants with HER2 amplification by ISH and HER2 IHC 0 or IHC 1+; results from this group do not support the present application because they do not represent the indicated population		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable Not applicable Not applicable
Hypothesis	Not applicable		
Treatments groups	Cohort 1		zanidatamab monotherapy 20 mg/kg IV Q2W
Endpoints and definitions	Primary endpoint	Confirmed objective response rate (ORR)	Achieving a best overall response (BOR) of complete response (CR) or partial response (PR) by RECIST v1.1 assessed by independent central review (ICR)
	Secondary endpoint	Duration of response (DOR)	Time from the first confirmed objective response of CR or PR to documented progressive disease (PD) per RECIST v1.1 or death from any cause.

	Secondary endpoint	Time to first confirmed objective response	Time from the first dose of study treatment to the earliest date a participant had a confirmed ORR
	Secondary endpoint	Progression-free survival (PFS)	Time from the first dose of study treatment to the date of documented disease progression (per RECIST v1.1) or death from any cause, whichever occurred first; this endpoint was evaluated according to ICR assessment and investigator assessment of PD
	Secondary endpoint	Overall survival (OS)	Time from the first dose of study treatment to the date of death from any cause or date last known alive for participants who did not die
Database lock	Data cut-off: 28 July 2023		
Results and Analysis			
Analysis description	**Primary Analysis (ICR Assessment)**		
Analysis population and time point description	Efficacy analysis set = all treated participants Time point = not applicable		
Descriptive statistics and estimate variability	Treatment group	ICH 3+	
	Number of subjects	62	
	Confirmed ORR, % (95% CI)	51.6% (38.6, 64.5)	
	DOR, median (95% CI)	14.92 months (7.39, 24.0)	
	OS, median (95% CI)	18.1 months (12.2, 22.9)	

2.3.5.3. Clinical studies in special populations

Table 58 Clinical studies in special populations

	Controlled Trials	Non-controlled trials
Renal impairment* patients (Subjects number /total number)	0	0
Hepatic impairment** patients (Subjects number /total number)	0	0
Paediatric patients <18 years (Subjects number /total number)	0	0
Age 65-74 (Subjects number /total number)	0	66/194***(34.0%)
Age 75-84 (Subjects number /total number)	0	5/194 (2.6%)
Age 85+ (Subjects number /total number)	0	2/194 (1.0%)
Other (Subjects number /total number)	0	0

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition).
** Hepatic impairment is defined as having Child-Pugh score B or C.
*** 194 represents patients with IHC3+ all dose levels, all indications.

2.3.5.4. In vitro biomarker test for patient selection for efficacy

Tumour biopsies or archival tissues were assessed for HER2 amplification, protein expression by IHC, and exploratory biomarkers of response.

HER2 testing

In study 203 Cohort 1, 62 (77.5%) participants had IHC 3+ score per central laboratory assessment, while the remaining 18 (22.5%) participants had IHC 2+ score. Of note, there were differences in the HER2 testing strategy between study 101 and study 203. In study 101 HER2 positive status was defined as IHC 3+ or IHC 2+/amplified as identified by local testing and retrospectively confirmed at a central laboratory with a commercially available HER2 IHC and FISH tests. In study 203, centrally obtained HER2 results with investigational Ventana IHC (4B5) and Ventana Dual ISH) assays were used for the selection of participants and to define the primary analysis cohort. In study 203 for Cohort 1, HER2 overexpression was defined as IHC 3+/Dual In Situ Hybridization (DISH) amplified or IHC 2+/DISH amplified.

2.3.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.3.5.6. Supportive study

Study 101 was a first-in-human, multicenter, global, phase 1, open-label, 3-part study designed to investigate the safety, tolerability, PK, and preliminary anti-tumour activity of zanidatamab monotherapy (Parts 1 and 2) and zanidatamab in combination with selected anticancer agents (Part 3) in participants with locally advanced (unresectable) and/or metastatic HER2-expressing cancer.

The study design is summarized in Figure 32. An interim CSR is provided with a clinical data cut-off date of 14 January 2022.

Part 1: Dose Escalation

Please refer to 2.6.5.1.

Part 2: Monotherapy Expansion Cohorts

Monotherapy expansion cohorts were opened to enrolment as determined by the SMC and the sponsor for treatment of subjects at an RD identified in Part 1 of the study.

Subject Disposition

Of the 250 subjects screened for Part 2 of the study, 146 were enrolled to receive study treatment. As of the data cut-off date (14 January 2022), 136 of the 146 subjects (93%) had discontinued study treatment, and 135 subjects (92%) had discontinued from the study. The most common reason for treatment discontinuation was radiographic progression (102 subjects; 75%) and a further 18 subjects (13%) discontinued treatment due to clinical progression. The most common reason for study discontinuation was disease progression (100 subjects; 74%).

Baseline demographics and disease characteristics

Table 59 Part 2: Subject Demographics (Safety Analysis Set)

Parameter	Breast (N=31)	GEA (N=29)	CRC (N=28)	Biliary (N=22)	All Other (N=36)	Total (N=146)
Age at informed consent (yrs)						
Median	55.0	61.0	60.0	62.5	63.0	60.0
Min, Max	27, 79	24, 86	36, 72	42, 78	43, 82	24, 86
Age category, n (%)						
< 65 years	24 (77)	19 (66)	21 (75)	14 (64)	20 (56)	98 (67)
≥ 65 years	7 (23)	10 (34)	7 (25)	8 (36)	16 (44)	48 (33)
Sex, n (%)						
Female	30 (97)	6 (21)	14 (50)	14 (64)	15 (42)	79 (54)
Male	1 (3)	23 (79)	14 (50)	8 (36)	21 (58)	67 (46)
Ethnicity, n (%)						
Hispanic or Latino	3 (10)	2 (7)	0	0	2 (6)	7 (5)
Not Hispanic or Latino	25 (81)	27 (93)	28 (100)	22 (100)	34 (94)	136 (93)
Unknown	3 (10)	0	0	0	0	3 (2)
Race[a], n (%)						
American Indian or Alaska Native	0	1 (3)	0	0	0	1 (1)
Asian	0	11 (38)	17 (61)	15 (68)	20 (56)	63 (43)
Black or African American	3 (10)	0	0	1 (5)	1 (3)	5 (3)
White	25 (81)	17 (59)	11 (39)	5 (23)	14 (39)	72 (49)
Other	1 (3)	0	0	0	0	1 (1)
Not reported	2 (6)	1 (3)	0	1 (5)	2 (6)	6 (4)
Baseline ECOG PS, n (%)						
0	9 (29)	2 (7)	11 (39)	2 (9)	8 (22)	32 (22)
1	22 (71)	27 (93)	17 (61)	20 (91)	28 (78)	114 (78)

CRC = colorectal cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; GEA = gastroesophageal carcinoma; Max = maximum; Min = minimum; yrs = years.

a Subjects may select more than one race category.

Table 60 Part 2: Baseline Disease Characteristics and Disease History (Safety Analysis Set)

Characteristic	Breast (N=31)	GEA (N=29)	CRC (N=28)	Biliary (N=22)	All Other (N=36)	Total (N=146)
Stage at initial diagnosis, n (%)						
I, IB	4 (13)	1 (3)	1 (4)	1 (5)	1 (3)	8 (5)
II, IIA, IIB	10 (32)	1 (3)	2 (7)	3 (14)	5 (14)	21 (14)
III, IIIA, IIIA/B, IIIB, IIIC	7 (23)	2 (7)	2 (7)	5 (23)	9 (25)	25 (17)
IV, IVA, IVB	8 (26)	25 (86)	23 (82)	12 (55)	16 (44)	84 (58)
Unknown	2 (6)	0	0	1 (5)	5 (14)	8 (5)
Time from initial diagnosis to metastatic disease (yrs) [a]						
n	30	29	28	21	35	143
Median	3.0	0.0	1.0	0.0	1.0	1.0
Min, Max	0.0, 29.0	0.0, 3.0	0.0, 5.0	0.0, 3.0	0.0, 3.0	0.0, 29.0
HER2 status: IHC 3+ or IHC 2+/FISH+, n (%)						
Yes	23 (74)	28 (97)	28 (100)	22 (100)	35 (97)	136 (93)
No [b]	8 (26)	1 (3)	0	0	1 (3)	10 (7)
Brain metastases at screening, n (%)						
Yes	4 (13)	0	0	0	1 (3)	5 (3)
No	27 (87)	29 (100)	28 (100)	22 (100)	35 (97)	141 (97)

CRC = colorectal cancer; FISH = fluorescence in situ hybridization; GEA = gastroesophageal adenocarcinoma; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; Max = maximum; Min = minimum; yrs = years.

a Subjects that were Stage IV, IVA, or IVB at initial diagnosis and had no time to metastatic disease indicated are assumed to have a value of 0 years.

b Subjects who were not (IHC 3+ or IHC 2+/FISH+).

Efficacy

Table 61 Part 2: Disease Response Endpoints per Investigator Assessment Using RECIST v 1.1. (Measurable Disease Analysis Set)

Endpoint	Breast (N=30)	GEA (N=29)	CRC (N=28)	Biliary (N=22)	All Other (N=36)	Total (N=145)
Confirmed BOR, n (%)						
Partial response (PR)	2 (6.7)	9 (31.0)	10 (35.7)	8 (36.4)	13 (36.1)	42 (29.0)
Stable disease (SD)	16 (53.3)	8 (27.6)	10 (35.7)	5 (22.7)	16 (44.4)	55 (37.9)
Progressive disease (PD) [a]	12 (40.0)	11 (37.9)	6 (21.4)	8 (36.4)	7 (19.4)	44 (30.3)
Radiographic progression	10 (33.3)	9 (31.0)	4 (14.3)	7 (31.8)	6 (16.7)	36 (24.8)
Clinical progression	1 (3.3)	1 (3.4)	2 (7.1)	0	1 (2.8)	5 (3.4)
Death	1 (3.3)	1 (3.4)	0	1 (4.5)	0	3 (2.1)
Not Evaluable (NE)	0	1 (3.4)	2 (7.1)	1 (4.5)	0	4 (2.8)
Confirmed ORR [b]						
n (%)	2 (6.7)	9 (31.0)	10 (35.7)	8 (36.4)	13 (36.1)	42 (29.0)
95% CI	(0.8, 22.1)	(15.3, 50.8)	(18.6, 55.9)	(17.2, 59.3)	(20.8, 53.8)	(21.7, 37.1)
ORR						
n (%)	4 (13.3)	11 (37.9)	13 (46.4)	8 (36.4)	14 (38.9)	50 (34.5)
95% CI	(3.8, 30.7)	(20.7, 57.7)	(27.5, 66.1)	(17.2, 59.3)	(23.1, 56.5)	(26.8, 42.8)
CBR [c]						
n (%)	4 (13.3)	11 (37.9)	15 (53.6)	8 (36.4)	19 (52.8)	57 (39.3)
95% CI	(3.8, 30.7)	(20.7, 57.7)	(33.9, 72.5)	(17.2, 59.3)	(35.5, 69.6)	(31.3, 47.8)
DCR [d]						
n (%)	18 (60.0)	17 (58.6)	20 (71.4)	13 (59.1)	29 (80.6)	97 (66.9)
95% CI	(40.6, 77.3)	(38.9, 76.5)	(51.3, 86.8)	(36.4, 79.3)	(64.0, 91.8)	(58.6, 74.5)

BOR = best overall response; CBR = clinical benefit rate; CI = confidence interval; CR = complete response; CRC = colorectal cancer; DCR = disease control rate; GEA = gastroesophageal adenocarcinoma; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

a Subjects who died or who had clinical progression before radiographic progression was observed are imputed as PD.

b Only CR and PR are confirmed.

c SD ≥ 24 weeks or confirmed BOR of CR or PR.

d Best overall response of CR, PR, or SD.

Table 62 Part 2: Duration of Response per Investigator Assessment Using RECIST v1.1 (Response Evaluable Analysis Set)

Endpoint	Breast (N=2)	GEA (N=9)	CRC (N=10)	Biliary (N=8)	All Other (N=13)	Total (N=42)
Subjects with event, n/N (%)	0/2	8/9 (89)	9/10 (90)	6/8 (75)	7/13 (54)	30/42 (71)
Radiographic progression	0/2	6/9 (67)	9/10 (90)	6/8 (75)	7/13 (54)	28/42 (67)
Clinical progression	0/2	2/9 (22)	0/10	0/8	0/13	2/42 (5)
Death	0/2	0/9	0/10	0/8	0/13	0/42
Subjects censored, n/N (%)	2/2 (100)	1/9 (11)	1/10 (10)	2/8 (25)	6/13 (46)	12/42 (29)
On treatment	2/2 (100)	0/9	1/10 (10)	0/8	4/13 (31)	7/42 (17)
Ended treatment	0/2	1/9 (11)	0/10	2/8 (25)	2/13 (15)	5/42 (12)
Total, n/N (%)	2/2 (100)	9/9 (100)	10/10 (100)	8/8 (100)	13/13 (100)	42/42 (100)
Duration of response (months)						
Median (95% CI)	NE (NE, NE)	6.7 (1.9, 11.1)	5.6 (2.8, 16.7)	8.5 (3.2, NE)	9.7 (3.7, NE)	7.4 (5.6, 12.1)
Min, Max	37.0+, 41.4+	1.7, 14.7	2.8, 18.4	3.2, 22.1	1.9, 26.0+	1.7, 41.4+

CI = confidence interval; CR = complete response; CRC = colorectal cancer; GEA = gastroesophageal adenocarcinoma; Max = maximum; Min = minimum; NE = not estimable; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors v1.1.
+ censored, subject still on treatment.
Notes: Duration of response defined as time from 1st objective response (CR or PR) that is subsequently confirmed, until disease progression or death.
Only subjects who had a confirmed objective response included in the analysis.
Subjects are no longer followed beyond the safety reporting period once treatment has been discontinued.

2.3.6. Discussion on clinical efficacy

Dose finding and dose recommendation Study 101 (ZWI-ZW25-101)

Study 101 was a first-in-human, multicentre, global, phase I, open-label, 3-part study designed to investigate the safety, tolerability, PK, and preliminary anti-tumour activity of zanidatamab monotherapy (Parts 1 and 2) and zanidatamab in combination with selected anticancer agents (Part 3) in participants with locally advanced (unresectable) and/or metastatic HER2-expressing cancer. Part 1 was for dose escalation. The following dose levels of zanidatamab were prespecified for evaluation: 5 mg/kg IV weekly (QW), 10 mg/kg IV QW, 15 mg/kg IV QW, 20 mg/kg IV once every 2 weeks (Q2W), 25 mg/kg IV Q2W, 30 mg/kg IV Q2W, and/or 30 mg/kg IV once every 3 weeks (Q3W).

Decreases in tumour size were observed with zanidatamab monotherapy in all dose regimens evaluated, including 5 mg/kg QW, the lowest dose exposure evaluated in Part 1. At the time of the data cut-off, the median study follow-up time was 2.9 months. Only the 10 mg/kg QW and the 20 mg/kg Q2W dose regimens were evaluated in Part 2 of this study.

Design and conduct of clinical studies

The efficacy of zanidatamab for a conditional approval in the proposed indication is based on results from cohort 1 of the pivotal study 203 and supportive data from study 101. Pivotal study 203 is a single-arm, uncontrolled, and open-label study, and was conducted in patients with advanced biliary tract cancer (BTC), who had previously received gemcitabine-containing chemotherapy. Patients were enrolled at 32 investigative sites in a total of 9 counties in North America, South America, Europe and Asia over less than 2 years and the current DCO is 28 July 2023, so the median (range) duration of study follow-up was 33.4 months (28 to 45 months). A total of 87 patients were included in the pivotal study; however, only the 80

patients from Cohort 1 were initially relevant for the efficacy assessment of zanidatamab, since cohort 2 included patients with HER2 expression of IHC 0 or 1+ and ISH+ (n=7); and the initially applied indication pertained to patients with tumours that expressed IHC 2+ or 3+.

Included patients should have histologically or cytologically confirmed BTC, including intrahepatic (ICC) and extrahepatic (ECC) localization, or gallbladder cancer (GBC), and the disease should be locally advanced or metastatic and not eligible for curative resection, transplantation, or ablative therapies. The primary endpoint was confirmed ORR per RECIST v1.1 and evaluated by independent blinded review (ICR), while other relevant secondary endpoints are duration of response (DoR) and OS.

Baseline characteristics

In the pivotal study 203, the mean age was 62.5 years, slightly more females were included (56.3% vs 43.8% men), and the vast majority was Asian (65%) or white (~29%). This is considered to be reflecting the global population with the targeted disease, but to a lesser extent the EU population. However, the applicant has presented a systematic literature review and meta-analysis of published data on HER2 positive BTC, which indicated that rates of HER2 overexpression/gene amplification do not appear to differ by geographic region (Galdy et al. 2017). For now, it is unknown whether response to standard of care treatment is dependent on HER2 status across regions. Since White patients represented almost a third of all patients, the results from this subgroup will support the extrapolation of the results from study 203 to the EU population.

Patients were of good ECOG Performance status (PS), either of ECOG PS 1 (72.5%) or ECOG PS 0 (27.5%). Half of the patients had gallbladder cancer (51.3%), while the majority of the rest had either intrahepatic (28.8%) or extrahepatic cholangiocarcinoma (20%). The median number of previous lines of anticancer therapies was 1 (range 1-7) and the most common were cisplatin (76.3%) with gemcitabine, followed by fluoropyrimidine-based regimens (33.8%), and PD-1/PD-L1 inhibitors (26.3%). It should be noted that 15% had oxaliplatin-based therapy, so almost all (91%) had prior platinum-based chemotherapy. Prior radiotherapy and any prior surgery with curative intent were also reported in 16.3% and 31.3% of the patients, respectively. The median number of prior surgeries was 1 (range: 1 to 4). Overall, this is considered reflective of the targeted patient population in the 2L+ setting of advanced HER2-positive BTC. Since all patients had at least 1 prior systemic therapy before inclusion, this has adequately been reflected in the wording of the indication.

In the IHC3+ subgroup population (n=62), the baseline characteristics were similar as in cohort 1 (N=80)

Efficacy data and additional analyses

The primary endpoint of confirmed overall response rate (ORR) by independent central review (ICR) showed that 41.3% (95%CI: 30.4, 52.8) of the patients responded to treatment with zanidatamab in the ITT population. The median duration of response was 14.92 months (95%CI: 7.39, 23.98). Considering the targeted setting, where no SoC approach exists, the reported confirmed ORR is considered clinically meaningful. Moreover, the apparently long median duration of the induced responses of more than 1 year is promising and supports the applied conditional approval of zanidatamab in the second-line setting of advanced HER2-positive BTC.

Supportive data was provided from 22 patients with HER2-expressing BTC, who were included in the phase I study 101. For these BTC patients treated with zanidatamab monotherapy, the observed confirmed ORR was 36.4% and the median DOR was 8.5 months, which is considered to support the further development of zanidatamab that took place in HER2+ BTC. Several HER2+ cancers were treated in this study and the value

of these non-comparative data in heavily pre-treated patients is limited, and therefore no efficacy updates are requested although the cut-off date is more than 2 years ago (14 January 2022). Moreover, inclusion of the results of study 101 in section 5.1 of the SmPC is not considered necessary.

Subgroup analyses of confirmed ORR (cORR) per ICR for the relevant subgroups of disease subtype, prior regimens, geographic region (North America, Asia, other), sex, baseline ECOG PS, and disease stage, show that the point estimates were within the 95% CIs for the cORR for the overall population, which is considered clinically meaningful.

Based on zanidatamab's mechanism of action and the non-clinical in vitro and in vivo pharmacology results (see sections 2.5.2. and 2.5.6.), it is clear that there is a large variation in tumour growth inhibition and efficacy in general, depending on the HER2 expression level of the investigated cancer cell lines. Tumour cells expressing high levels of HER2 receptors (HER 3+) was by far the most responsive cell types. For the very important subgroup analysis of IHC expression of HER2 (3+ vs 2+), the analysis shows that the patients with HER2 IHC 2+ had an cORR of only 5.6%. The applicant argued that this cORR is comparable to the results with FOLFOX chemotherapy – which is not the standard of care in the EU and results in a median cORR of 5% (Lamarca, 2024). However, such an argument was not considered acceptable as an cORR of 5.6% is not considered clinically relevant and such result is considered insufficient and does not provide convincing evidence of zanidatamab's clinically relevant benefit for patients with HER2 IHC 2+ expression in the targeted second-line setting of HER2 positive BTC. Considering that the effects observed in study 203 were driven by the HER2-high expressors, the indication has therefore been restricted to the HER2 ICH 3+ population, which had a confirmed ORR of 51.6% (95%CI: 38.6; 64.5), and a median DoR of 14.92 months (95%CI: 7.39; 24.0).

In the IHC3+ subgroup, the median study follow-up time was 34 months and, in that context, the median OS of 18.1 months (95%CI: 12.2; 22.9) is considered reassuring in this advanced setting after at least one prior treatment. However, the regulatory relevance of uncontrolled OS results is limited.

The applicant has used the investigational Ventana IHC (4B5) and Ventana Dual ISH assays test for HER2-testing and selection of the relevant study population, which is clearly stated in section 5.1 of the SmPC.

Additional efficacy data needed in the context of a conditional MA

In the context of seeking a CMA for zanidatamab in such rare population, a single-arm study is acceptable.

To confirm the clinical benefit of zanidatamab in adults patients with unresectable locally advanced or metastatic HER2+ BTC previously treated with at least one prior line of systemic therapy as demonstrated in the pivotal study 203, the applicant is conducting a phase III, open-label, randomised study, study JZP598-302 in the first line setting. The confirmatory study JZP598-302 investigates the efficacy and safety of zanidatamab plus cisplatin and gemcitabine (CisGem for up to 8 cycles) with or without PD-1/L1 inhibitor (physician's choice of either durvalumab or pembrolizumab) as first-line treatment for patients with HER2-positive advanced BTC, and plans to enrol approximately 286 patients, who will be randomised 1:1 to zanidatamab plus standard of care versus standard of care alone, and approximately 75% are projected to be in the IHC 3+ subgroup. The primary endpoint for study JZP598-302 is PFS by investigator per RECIST 1.1 in the IHC 3+ subgroup, while the key secondary endpoints are OS in the IHC3+ subgroup, PFS per RECIST 1.1 in the overall population, and OS in the overall population. A copy of each scan will be sent to the BIRC for independent read of all scans for supportive analysis. The use of PFS by RECIST 1.1 assessed by an investigator is questionable in view of the open-label design. The applicant is advised to utilize PFS assessment by the BIRC for all patients to ensure an unbiased estimate.

The applicant should include a sufficient fraction of EU-like patients in the confirmatory study JZP598-302 as the results needs to be confirmative of a positive B/R in the EU (like) population.

According to the design of this confirmatory study, the efficacy will be confirmed in the IHC 3+ subgroup, which is also the population of the revised indication in this present application for a CMA. It is however considered to be acceptable that the confirmatory study JZP598-302 will be stratified according to tumour HER2 status (IHC 3+ vs. IHC 2+/ISH+). It is acknowledged that patients with HER2 IHC 2+ tumours are included in the confirmatory study JZP598-302 and this is considered acceptable, as it can be agreed that some patients with IHC 2+ ISH-amplified tumours may benefit from adding zanidatamab on top of SoC, but the currently available data from study 203 does not support treatment with zanidatamab as monotherapy for these patients.

The applicant did provide an update on the status of the confirmatory study JZP598-302, including recruitment status and estimated timelines. Since there is no SoC for the targeted HER2 positive BTC population in the 2L+ setting, it is considered acceptable to conduct the confirmatory study in the first-line setting and through a different study design, where zanidatamab is used as an add-on to SoC in 1L in comparison to SOC alone. This is because zanidatamab is used to treat the same targeted disease and there is a strong scientific rationale that zanidatamab will be effective in this earlier line setting as well. It has also previously been accepted by the CHMP that monotherapy treatment with a medicinal product is confirmed by a combination treatment, and in this case, it is acknowledged that the randomised confirmatory study should be conducted in a setting with SoC options, so the approach to use zanidatamab as an add-on in 1L is endorsed.

The applicant will submit as a specific obligation (SOB) the results of study JZP598-302. Results from this study are intended to provide a comprehensive data package and with the intent to 'convert the conditional MA into a full MA.

2.3.7. Conclusions on the clinical efficacy

The efficacy results of the pivotal single arm study 203 of zanidatamab monotherapy for the treatment of advanced HER2-positive ICH 3+ BTC showed a clinically relevant overall response rate of 51.6% (95%CI: 38.6; 64.5), which appears durable with a median DoR of 14.92 months (95%CI: 7.39; 24.0).

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to confirm the efficacy and safety of zanidatamab in the treatment of adults with unresectable locally advanced or metastatic HER2-positive biliary tract cancer previously treated with at least one prior line of systemic therapy, the MAH should submit the results of the ongoing open-label phase III randomised clinical study JZP598-302 to evaluate the efficacy and safety of zanidatamab plus standard-of-care therapy versus standard-of-care therapy alone for advanced HER2-positive biliary tract cancer.

2.3.8. Clinical safety

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

- Study 203 safety population (N = 87): All participants with BTC treated with zanidatamab in Cohort 1 & 2 of study 203.

- 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 tumour type, to provide a broader assessment of safety among study participants who were treated with the proposed zanidatamab dosage regimen. This included 87 participants with BTC in study 203 and 146 participants with different tumour types (including 22 with BTC) in study 101.

Table 63 Overview of Studies Providing Safety Data

Study (Phase)	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 [b] Study Start/ DCO
Pivotal Study – *Pooled Safety Analysis*						
ZWI-ZW25-203 (Pivotal Phase 2b) CSR Version 02	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 Safety Endpoints: AEs, Change in clinical laboratory tests, concomitant medications, physical examination findings, ECOG performance status, 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 DCO: 28 Jul 2023
Supportive Study – *Pooled Safety Analysis*						
ZWI-ZW25-101 (Phase 1) Interim CSR (Parts 1 & 2)	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: combination therapy expansion cohorts treated at zanidatamab MTD, OBD, or RD plus selected antineoplastic agents Objectives: Safety and tolerability, PK, immunogenicity, antitumor activity 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 3:** In combination • 20 mg/kg IV Q2W • 25 mg/kg IV Q2W • 30 mg/kg IV Q3W	**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 DCO: 14 Jan 2022
Supportive Studies – *Studies providing limited supportive monotherapy safety data*						
Study ZWI-ZW25-102 (Phase 1) Enrolling	Japan (4)	Japanese participants with locally advanced (unresectable) and/or metastatic HER2-expressing cancers	Design: Open-label, 2-part, single-arm Objectives: Safety and tolerability, PK, immunogenicity, antitumor activity Safety Endpoints: DLTs, AEs, clinical laboratory values, ECG, LVEF, ECOG PS, dose reductions, ADAs and NAbs	Weight-based dose: • 20 mg/kg IV Q2W • 30 mg/kg IV Q3W • 15 mg/kg IV Q2W (if needed for dose reduction) Flat dose by participant weight: • < 70 kg: 1800 mg IV Q3W • ≥ 70 kg: 2400 mg IV Q3W	NA	21/NA/NA Start: Aug 2021 DCO: 01 Feb 2023
Study ZWI-ZW25-EAP (Phase NA) Enrolling	N Am (4) EU (14)	HER2-positive advanced solid tumors	Design: Open-label, single-arm, compassionate use Objectives: Safety Safety Endpoints: AEs	Monotherapy 20 mg/kg IV Q2W	NA	26/NA/NA Start: Jun 2021 DCO: 01 Feb 2023

Abbreviations: AE = adverse event; BTC = biliary tract cancer; CSR = clinical study report; DCO = data cutoff; DLT = dose-limiting toxicity; EAP = expanded access protocol; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EU = European Union; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; IHC = immunohistochemistry; ISH = in situ hybridization; IV = intravenous; LVEF = left ventricular ejection fraction; M/F = male/female; MTD = maximum tolerated dose; MUGA = multi-gated acquisition; N Am = North America; NA = not available; no = number; OBD = optimal

biologic dose; PK = pharmacokinetic; 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.
b - Ongoing on study at the time of DCO.

2.3.8.1. Patient exposure

Table 64 Patient Exposure

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term safety data
Blinded studies (placebo-controlled)	N/A	N/A	N/A	N/A
Blinded studies (active -controlled)	N/A	N/A	N/A	N/A
Open studies	BTC: 87 All other: 233	BTC: 87 All other: 233	BTC: 87 All other: 233	N/A
Post marketing	N/A	N/A	N/A	N/A
Compassionate use	26	26	26	N/A

Abbreviations: BTC = biliary tract cancer; N/A = not applicable.
* Received at least 1 dose of active treatment

Table 65 Summary of Zanidatamab Exposure in the Safety Populations

	Statistic	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Duration of treatment (months)	Mean (StD)	7.51 (6.934)	6.99 (7.142)
	Median (min, max)	5.06 (0.5, 27.2)	4.70 (0.2, 44.6)
Relative dose intensity [a] (%)	Mean (StD)	97.627 (6.1652)	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).

2.3.8.2. Adverse events

Table 66 Overall Summary of Adverse Events, Frequency of Events

Adverse Events, n (%)	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Treatment-emergent [a]	84 (96.6)	228 (97.9)
Grade 1	11 (12.6)	26 (11.2)
Grade 2	18 (20.7)	86 (36.9)
Grade 3	47 (54.0)	98 (42.1)
Grade 3 or higher	55 (63.2)	116 (49.8)
Grade 4	5 (5.7)	12 (5.2)
Grade 5 (Deaths)	**3 (3.4)**	**6 (2.6)**
Action taken with ZW25	47 (54.0)	106 (45.5)
Dose reduced	3 (3.4)	5 (2.1)
Infusion interrupted	22 (25.3)	65 (27.9)
Dose held/delayed	36 (41.4)	57 (24.5)
Discontinued	2 (2.3)	7 (3.0)
No action taken with ZW25	37 (42.5)	122 (52.4)
Serious TEAE	**45 (51.7)**	**85 (36.5)**
Treatment-emergent AESI/select AEs		
Infusion related reactions	29 (33.3)	71 (30.5)
Potential cardiac events [b]	11 (12.6)	23 (9.9)
Confirmed cardiac events [c]	5 (5.7)	10 (4.3)
Pneumonitis	1 (1.1)	1 (0.4)
Diarrhoea	40 (46.0)	113 (48.5)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BTC = biliary tract cancer; LVEF = left ventricular ejection fraction; Q2W = once every 2 weeks; SMQ = standardised MedDRA query; TEAE = treatment-emergent adverse event; ZW25 = zanidatamab.

[a] Treatment-emergent AE is defined as an AE with onset on or after first dose of study treatment through 30 days after final dose of study treatment inclusive.

[b] Potential cardiac events are defined as Grade ≥ 2 treatment-emergent adverse events meeting the broad cardiac failure SMQ or echocardiogram or multi-gated acquisition scan results for LVEF decrease ≥ 10 percentage points from pretreatment baseline with LVEF < 50%. LVEF decreases are only counted in the event a corresponding AE is not also logged.

[c] Confirmed cardiac events are the subset of potential cardiac events that have been clinically reviewed by the sponsor and determined to be consistent with cardiac events of absolute decrease in LVEF of ≥ 10 percentage points from pretreatment.

Note: The worst toxicity grade per participant is summarized. Participants may have more than 1 action taken (dose reduced, dose interrupted, dose held, drug discontinued) across all their events.

Table 67 Incidence of Treatment Emergent Adverse Events by SOC and Preferred Term for Treatment Emergent, Treatment-Related Events Only with FMQ Groupings (Safety Analysis Set)

System Organ Class Preferred Term	Zanidatamab 20 mg/kg Q2W Monotherapy Dose Regimen ZW25-203 Cohort 1 (N=80)	ZW25-203 Cohorts 1 & 2 (N=87)	ZW25-101 Part 2 BTC and ZW25-203 (N=109)	ZW25-101 Part 1 & 2 all indications and ZW25-203 (N=233)
Any AE	76 (95.0)	81 (93.1)	103 (94.5)	217 (93.1)
Gastrointestinal disorders	59 (73.8)	61 (70.1)	76 (69.7)	160 (68.7)
Diarrhoea	40 (50.0)	40 (46.0)	50 (45.9)	113 (48.5)
Abdominal pain [a]	23 (28.8)	23 (26.4)	28 (25.7)	45 (19.3)
Nausea	14 (17.5)	14 (16.1)	17 (15.6)	45 (19.3)
Vomiting	13 (16.3)	14 (16.1)	18 (16.5)	33 (14.2)
Dyspepsia	5 (6.3)	6 (6.9)	8 (7.3)	17 (7.3)
Constipation	5 (6.3)	5 (5.7)	5 (4.6)	15 (6.4)
Stomatitis	3 (3.8)	3 (3.4)	5 (4.6)	11 (4.7)
Abdominal distension	4 (5.0)	4 (4.6)	6 (5.5)	10 (4.3)
Gastrooesophageal reflux disease	1 (1.3)	1 (1.1)	2 (1.8)	3 (1.3)
Enteritis	2 (2.5)	2 (2.3)	2 (1.8)	2 (0.9)
Haematochezia	2 (2.5)	2 (2.3)	2 (1.8)	2 (0.9)
Hypoaesthesia oral	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Investigations	37 (46.3)	41 (47.1)	52 (47.7)	91 (39.1)
Alanine aminotransferase increased	16 (20.0)	17 (19.5)	21 (19.3)	29 (12.4)
Aspartate aminotransferase increased	16 (20.0)	17 (19.5)	18 (16.5)	27 (11.6)
Weight decreased	11 (13.8)	12 (13.8)	15 (13.8)	25 (10.7)
Blood creatinine increased	6 (7.5)	7 (8.0)	8 (7.3)	19 (8.2)
Blood bilirubin increased	10 (12.5)	10 (11.5)	11 (10.1)	18 (7.7)
Ejection fraction decreased	11 (13.8)	11 (12.6)	12 (11.0)	17 (7.3)
Blood alkaline phosphatase increased	7 (8.8)	9 (10.3)	10 (9.2)	16 (6.9)
Gamma-glutamyltransferase increased	7 (8.8)	8 (9.2)	11 (10.1)	14 (6.0)
Platelet count decreased	3 (3.8)	4 (4.6)	4 (3.7)	6 (2.6)
Neutrophil count decreased	2 (2.5)	2 (2.3)	2 (1.8)	5 (2.1)
Blood lactate dehydrogenase increased	4 (5.0)	4 (4.6)	4 (3.7)	4 (1.7)
Bilirubin conjugated increased	2 (2.5)	2 (2.3)	2 (1.8)	2 (0.9)
Lipase increased	1 (1.3)	1 (1.1)	1 (0.9)	2 (0.9)
Alpha hydroxybutyrate dehydrogenase increased	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)

System Organ Class Preferred Term	Zanidatamab 20 mg/kg Q2W Monotherapy Dose Regimen ZW25-203 Cohort 1 (N=80)	ZW25-203 Cohorts 1 & 2 (N=87)	ZW25-101 Part 2 BTC and ZW25-203 (N=109)	ZW25-101 Part 1 & 2 all indications and ZW25-203 (N=233)
Blood bilirubin unconjugated increased	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Glutathione reductase activity increased	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
General disorders and administration site conditions	25 (31.3)	26 (29.9)	34 (31.2)	78 (33.5)
Fatigue [b]	20 (25.0)	21 (24.1)	26 (23.9)	61 (26.2)
Oedema peripheral	5 (6.3)	5 (5.7)	7 (6.4)	19 (8.2)
Chills	2 (2.5)	2 (2.3)	5 (4.6)	9 (3.9)
Chest discomfort	1 (1.3)	1 (1.1)	1 (0.9)	2 (0.9)
Xerosis	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Metabolism and nutrition disorders	27 (33.8)	28 (32.2)	36 (33.0)	72 (30.9)
Decreased appetite	13 (16.3)	13 (14.9)	16 (14.7)	37 (15.9)
Hypokalaemia	11 (13.8)	11 (12.6)	14 (12.8)	30 (12.9)
Hypoalbuminaemia	6 (7.5)	6 (6.9)	8 (7.3)	15 (6.4)
Hypomagnesaemia	5 (6.3)	5 (5.7)	6 (5.5)	9 (3.9)
Hyponatraemia	3 (3.8)	4 (4.6)	5 (4.6)	9 (3.9)
Hyperkalaemia	1 (1.3)	1 (1.1)	2 (1.8)	3 (1.3)
Skin and subcutaneous tissue disorders	24 (30.0)	24 (27.6)	31 (28.4)	72 (30.9)
Rash [c]	14 (17.5)	14 (16.1)	20 (18.3)	50 (21.5)
Pruritus	11 (13.8)	11 (12.6)	12 (11.0)	22 (9.4)
Dry skin	1 (1.3)	1 (1.1)	1 (0.9)	10 (4.3)
Palmar-plantar erythrodysaesthesia syndrome	2 (2.5)	2 (2.3)	3 (2.8)	5 (2.1)
Erythema	1 (1.3)	1 (1.1)	1 (0.9)	4 (1.7)
Nail discolouration	1 (1.3)	1 (1.1)	2 (1.8)	3 (1.3)
Nail disorder	2 (2.5)	2 (2.3)	2 (1.8)	3 (1.3)
Nail pigmentation	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Pain of skin	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)

System Organ Class Preferred Term	Zanidatamab 20 mg/kg Q2W Monotherapy Dose Regimen ZW25-203 Cohort 1 (N=80)	ZW25-203 Cohorts 1 & 2 (N=87)	ZW25-101 Part 2 BTC and ZW25-203 (N=109)	ZW25-101 Part 1 & 2 all indications and ZW25-203 (N=233)
Injury, poisoning and procedural complications	28 (35.0)	29 (33.3)	36 (33.0)	71 (30.5)
Infusion related reaction	28 (35.0)	29 (33.3)	36 (33.0)	71 (30.5)
Blood and lymphatic system disorders	20 (25.0)	23 (26.4)	29 (26.6)	53 (22.7)
Anaemia	19 (23.8)	22 (25.3)	28 (25.7)	51 (21.9)
Leukopenia	1 (1.3)	1 (1.1)	1 (0.9)	2 (0.9)
Nervous system disorders	15 (18.8)	15 (17.2)	15 (13.8)	41 (17.6)
Headache	3 (3.8)	3 (3.4)	3 (2.8)	21 (9.0)
Dizziness	7 (8.8)	7 (8.0)	7 (6.4)	14 (6.0)
Peripheral sensory neuropathy	6 (7.5)	6 (6.9)	6 (5.5)	8 (3.4)
Paraesthesia	1 (1.3)	1 (1.1)	1 (0.9)	2 (0.9)
Dysaesthesia	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Hypoaesthesia	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Musculoskeletal and connective tissue disorders	9 (11.3)	9 (10.3)	11 (10.1)	32 (13.7)
Arthralgia	3 (3.8)	3 (3.4)	4 (3.7)	13 (5.6)
Muscle spasms	3 (3.8)	3 (3.4)	3 (2.8)	10 (4.3)
Pain in extremity	3 (3.8)	3 (3.4)	4 (3.7)	9 (3.9)
Muscular weakness	1 (1.3)	1 (1.1)	1 (0.9)	5 (2.1)
Limb discomfort	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Cardiac disorders	3 (3.8)	3 (3.4)	4 (3.7)	6 (2.6)
Sinus tachycardia	1 (1.3)	1 (1.1)	2 (1.8)	4 (1.7)
Aortic valve incompetence	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Atrial tachycardia	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Mitral valve incompetence	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Supraventricular extrasystoles	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Tricuspid valve incompetence	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Ventricular extrasystoles	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)

System Organ Class Preferred Term	Zanidatamab 20 mg/kg Q2W Monotherapy Dose Regimen ZW25-203 Cohort 1 (N=80)	ZW25-203 Cohorts 1 & 2 (N=87)	ZW25-101 Part 2 BTC and ZW25-203 (N=109)	ZW25-101 Part 1 & 2 all indications and ZW25-203 (N=233)
Immune system disorders	3 (3.8)	4 (4.6)	4 (3.7)	4 (1.7)
Drug hypersensitivity	3 (3.8)	4 (4.6)	4 (3.7)	4 (1.7)
Renal and urinary disorders	1 (1.3)	1 (1.1)	1 (0.9)	3 (1.3)
Proteinuria	1 (1.3)	1 (1.1)	1 (0.9)	3 (1.3)
Vascular disorders	2 (2.5)	2 (2.3)	2 (1.8)	3 (1.3)
Flushing	2 (2.5)	2 (2.3)	2 (1.8)	3 (1.3)
Hepatobiliary disorders	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Biliary colic	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Infections and infestations	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Oral candidiasis	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Pneumonitis	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)

FMQ = FDA Medical Query.
Events are presented by decreasing frequency of SOC and preferred term within an SOC. Counts presented for Abdominal pain, Fatigue, and Rash contain subjects with any treatment emergent adverse event with a grouped preferred term meeting the FMQ (narrow) criteria (FDA-2022-1961-0001). The preferred terms for the groupings are presented under system organ classes of Gastrointestinal disorders, General disorders and administration site conditions, and Skin and subcutaneous tissue disorders, respectively. Multiple occurrences of an event within a subject are counted only once.
AEs coded using MedDRA version 25.0.
[a] Abdominal pain includes Abdominal pain and Abdominal pain upper.
[b] Fatigue includes Asthenia, Fatigue, and Malaise.
[c] Rash includes Dermatitis acneiform, Rash, Rash maculo-papular, Rash pruritic, and Urticaria.
Program: t-teae-soc-fmq.sas Data cutoffs: ZWI-ZW25-203:11JUL2024; ZWI-ZW25-101:14JAN2022 Date/Time of Run: 17FEB2025:20:11

Table 68 Grade 3 or Higher Treatment-Emergent Adverse Events with Incidence ⩾ 2% in Any Population, by SOC and PT

System Organ Class, n (%) **Preferred Term**	**Study 203** **(N = 87)**	**20 mg/kg Q2W** **(N = 233)**
Any AE	55 (63.2)	116 (49.8)
Gastrointestinal disorders	**19 (21.8)**	**39 (16.7)**

System Organ Class, n (%) Preferred Term	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Diarrhoea	7 (8.0)	12 (5.2)
Obstruction gastric	3 (3.4)	4 (1.7)
Melaena	2 (2.3)	3 (1.3)
Ascites	1 (1.1)	5 (2.1)
Hepatobiliary disorders	**19 (21.8)**	**24 (10.3)**
Jaundice cholestatic	5 (5.7)	5 (2.1)
Biliary obstruction	4 (4.6)	4 (1.7)
Cholangitis	4 (4.6)	6 (2.6)
Infections and infestations	**17 (19.5)**	**28 (12.0)**
Pneumonia	5 (5.7)	10 (4.3)
Sepsis	4 (4.6)	6 (2.6)
Biliary tract infection	2 (2.3)	2 (0.9)
Device related infection	2 (2.3)	2 (0.9)
Urinary tract infection	2 (2.3)	2 (0.9)
Investigations	**17 (19.5)**	**31 (13.3)**
Alanine aminotransferase increased	4 (4.6)	4 (1.7)
Aspartate aminotransferase increased	4 (4.6)	5 (2.1)
Blood alkaline phosphatase increased	4 (4.6)	6 (2.6)
Ejection fraction decreased	3 (3.4)	3 (1.3)
Blood bilirubin increased	2 (2.3)	7 (3.0)
Gamma glutamyltransferase increased	3 (3.4)	6 (2.6)
Blood and lymphatic system disorders	**13 (14.9)**	**27 (11.6)**
Anaemia	11 (12.6)	24 (10.3)
Vascular disorders	**8 (9.2)**	**15 (6.4)**
Hypertension	6 (6.9)	12 (5.2)
Metabolism and nutrition disorders	**7 (8.0)**	**16 (6.9)**
Hypokalaemia	4 (4.6)	5 (2.1)
Decreased appetite	0	3 (1.3)
Respiratory, thoracic and mediastinal disorders	**7 (8.0)**	**11 (4.7)**
Pleural effusion	2 (2.3)	3 (1.3)
General disorders and administration site conditions	**6 (6.9)**	**15 (6.4)**
Asthenia	2 (2.3)	2 (0.9)
Fatigue	1 (1.1)	7 (3.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**3 (3.4)**	**3 (1.3)**
Nervous system disorders	**3 (3.4)**	**6 (2.6)**

System Organ Class, n (%) Preferred Term	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Cardiac disorders	**2 (2.3)**	**5 (2.1)**

Abbreviations: AE = adverse event; BTC = biliary tract cancer; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; Q2W = once every 2 weeks; SOC = system organ class.
Notes: Events are presented by decreasing frequency of SOC and then PT within an SOC based on the Primary Safety Population column.
Multiple occurrences of an event within a participant are counted only once.
AEs coded using MedDRA version 25.0.

2.3.8.3. Adverse drug reactions

Pooled data from studies 101 and 203 (N=233) were used to evaluate the safety profile of zanidatamab and identify adverse drug reactions.

The adverse reaction frequencies are based on all-causality AE frequencies, for which, after thorough comprehensive medical evaluation of all TEAEs, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility as recommended in the SmPC guideline (https://health.ec.europa.eu/document/download/6a043dea-7d0f-4252-947b-cef58f53d37e_en).

Objective criteria were applied to the data for AEs to screen for potential ADRs, which were then subject to clinical review. Any TEAE from the Primary Safety Population was included as an ADR if it was reported in at least 15% of participants and assessed as causally related to zanidatamab treatment by either the investigator or sponsor in at least 1 participant in either the Primary Safety Population (study 203 [Cohort 1], N = 80), Study 203 Safety Population (N = 87), or BTC Indication Population (N = 109). Additional TEAEs with reporting frequency of 15% or higher in the 20 mg/kg Q2W Population (N = 233) and Pooled Monotherapy Safety Population (N = 279) were also reviewed to assess if any TEAEs should be considered as ADRs based on biological plausibility. Treatment-emergent AEs reported in fewer than 15% of participants and with higher grade severity (Grade 4 and 5) were also reviewed to assess if a strong causal relationship with zanidatamab was suggested based on medical assessment of the case. Based on the analysis, the ADRs, as summarised in the ADR table below were identified for zanidatamab.

Table 69 Adverse drug reactions in patients receiving Ziihera as monotherapy reported in the pooled safety population (N=233)

System organ class	Frequency	Adverse reactions	All indications[d] (N=233) Number of patients (%)
Blood and lymphatic system disorders	Very common	Anaemia	51 (21.9)
Metabolism and nutrition disorders	Very common	Decreased appetite	37 (15.9)
Cardiac disorders	Common	Ejection fraction decreased	17 (7.3)
Gastrointestinal disorders	Very common	Diarrhoea	113 (48.5)
		Abdominal pain[a]	45 (19.3)
		Nausea	45 (19.3)
		Vomiting	33 (14.2)
Hepatobiliary disorders	Very common	Alanine aminotransferase increased	29 (12.4)
		Aspartate aminotransferase increased	27 (11.6)
Skin and subcutaneous tissue disorders	Very common	Rash[b]	50 (21.5)
General disorders and administration site conditions	Very common	Fatigue[c]	61 (26.2)
Injury, poisoning and procedural complications	Very common	Infusion related reaction	71 (30.5)
Respiratory, thoracic and mediastinal disorders	Uncommon	Pneumonitis	1 (0.4)

a Abdominal pain includes abdominal pain and abdominal pain upper.
b Rash includes dermatitis acneiform, rash, rash maculo-papular, rash pruritic, and urticaria.
c Fatigue includes asthenia, fatigue, and malaise.
d Source: Table 14.3.3.9.1.1

2.3.8.4. Serious adverse event/deaths/other significant events

AEs of special interest (AESI) and Select Adverse Events

AEs of special interest and selected AEs include infusion-related reaction, diarrhoea, cardiac AEs (left ventricular systolic dysfunction; decreased ejection fraction), and pneumonitis as these have been reported in anti-HER2 antibody class drugs. Infusion-related reactions have been very commonly observed in patients receiving anti-HER2 antibodies and require immediate attention and management. Cardiac AEs are also well recognized with HER2-targeted therapies characterized by left ventricular systolic dysfunction. Anti-HER2 antibodies have previously been associated with pneumonitis.

Table 70 Overall Summary of TEAEs of Special Interest and Select Adverse Events, by Preferred Term (Safety Analysis Set)

AESI/Select AE, n (%) Parameter or Preferred Term	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Infusion related reaction	29 (33.3)	71 (30.5)
Left ventricular dysfunction [a]	11 (12.6)	23 (9.9)
LVEF decrease based on ECHO/MUGA	5 (5.7)	9 (3.9)
Grade ≥ 2 Broad Cardiac Failure SMQ	11 (12.6)	23 (9.9)
Ejection fraction decreased	11 (12.6)	17 (7.3)
Pneumonitis	1 (1.1)	1 (0.4)
Diarrhoea	40 (46.0)	113 (48.5)
Embryo-fetal toxicities[e]	0	0

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BTC = biliary tract cancer; CTCAE = Common Terminology Criteria for Adverse Events; ECHO = echocardiogram; LVEF = left ventricular ejection fraction; MedDRA = Medical Dictionary for Regulatory Activities; MUGA = multi-gated acquisition; Q2W = once every 2 weeks; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

[a] Left ventricular dysfunction are defined as Grade ≥ 2 treatment-emergent adverse events meeting the broad cardiac failure SMQ or ECHO or MUGA scan results for LVEF decrease ≥ 10 percentage points from pretreatment baseline with LVEF < 50%. For the overall row, LVEF decreases are only counted in the event a corresponding AE is not also logged.

Notes: Multiple occurrences of an event within a participant are counted only once. Preferred terms are presented by total decreasing frequency. AEs coded using MedDRA version 25.0.

Diarrhoea

Diarrhoea was reported in 48.5% of patients who received Ziihera. Grade 3 reported event incidence in patients was 5.2%, Grade 4 and Grade 5 events were not observed. Median time to first onset was 10 days and median time to resolution was 3 days. The dose of Ziihera was reduced due to diarrhoea in 1.3% of patients and was held or delayed in 2.6% of patients. There were no discontinuations of treatment due to diarrhoea.

Infusion related reactions

Infusion related reactions (IRRs) were reported in 30.5% of patients who received Ziihera. Grade 3 reported event incidence in patients was 0.4%, Grade 4 and Grade 5 events were not observed. Median time to first onset was 1 day and median time to resolution was 1 day. Ziihera infusion was interrupted in 25.3% of patients and discontinued in 0.4% of patients due to IRRs.

Anaemia

Anaemia was reported in 21.9% of patients who received Ziihera. Grade 3 reported event incidence in patients was 9.9%, Grade 4 was 0.4% and no Grade 5 events were observed. Median time to first onset was 42 days and median time to resolution was 14 days. Ziihera infusion was held or delayed in 0.4% of patients and there were no other actions taken with Ziihera due to anaemia.

ALT increased

ALT increased was reported in 12.4% of patients who received Ziihera. Grade 3 reported event incidence in patients was 1.7%, Grade 4 was 0.4% and no Grade 5 events were observed. Median time to first onset was 78 days and median time to resolution was 16 days. Ziihera infusion was held or delayed in 7 patients (3%) and there were no other actions taken with Ziihera due to ALT increased.

AST increased

AST increased was reported in 11.6% of patients who received Ziihera. Grade 3 reported event incidence in patients was 1.3%, Grade 4 was 0.9% and no Grade 5 events were observed. Median time to first onset was 87 days and median time to resolution was 15 days. Dose of Ziihera was held or delayed in 6 patients (2.6%) and there were no other actions taken with Ziihera due to AST increased.

Left ventricular dysfunction

Decreases in LVEF have been reported with medicinal products that block HER2 activity, including Ziihera. Twelve events of LVEF decreased were observed in 10 patients (4.3%) and one of these events was considered serious. Grade 3 reported event incidence in patients was 1.3%, Grade 4 and Grade 5 events were not observed. Median time to first onset was 171 days and median time to resolution was 27 days. The dose of Ziihera was reduced in 1 patient (0.4%), was held or delayed in 5 patients (2.1%) and was discontinued in 2 patients (0.9%).

Serious adverse events

Table 71 Incidence of Treatment Emergent Serious Adverse Events by Preferred Term for Treatment-Emergent, Treatment-Related Events Only with FMQ Groupings (Safety Analysis Set)

	Zanidatamab 20 mg/kg Q2W Monotherapy Dose Regimen			
Preferred Term	ZW25-203 Cohort 1 (N=80)	ZW25-203 Cohorts 1 & 2 (N=87)	ZW25-101 Part 2 BTC and ZW25-203 (N=109)	ZW25-101 Part 1 & 2 all indications and ZW25-203 (N=233)
Any AE	13 (16.3)	14 (16.1)	16 (14.7)	19 (8.2)
Diarrhoea	2 (2.5)	2 (2.3)	3 (2.8)	4 (1.7)
Fatigue [a]	2 (2.5)	2 (2.3)	3 (2.8)	3 (1.3)
Alanine aminotransferase increased	2 (2.5)	2 (2.3)	2 (1.8)	2 (0.9)
Abdominal pain [b]	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Anaemia	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Aspartate aminotransferase increased	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Bilirubin conjugated increased	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Blood bilirubin increased	0	0	0	1 (0.4)
Decreased appetite	0	0	0	1 (0.4)
Dyspepsia	0	1 (1.1)	1 (0.9)	1 (0.4)
Ejection fraction decreased	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Enteritis	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Gamma-glutamyltransferase increased	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Haematochezia	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Infusion related reaction	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Oral candidiasis	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)
Pneumonitis	1 (1.3)	1 (1.1)	1 (0.9)	1 (0.4)

Deaths

Table 72 Summary of All Deaths in BTC Clinical Studies with Zanidatamab

	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Any, n (%)	57 (65.5)	66 (28.3)
Within 30 days after last dose, n (%)	5 (5.7)	14 (6.0)
Disease progression	3 (3.4)	8 (3.4)
Adverse event	2 (2.3)	5 (2.1)
Other	0	1 (0.4)
More than 30 days after last dose, n (%)	52 (59.8)	52 (22.3)
Disease progression	35 (40.2)	35 (15.0)
Adverse event	1 (1.1)	1 (0.4)
Other[a]	3 (3.4)	3 (1.3)
Unknown[b]	13 (14.9)	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

Table 73 Incidence of Treatment-Emergent Adverse Events Resulting in Death, by Preferred Term (Safety Analysis Set)

MedDRA Preferred Term, n (%)	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Any AE	3 (3.4)	6 (2.6)
Cholangiocarcinoma	1 (1.1)	1 (0.4)
Hepatic failure	1 (1.1)	1 (0.4)
Cardiac arrest	0	1 (0.4)
Multiple organ dysfunction syndrome	1 (1.1)	1 (0.4)
Sudden death	0	2 (0.9)

Abbreviations: AE = adverse event; BTC = biliary tract cancer; MedDRA = Medical Dictionary for Regulatory Activities; Q2W = once every 2 weeks.
AEs coded using MedDRA version 25.0.

2.3.8.5. Laboratory findings

Table 74 Treatment-Emergent Laboratory Abnormalities with Incidence ⩾ 10% in Any Population, Participant Incidence (Safety Analysis Set)

Laboratory Parameter, n (%)	Directionality	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
All tests, any		86 (98.9)	227 (97.4)
Hematology, any		**84 (96.6)**	**208 (89.3)**
Hemoglobin	Low	77 (88.5)	193 (82.8)
Lymphocytes	Low	39 (44.8)	99 (42.5)

Laboratory Parameter, n (%)	Directionality	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Platelets	Low	25 (28.7)	51 (21.9)
Leukocytes	Low	21 (24.1)	52 (22.3)
Neutrophils	Low	19 (21.8)	40 (17.2)
Chemistry, any		**83 (95.4)**	**222 (95.3)**
Lactate dehydrogenase	High	45 (51.7)	45 (19.3)
Albumin	Low	47 (54.0)	119 (51.1)
Aspartate aminotransferase	High	40 (46.0)	98 (42.1)
Alanine aminotransferase	High	39 (44.8)	78 (33.5)
Alkaline phosphatase	High	35 (40.2)	122 (52.4)
Sodium	Low	32 (36.8)	62 (26.6)
Potassium	Low	28 (32.2)	60 (25.8)
Bilirubin	High	21 (24.1)	41 (17.6)
Reported calcium	Low	19 (21.8)	33 (14.2)
Urate	High	19 (21.8)	43 (18.5)
Magnesium	Low	15 (17.2)	15 (6.4)
Creatinine	High	18 (20.7)	38 (16.3)
Magnesium	High	12 (13.8)	12 (5.2)
Reported calcium	High	5 (5.7)	24 (10.3)
Glucose [a]	High	0	96 (41.2)
Gamma glutamyl transferase [a]	High	0	81 (34.8)
Cholesterol [a]	High	0	47 (20.2)
Triglycerides [a]	High	0	40 (17.2)
Phosphate [a]	Low	0	23 (9.9)

Abbreviations: BTC = biliary tract cancer; CTCAE = Common Terminology Criteria for Adverse Events; Q2W = once every 2 weeks.

[a] Not assessed in Study 203.

Notes: Abnormalities are presented by decreasing frequency based on the Primary Safety Population column and then the Pooled Monotherapy Safety Population column. Multiple occurrences of a toxicity within a participant are counted only once, using the highest toxicity grade.

Laboratory test results are graded by the sponsor using CTCAE version 5.0 grading criteria for Study 203 and CTCAE version 4.03 for Study 101.

Table 75 Grade 3 and Higher Treatment-Emergent Laboratory Abnormalities with Incidence ≥ 2% in Any Population, Participant Incidence (Safety Analysis Set)

Laboratory Parameter, n (%)	Directionality	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
All tests, any		41 (47.1)	104 (44.6)
Hematology, any		**18 (20.7)**	**44 (18.9)**
Hemoglobin	Low	12 (13.8)	26 (11.2)
Lymphocytes	Low	6 (6.9)	20 (8.6)
Neutrophils	Low	2 (2.3)	3 (1.3)
Chemistry, any		**32 (36.8)**	**82 (35.2)**
Aspartate aminotransferase	High	8 (9.2)	16 (6.9)
Sodium	Low	11 (12.6)	18 (7.7)
Bilirubin	High	7 (8.0)	10 (4.3)
Alanine aminotransferase	High	6 (6.9)	7 (3.0)
Alkaline phosphatase	High	5 (5.7)	15 (6.4)
Potassium	Low	4 (4.6)	8 (3.4)
Reported calcium	High	3 (3.4)	3 (1.3)
Magnesium	Low	2 (2.3)	2 (0.9)
Gamma glutamyl transferase [a]	High	0	29 (12.4)
Glucose [a]	High	0	8 (3.4)
Albumin	Low	0	6 (2.6)

Abbreviations: BTC = biliary tract cancer; CTCAE = Common Terminology Criteria for Adverse Events; Q2W = once every 2 weeks.
[a] Not assessed in Study 203.
Notes: Abnormalities are presented by decreasing frequency based on the Primary Safety Population column and then the Pooled Monotherapy Safety Population column. Multiple occurrences of a toxicity within a participant are counted only once, using the highest toxicity grade.
Laboratory test results are graded by the sponsor using CTCAE version 5.0 grading criteria for Study 203 and CTCAE version 4.03 for Study 101.

Table 76 Incidence of Hy's Law Biochemistry Criteria (Safety Analysis Set)

Elevation	Cohort 1 (N = 80)	Cohort 2 (N = 7)	Total (N = 87)
ALT ≥ 3 × ULN + total bilirubin ≥ 2 × ULN	5 (6.3)	0	5 (5.7)
AST ≥ 3 × ULN + total bilirubin ≥ 2 × ULN	8 (10.0)	0	8 (9.2)
(AST and/or ALT) ≥ 3 × ULN + total bilirubin ≥ 2 × ULN	8 (10.0)	0	8 (9.2)

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal.
Note: Counts participants with concurrent treatment-emergent elevations (i.e., those reported from the same sample).

In 203 study, eight participants met one or more of the laboratory criteria for potential treatment-emergent Hy's Law cases and 1 additional participant had laboratory tests performed outside the treatment-emergent period that met criteria for potential Hy's law case. Clinical review conducted by the sponsor ruled out drug-induced liver injury in all 9 cases. Five of the participants met the criteria at or within a month of the EOT visit concurrent with TEAEs such as hepatic failure, hepatobiliary disease, and jaundice cholestatic that were associated with progression of their underlying disease. One participant met the criteria concurrent with a TEAE of bile duct stenosis.

Five participants who received zanidatamab at the 20 mg/kg Q2W dose regimen in study 101 met the potential Hy's Law biochemistry criteria, for a total of 13 (5.6%) participants overall in the 20 mg/kg Q2W Population. None of these cases were confirmed as DILI associated with zanidatamab due to involvement of the liver by the primary disease, concomitant medications, or concurrent illnesses.

Electrocardiograms (ECGs)

Table 77 QTcF Interval Changes During the Study Period (Safety Analysis Set)

	Cohort 1 (N=80)	Cohort 2 (N=7)	Total (N=87)
Maximum increase from baseline			
None	27 (33.8)	4 (57.1)	31 (35.6)
>0 to <30 msec	19 (23.8)	0	19 (21.8)
30 to 60 msec	4 (5.0)	0	4 (4.6)
>60 msec	1 (1.3)	0	1 (1.1)
Not evaluable[a]	29 (36.3)	3 (42.9)	32 (36.8)
Maximum value post-baseline			
<450 msec	47 (58.8)	4 (57.1)	51 (58.6)
450-480 msec	2 (2.5)	0	2 (2.3)
>480 msec – 500 msec	2 (2.5)	0	2 (2.3)
>500 msec	0	0	0
Not evaluable[a]	29 (36.3)	3 (42.9)	32 (36.8)

[a] Missing baseline and/or treatment-emergent post-baseline QTcF values.

No participant had post-baseline QTcF > 500 msec. Two participants (2.3%) had a post-baseline QTcF of > 480 but not more than 500 msec.

Five (2.1%) participants from study 101 that received zanidatamab at the 20 mg/kg Q2W dose regimen had 6 events of nonserious Grade 1 or Grade 2 AEs (3 events each) of electrocardiogram QT prolonged. Five of the 6 events resolved without dose modification of zanidatamab. The ongoing event was the second occurrence of prolonged electrocardiogram QT in a participant with ampullary cancer who had prolongation of the QT interval before initiating therapy with zanidatamab; both events were assessed by the investigator to be unrelated to zanidatamab. None of these 5 participants experienced a severe cardiovascular event, such as cardiac arrest or sudden death, concurrently with the prolonged QT interval.

2.3.8.6. Safety in special populations

Table 78 Safety in Special Populations Zanidatamab 20 mg/kg Q2W (n=233)

MedDRA Terms	**Age <65 n=141 number (percentage)**	**Age 65-74 n=78 number (percentage)**	**Age 75-84 n=13 number (percentage)**	**Age 85+ n=1 number (percentage)**
Total AEs	137 (97.2)	77 (98.7)	13 (100)	1 (100)
Serious AEs – Total	45 (31.9)	30 (38.5)	4 (30.8)	0
- Fatal	5 (3.5)	2 (2.6)	0	0
- Hospitalization/prolong existing hospitalization	44 (31.2)	28 (35.9)	4 (30.8)	0
- Life-threatening	4 (2.8)	2 (2.6)	1 (7.7)	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	2 (1.4)	3 (3.8)	0	0
AE leading to drop-out	4 (2.8)	3 (3.8)	0	0
Psychiatric disorders	18 (12.8)	8 (10.3)	2 (15.4)	0
Nervous system disorders	36 (25.5)	21 (26.9)	2 (15.4)	0
Accidents and injuries	43 (30.5)	31 (39.7)	8 (61.5)	0
Cardiac disorders	13 (9.2)	5 (6.4)	0	0
Vascular disorders	21 (14.9)	14 (17.9)	2 (15.4)	0
Cerebrovascular disorders	0	0	0	0
Infections and infestations	51 (36.2)	33 (42.3)	7 (53.8)	0
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	6 (4.3)	12 (15.4)	3 (23.1)	0

Abbreviations: AE = adverse event; MedDRA= medical dictionary for regulatory activities; n = number

2.3.8.7. Safety related to drug-drug interactions and other interactions

No dedicated clinical studies evaluating the drug interaction potential of zanidatamab have been conducted. Zanidatamab is an antibody that is not expected to impact the cytochrome P450 enzymes. In addition, zanidatamab is not known to target mechanisms related to proinflammatory cytokines or any mechanism related to proinflammatory cytokines that may impact the PK of concomitant medicines.

2.3.8.8. Discontinuation due to adverse events

Discontinuation due to adverse events

Table 79 Treatment-Emergent Adverse Events that Led to Discontinuation of Zanidatamab, by SOC and PT (Safety Analysis Set)

System Organ Class, n (%) Preferred Term	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Any AE	2 (2.3)	7 (3.0)
Investigations	1 (1.1)	3 (1.3)
Ejection fraction decreased	1 (1.1)	2 (0.9)
Weight decreased	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (1.1)	2 (0.9)
Pneumonitis	1 (1.1)	1 (0.4)
Pulmonary embolism	0	1 (0.4)
General disorders and administration site conditions	0	1 (0.4)
Sudden death	0	1 (0.4)
Injury, poisoning and procedural complications	0	1 (0.4)
Infusion related reaction	0	1 (0.4)
Nervous system disorders	0	0
Brain oedema	0	0

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

Dose modification

Table 80 Incidence of Treatment Emergent Adverse Events That Led to Dose Modification of Zanidatamab With Incidence ⩾ 2% in Any Population, by SOC and PT (Safety Analysis Set)

System Organ Class, n (%) Preferred Term	Study 203 (N = 87)	20 mg/kg Q2W (N = 233)
Any AE	46 (52.9)	104 (44.6)
Injury, poisoning and procedural complications	23 (26.4)	60 (25.8)
Infusion related reaction	22 (25.3)	59 (25.3)
Infections and infestations	12 (13.8)	19 (8.2)
Pneumonia	3 (3.4)	4 (1.7)
Hepatobiliary disorders	1 (12.6)	13 (5.6)
Cholangitis	3 (3.4)	4 (1.7)
Jaundice cholestatic	3 (3.4)	3 (1.3)
Biliary obstruction	2 (2.3)	2 (0.9)
Gastrointestinal disorders	9 (10.3)	18 (7.7)
Diarrhoea	5 (5.7)	8 (3.4)
Abdominal distension	2 (2.3)	2 (0.9)
Investigations	10(11.5)	17 (7.3)
Alanine aminotransferase increased	4 (4.6)	6 (2.6)
Aspartate aminotransferase increased	4 (4.6)	5 (2.1)
Ejection fraction decreased	4 (4.6)	7 (3.0)
Blood creatinine increased	2 (2.3)	2 (0.9)
General disorders and administration site conditions	5 (5.7)	10 (4.3)
Fatigue	2 (2.3)	6 (2.6)
Metabolism and nutrition disorders	4 (4.6)	5 (2.1)
Hypokalaemia	2 (2.3)	2 (0.9)
Respiratory, thoracic and mediastinal disorders	4 (4.6)	8 (3.4)
Musculoskeletal and connective tissue disorders	2 (2.3)	3 (1.3)
Nervous system disorders	2 (2.3)	3 (1.3)

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

2.3.8.9. Post marketing experience

Not applicable.

2.3.9. Discussion on clinical safety

Safety datasets and exposure

The two safety sets, *study 203 safety population* (n = 87) and the *20 mg/kg Q2W Population* (n = 233) are presented for the assessment of safety for zanidatamab monotherapy. The median duration of treatment in both datasets was comparable (5.1 and 4.7 months, respectively).

The safety datasets are considered of limited size and follow-up. However, they do allow for a preliminary characterization of the safety profile of this novel monotherapy in the context of a conditional MA.

There are currently no available zanidatamab clinical trial data with a comparator, which is considered a major limitation with regards to isolating toxicity and harms caused by zanidatamab's exposure. Moreover, the overall safety dataset is considered small and should therefore be interpreted with caution as rare adverse events may not be observed in such a small sample, leading to an underestimation of true risks and harms.

However, there are a number of approved anti-HER2 products in other indications (mostly HER2+ breast and/or gastric cancer), and their safety profile, particularly regarding LVEF decrease, pneumonitis and/or diarrhoea, is already well known.

Adverse events

In the '20 mg/kg Q2W Population', most participants (97.9%) experienced at least 1 AE, and 172 (73.8%) participants experienced AEs considered by the investigator to be related to zanidatamab treatment. As expected in this clinical setting, nearly all patients experienced AEs.

The most common AEs by PT (≥ 20% of participants) were diarrhoea (48.5%), IRR (30.5%), anaemia (21.9%), rash (21.5%) and fatigue (21.0%). The SOC with the highest incidence of participants with AEs was the Gastrointestinal Disorders SOC (74.7%), followed by Investigations (42.5%); General Disorders and Administration Site Conditions (42.1%); Infections and Infestations and Metabolism and Nutrition Disorders (each in 36.9%); Injury, Poisoning and Procedural Complications (35.2%); and Skin and Subcutaneous Tissue Disorders (32.2%). Some of the common symptoms reported as AEs are expected and likely attributable to the underlying disease e.g. abdominal pain, ALT & AST increased, pruritus, blood bilirubin and alkaline phosphatase increased, and to some degree diarrhoea and pruritus. Anaemia is also a common finding in chronically ill patients with metastatic cancer disease treated in the advanced setting, particularly in this case, when all patients have been previously exposed to one or more systemic chemotherapy regimens.

Grade 3 or higher AEs were reported in 116 out of 233 (49.8%) participants. Anaemia (10.3%) was the only Grade 3 or higher AE by PT reported in ≥ 10% of participants; all events of anaemia were Grade 3, except for 1 participant with a Grade 4 event. Other Grade 3 or higher AEs (≥ 5% of participants) included diarrhoea and hypertension (each in 5.2%). Twelve (5.2%) participants experienced 18 Grade 4 events that included AST increased and sepsis (each in 2 participants); and anaemia, ALT increased, biliary obstruction, hypokalaemia, pneumonia, cholangitis, GGT increased, atrial fibrillation, cerebrovascular accident, pleural effusion, upper gastrointestinal haemorrhage, hyperuricemia, intestinal perforation, and *pneumocystis jirovecii* pneumonia (each in 1 participant). Grade 5 AEs were reported in 6 (2.6%) participants.

ADRs

Pooled data from studies 101 and 203 (N=233) were used to evaluate the safety profile of zanidatamab and to select the ADRs for section 4.8 of the SmPC. The ADR frequencies were based on all-causality AE frequencies, as recommended in the Guideline on summary of product characteristic. Objective criteria were applied to the data for AEs to screen for potential ADRs, which were then subject to clinical review. Based on the analysis, the ADRs, as summarised in the ADR table, were identified for zanidatamab.

Adverse events of special interest

Adverse events of special interest and selected adverse events include the following: infusion-related reactions, pneumonitis, left ventricular dysfunction.

Infusion-related reactions

As per recommendations in sections 4.2 and 4.4 of the SmPC, premedication (recommended to include a corticosteroid, antihistamine, and antipyretic) to reduce the risk of IRRs should be administered 30 to 60 minutes prior to each dose of zanidatamab. Patients should be monitored for signs and symptoms of IRRs during administration and as clinically indicated after completion of infusion. Appropriate emergency medicine and equipment to treat IRRs should be available for immediate use. Management of infusion related reaction (IRRs) may require reduced infusion rate, dose interruption, or treatment discontinuation of zanidatamab.

Pneumonitis

As per recommendations in sections 4.2 and 4.4 of the SmPC, patients should be monitored for signs and symptoms of pneumonitis. In the event of confirmed Grade ≥2 pneumonitis, treatment should be permanently discontinued.

Left ventricular dysfunction

As per recommendations in sections 4.2 and 4.4. of the SmPC, decreases in LVEF have been reported with medicinal products that block HER2 activity, including zanidatamab. LVEF should be assessed prior to initiation of zanidatamab by echocardiogram or multigated acquisition (MUGA) scan and at regular intervals during treatment to ensure that LVEF is within normal limits. If the LVEF declines and has not improved, or has declined further at the subsequent assessment, zanidatamab should be discontinued. Zanidatamab has not been studied in patients with a pre-treatment LVEF value of < 50%; history of myocardial infarction or unstable angina within 6 months; troponin levels consistent with myocardial infarction, or clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic congestive heart failure (CHF).

SAEs

Serious adverse events were reported in 78 of 233 participants (33.5%) in the 20 mg/kg Q2W Population. The most frequently reported SAEs (≥ 2% of participants) were pneumonia (4.7%), sepsis and cholangitis (each in 2.6%), and jaundice cholestatic (2.1%). Ten (4.3%) participants had zanidatamab-related SAEs, as assessed by the investigator. In addition to the 8 participants from study 203, 2 participants from study 101 had SAEs of diarrhoea (in a participant with GEA) and fatigue (in a participant with BTC) that were assessed by the investigator to be related to zanidatamab treatment.

The SOC with the highest incidence of participants with SAEs was the Infections and Infestations SOC (12.4%), followed by Gastrointestinal Disorders (10.7%) and Hepatobiliary Disorders (10.3%).

Regarding SAEs related to infections, in the study 203 (N=87) safety data set, there was 1 (1.1%) SAE of pneumocystis jirovecii pneumonia and 1 (1.1%) SAE of liver abscess and 1 (1.1%) SAE event of pseudomembranous colitis.

It is likely that many of the hepatobiliary SAEs can be adjudicated due to the underlying cancer disease that increases the risk of obstructive hepatobiliary disease and cholangitis.

Deaths

Six (2.6%) participants in the 20 mg/kg Q2W Population had AEs leading to death. In addition to the 3 participants from study 203, 2 participants (1 with breast cancer, and 1 with hepatocellular carcinoma) from study 101 had AEs of sudden death, and another participant (with BTC) from study 101 had an AE of cardiac arrest. None of these 3 additional events was assessed by the investigator to be related to zanidatamab treatment.

Laboratory findings

Anaemia

Anaemia was reported in 21.9% of patients who received zanidatamab. Grade 3 reported event incidence in patients was 9.9%, Grade 4 was 0.4% and no Grade 5 events were observed. Median time to first onset was 42 days and median time to resolution was 14 days. Zanidatamab infusion was held or delayed in 0.4% of patients and there were no other actions taken with Ziihera due to anaemia.

ALT increased

ALT increased was reported in 12.4% of patients who received zanidatamab Grade 3 reported event incidence in patients was 1.7%, Grade 4 was 0.4% and no Grade 5 events were observed. Median time to first onset was 78 days and median time to resolution was 16 days. Zanidatamab infusion was held or delayed in 7 patients (3%) and there were no other actions taken with zanidatamab due to ALT increased.

AST increased

AST increased was reported in 11.6% of patients who received zanidatamab. Grade 3 reported event incidence in patients was 1.3%, Grade 4 was 0.9% and no Grade 5 events were observed. Median time to first onset was 87 days and median time to resolution was 15 days. The dose of zanidatamab was held or delayed in 6 patients (2.6%) and there were no other actions taken with zanidatamab due to AST increased.

Safety in special populations

There was no evidence of age, sex, race or baseline hepatic impairment affecting the safety profile of zanidatamab.

Based on the mechanism of action, zanidatamab may cause foetal harm when administered to a pregnant woman. In post-marketing reports of other HER2-directed antibodies, use during pregnancy resulted in cases of oligohydramnios manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Patients should be advised to avoid becoming pregnant while receiving zanidatamab. A pregnancy test should be performed before initiating treatment with zanidatamab to exclude pregnancy.

Female patients of childbearing potential should use an effective method of contraception while receiving zanidatamab and for 4 months following the last dose.

Women who received zanidatamab during pregnancy or within 4 months prior to conception should be monitored for oligohydramnios. If oligohydramnios occurs, foetal testing that is appropriate for gestational age and consistent with local standard of care should be performed.

It is not known whether zanidatamab is excreted in human milk, or what effect it has on a breast-fed child or milk production.

A decision should be made whether to discontinue breast-feeding or to discontinue treatment, taking into account the benefit of breast-feeding for the child and the benefit of zanidatamab therapy for the woman. This consideration should also take into account the washout period of 4 months.

Relevant statements have been included in sections 4.4 and 4.6 of the SmPC. Embryo-foetal Toxicity is an important potential risk in the RMP.

AEs leading to treatment discontinuation, dose reduction

Seven (3.0%) participants in the 20 mg/kg Q2W Population had AEs leading to zanidatamab discontinuation. Ejection fraction decreased was the only AE leading to zanidatamab discontinuation reported in 2 (0.9%) participants; all other events were reported in 1 (0.4%) participant each. Of these 7 participants, 4 (1.7%) had zanidatamab-related AEs, as assessed by the investigator, leading to discontinuation.

Among the 233 participants, 104 (44.6%) had AEs leading to dose modification and 71 (30.5%) participants had events considered related to zanidatamab treatment. Five (2.1%) participants experienced AEs that led to zanidatamab dose reduction. Additional AEs leading to dose reduction were Grade 3 diarrhoea (in a participant with breast cancer) and Grade 2 ejection fraction decreased (in a participant with GEA). All of these events were considered by the investigator to be related to zanidatamab treatment.

Additional safety data needed in the context of a conditional MA

Additional safety data including comparative data will be provided as part of the specific obligation in order to fulfil a CMA. Study JZP598-302 will allow a better characterisation of the long-term safety and a contextualisation of the safety data compared to the control arm.

2.3.10. Conclusions on the clinical safety

Zanidatamab exhibits an AE profile comparable with other anti-HER2 antibodies consistent with high frequencies of diarrhoea and IRR and also more concerning AEs like left ventricular dysfunction and pneumonitis. The safety data sets are considered of limited size and with limited follow-up; however, they do allow for a preliminary characterization of the safety profile of this novel monotherapy in the context of a conditional MA.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

In order to confirm the efficacy and safety of zanidatamab in the treatment of adults with unresectable locally advanced or metastatic HER2-positive biliary tract cancer previously treated with at least one prior line of systemic therapy, the MAH should submit the results of the ongoing open-label phase III randomised clinical study JZP598-302 to evaluate the efficacy and safety of zanidatamab plus standard-of-care therapy versus standard-of-care therapy alone for advanced HER2-positive biliary tract cancer.

2.4. Risk Management Plan

2.4.1. Safety concerns

Table 81 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryo-foetal Toxicity
Missing information	None

2.4.2. Pharmacovigilance plan

No additional pharmacovigilance activities are planned.

2.4.3. Risk minimisation measures

Table 82 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Embryo-foetal Toxicity	Routine risk minimisation measures: SmPC Section 4.4 where advice is given on Embryo-Foetal Toxicity, Contraception and Pregnancy. SmPC Section 4.6 where advice is given on Fertility, pregnancy, and lactation.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None proposed.

2.4.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.5. Pharmacovigilance

2.5.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.5.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 20.11.2024. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.6. Product information

2.6.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.6.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ziihera (zanidatamab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and as it is approved under a conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

The agreed indication reflecting the data evaluated is:

"Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy (for biomarker-based patient selection, see section 4.2)."

3.1.2. Available therapies and unmet medical need

There are no standard of care (SoC) treatments in the EU for the targeted population of patients with HER2-positive BTC previously treated with gemcitabine-containing chemotherapy i.e. second-line or beyond (2L+) setting. The current preferred approach in the first-line treatment setting is a combination chemotherapy with cisplatin and gemcitabine with or without an immune checkpoint inhibitor, either durvalumab or pembrolizumab (Kelley et al. 2023; NCCN, 2023; Vogel et al. 2023). Despite the addition of immune checkpoint inhibitors to the standard of care, expected survival is still poor for patients with advanced BTC, with only approximately one-quarter of patients alive at 2 years from the start of therapy (Oh et al. 2022).

There are no approved agents for HER2-amplified or HER2-expressing BTC; however, the 2023 NCCN guidelines and ESMO guidelines include the combination of trastuzumab and pertuzumab as a potential option for pre-treated HER2-positive advanced BTC (NCCN, 2023; Vogel et al. 2023) but none of these products are currently approved in the EU for such indication. The recently released 2025 ESMO guideline

include trastuzumab deruxtecan based on its FDA approval and zanidatamab based on its FDA accelerated approval (Vogel et al. 2025).

3.1.3. Main clinical studies

Pivotal evidence to support a conditional marketing authorisation for zanidatamab comes from study 203, which is an open-label, single-arm study of zanidatamab monotherapy for patients with advanced or metastatic HER2-positive BTC, who had previously received gemcitabine-containing chemotherapy. With the current DCO of 28 July 2023, the median duration of study follow-up is 34 months. A total of 87 patients were included in the pivotal study; however, only a subset of the 80 patients from Cohort 1 are relevant for the efficacy assessment of zanidatamab, since cohort 2 included patients with HER2 expression of IHC 0 or 1+ and ISH+ (n=7); and the final indication only pertains to patients with tumours that expressed IHC 3+ (n=62). Included patients should have histologically or cytologically confirmed BTC, including intrahepatic (ICC) and extrahepatic (ECC) localization, or gallbladder cancer (GBC), and the disease should be locally advanced or metastatic and not eligible for curative resection, transplantation, or ablative therapies.

The primary endpoint was confirmed ORR per RECIST v1.1 and evaluated by independent blinded review (ICR), while duration of response (DoR) was a secondary endpoint.

3.2. Favourable effects

At the DCO of 28 July 2023 for the relevant population of HER2 IHC3+ (n=62) after a median duration of study follow-up of 34 months:

- Confirmed ORR by ICR was 51.6% (95%CI: 38.6; 64.5)
- Median DoR by ICR was 14.92 months (95%CI: 7.39; 24.0).

3.3. Uncertainties and limitations about favourable effects

- The small sample size in the restricted indication IHC3+ (N=62)
- The single-arm design of the pivotal study 203.

The applicant will provide comprehensive efficacy and safety data from the confirmatory study JZP598-302 within a reasonable timeframe as a Special Obligation for the applied CMA for Zanidatamab.

3.4. Unfavourable effects

In the '20 mg/kg Q2W Population', most participants (97.9%) experienced at least 1 AE, and 73.8% participants experienced AEs considered by the investigator to be related to zanidatamab treatment.

The most common AEs by PT (≥ 20% of participants) were diarrhoea (48.5%), IRR (30.5%), anaemia (21.9%), rash (21.5%) and fatigue (21.0%).

Grade 3 or higher AEs were reported in 49.8% of participants: anaemia (10.3%), diarrhoea and hypertension (each with 5.2%).

AESIs are infusion-related reactions, pneumonitis, left ventricular dysfunction and diarrhoea.

SAEs were reported in 33.5% fo participants in the 20 mg/kg Q2W Population. The most frequently reported SAEs (≥ 2% of participants) were pneumonia (4.7%), sepsis and cholangitis (each in 2.6%), and jaundice cholestatic (2.1%). Ten (4.3%) participants had zanidatamab-related SAEs, as assessed by the investigator.

AEs leading to death: Grade 5 AEs were reported in 6 (2.6%) participants.

3.0% of participants in the 20 mg/kg Q2W Population had AEs leading to zanidatamab discontinuation. 1.7% had zanidatamab-related AEs, as assessed by the investigator, leading to discontinuation. 44.6% had AEs leading to dose modification and 30.5% of participants had events considered related to zanidatamab treatment. 2.1% experienced AEs that led to zanidatamab dose reduction.

3.5. Uncertainties and limitations about unfavourable effects

There are currently no available zanidatamab clinical trial data with a comparator, which is considered a major limitation with regards to isolating toxicity and harms caused by zanidatamab's exposure. Moreover, the overall safety dataset is considered small and should therefore be interpreted with caution as rare adverse events may not be observed in such a small sample, leading to an underestimation of true risks and harms. However, the available safety data sets do allow for a preliminary characterization of the safety profile of this novel monotherapy in the context of a conditional MA. Additional safety data including comparative data will be provided as part of the specific obligation in order to fulfil a CMA. Study JZP598-302 will allow a better characterisation of the long-term safety and a contextualisation of the safety data compared to the control arm.

3.6. Effects table

Table 83 Effects Table for Ziihera for advanced HER2 positive (IHC3+) BTC (data cut-off: 28 July 2023)

Effect	Short Description	Unit	Treatment Zanidatamab	Uncertainties/ Strength of evidence	References
Favourable Effects (Subset of Cohort 1, HER2 IHC 3+ N=62)					
cORR	Overall response rate	% (95%CI)	51.6% (38.6; 64.5)	Strengths: Mature data, By ICR Uncertainties: Open-label, non-comparative data	
DoR	Duration of response	Months (95%CI)	14.92 (7.39; 24.0)		
Unfavourable Effects (n=233, 20 mg/kg Q2W all indications pool)					
Grade ≥ 3		%	49.8		SCS
SAEs		%	36.5		
AEs leading to discontinuation		%	3.0		
AEs leading to death		%	2.6		
Diarrhoea		%	48.5		
Infusion related reaction		%	30.5		
Left ventricular dysfunction		%	9.9		

Abbreviations: ICR: Independent central review, ORR: Overall response rate, DoR: Duration of response, OS: Overall survival, AE: Adverse events, SAE; Serious adverse event
Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

It is acceptable that the efficacy of zanidatamab has been evaluated in a single arm study, which included 80 pre-treated patients with advanced HER2-positive biliary tract cancer (BTC) as the applicant is seeking a conditional marketing authorisation. In a subset of this cohort with HER2 IHC3+ (N=62), a clinically relevant confirmed ORR of 51.6% was shown and the responses were durable (~15 months). The observed OS after 34 months of follow-up was 18.1 months in the IHC 3+ subgroup, which is considered reassuring in this advanced setting after at least one prior treatment, although OS results in the absence of a control arm are difficult to interpret.

Relevant subgroup analyses show that in the biomarker-selected study population, using the HER2 expression status (IHC 2+ or 3 +), the efficacy was mainly driven by the patients harbouring tumours with high HER2 expression (3+), which led to the restriction of the indication to patients with IHC 3+ HER2 expression.

Confirmed ORR however only reflects the activity of zanidatamab and time to event endpoints (PFS and OS) cannot be interpreted in the context of a single arm trial. The confirmatory phase III study JZP598-302 will address the uncertainties concerning the impact of zanidatamab on time to event endpoints (with PFS as primary endpoint and OS as secondary endpoint). Since there is no SoC for the targeted HER2 positive BTC population in the 2L+ setting, it is considered acceptable to conduct the confirmatory study in the first-line setting and through a different study design, where zanidatamab is used as an add-on to SoC in 1L in comparison to SOC alone.

Zanidatamab exhibits a safety profile comparable with other anti-HER2 antibodies, so frequent adverse events are diarrhoea and infusion-related reactions (IRR), but also concerning AEs such as left ventricular dysfunction and pneumonitis. The currently available safety sets are considered small and with limited follow-up; however, they do allow for a preliminary characterization of the safety profile of this novel monotherapy in the context of a conditional MA.

Additional safety data including comparative data will be provided as part of the specific obligation in order to fulfil a CMA. Study JZP598-302 will allow a better characterisation of the long-term safety and a contextualisation of the safety data compared to the control arm. Overall, the uncertainties and limitations of the single arm, uncontrolled pivotal study are acceptable as there exists no standard of care for the targeted 2L+ setting of HER2-positive BTC.

3.7.2. Balance of benefits and risks

The reported clinically meaningful overall responses, which are durable, together with an acceptable safety profile in this setting support a positive B/R and conditional approval of zanidatamab in the 2L+ setting of HER2-positive (IHC3+) BTC.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product zanidatamab are not available, as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease. In addition, the product is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

The efficacy of zanidatamab in 2L+ HER2+ IHC3+ BTC has been established on the basis of durable confirmed ORR in a single-arm trial. Although the durable response is considered a clinically meaningful benefit, there is a need to further characterise the efficacy of zanidatamab in a comparative trial.

The applicant will submit the results of study JZP598-302 (study 302), an ongoing phase III, open-label, randomized study evaluating the efficacy and safety of the combination of zanidatamab plus cisplatin-gemcitabine (for up to 8 cycles) with or without PD-1/L1 inhibitor (physician's choice of either durvalumab or pembrolizumab, where approved under local regulations) as compared with cisplatin-gemcitabine with or without PD-1/L1 inhibitor as first-line treatment for participants with HER2-positive locally advanced (unresectable) or metastatic BTC and plans to enrol approximately 286 patients, who will be randomised 1:1 to zanidatamab plus standard of care versus standard of care alone. Of the approximately 286 randomized participants, 214 (approximately 75%) are expected to be in the IHC 3+ subgroup (approximately 107 per treatment arm). The primary endpoint for study 302 is PFS per RECIST 1.1 in the IHC 3+ subgroup, while the key secondary endpoints are OS in the IHC3+ subgroup, PFS per RECIST 1.1 in the overall population, and OS in the overall population. The use of PFS by RECIST 1.1 assessed by an investigator is questionable in view of the open-label design. The applicant is advised to utilize PFS assessment by the BIRC for all patients to ensure an unbiased estimate. As of 17 March 2025, 151 out of the total of 184 sites planned have been activated, a total of 296 potential participants have completed pre-screening and 49 potential participants have completed screening. There are 81 potential participants in pre-screening and 8 participants in screening. As of 17 March 2025, 23 participants have been randomized. Enrolment of this study is projected to be completed by mid-2027. The current status of ongoing study JZP598-302 is considered re-assuring. The final results of study JZP598-302 are due to be provided by September 2029 which is considered within an acceptable timeframe.

According to the design of the confirmatory study, the efficacy will be confirmed in the IHC 3+ subgroup, which is also the population of the revised indication. It is however considered to be acceptable that the confirmatory study 302 will be stratified according to tumour HER2 status (IHC 3+ vs. IHC 2+/ISH+). It is acknowledged that patients with HER2 IHC 2+ tumours are included in the confirmatory study 302 and this is considered acceptable, as is can be agreed that some patients with IHC 2+ ISH-amplified tumours may benefit from adding zanidatamab on top of SoC, but the currently available data does not support treatment with zanidatamab as monotherapy for these patients. Since there are no SoC for the targeted HER2 positive BTC population in the 2L+ setting, it is considered acceptable to conduct the confirmatory study in the first-line setting, where an appropriate comparator is used.

Based on the above, the CHMP considered that study JZP598-302 is likely to provide comprehensive data suitable to confirm the positive benefit-risk balance of Ziihera.

The currently proposed study is (also) a post-marketing requirement by the FDA.

- Unmet medical needs will be addressed.

Ziihera fulfils an unmet medical need, as unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy is a condition where no treatments are approved in the EU and there is currently no standard of care for 2L+ BTC. Historically, chemotherapies have shown modest clinical benefit in the second-line or later setting and are associated with significant toxicity burden for these patients. 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 et al. 2018). The 2023 NCCN and ESMO guidelines include the combination of trastuzumab and pertuzumab as an option for pretreated HER2-positive advanced BTC (NCCN, 2023; Vogel et al. 2023), but none of these products are currently approved in the EU for such indication. The recently released 2025 ESMO guideline include trastuzumab deruxtecan based on its FDA approval and zanidatamab based on its FDA accelerated approval (Vogel et al. 2025).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

In view of the fact that no treatments are approved in the EU in this orphan indication, the immediate availability of Ziihera on the market outweighs the risk inherent in the fact that additional data are still required.

3.8. Conclusions

The overall benefit/risk balance of Ziihera is positive, subject to the conditions stated in section ‘Recommendations.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ziihera is not similar to Tibsovo and Pemazyre within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ziihera is favourable in the following indication:

“Ziihera as monotherapy is indicated for the treatment of adults with unresectable locally advanced or metastatic HER2-positive (IHC3+) biliary tract cancer (BTC) previously treated with at least one prior line of systemic therapy (for biomarker-based patient selection, see section 4.2).”

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to confirm the efficacy and safety of zanidatamab in the treatment of adults with unresectable locally advanced or metastatic HER2-positive biliary tract cancer previously treated with at least one prior line of systemic therapy, the MAH should submit the results of the ongoing open-label phase III randomised clinical study JZP598-302 to evaluate the efficacy and safety of zanidatamab plus standard-of-care therapy versus standard-of-care therapy alone for advanced HER2-positive biliary tract cancer.	30 September 2029

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that zanidatamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).