Protocol Number:	ZWI-ZW25-203
Version:	Amendment 3; 08 September 2023
Protocol Title:	A Phase 2b, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers
Study Short Name:	HERIZON-BTC-01
Investigational Drug:	zanidatamab (ZW25, JZP598)
Phase:	2b
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Sponsor (Rest of World):	Jazz Pharmaceuticals Ireland, Limited Waterloo Exchange, Waterloo Road Dublin 4, Ireland
US Sponsor Representative:	Jazz Pharmaceuticals, Inc 3170 Porter Drive Palo Alto, CA 94304
Sponsor (China and South Korea):	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA BeiGene (Beijing) Co., Ltd, Room 101, 201, 402, 502, Building 1, No. 30 Science Park Road, Changping District, 102206, Beijing, China
Medical Monitor (Rest of World):	[redacted] MD, PhD Jazz Pharmaceuticals, Inc Sr. Medical Director Contact information appears in the trial site binder (or equivalent)
Medical Monitor (China and South Korea):	[redacted] MD BeiGene, Ltd Senior Physician Clinical Development Tel: [redacted]

PROTOCOL SYNOPSIS

Protocol Number ZWI-ZW25-203 **Version** Amendment 3; 08 September 2023 **Phase** 2b	**Product Name** zanidatamab (ZW25, JZP598) **Sponsor** Jazz Pharmaceuticals Ireland, Limited Waterloo Exchange, Waterloo Road Dublin 4, Ireland **US Sponsor Representative:** Jazz Pharmaceuticals, Inc 3170 Porter Drive Palo Alto, CA 94304

Protocol Title

A Phase 2b, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers

Study Objectives and Endpoints	
Objectives	**Endpoints**
Primary: • To evaluate the anti-tumor activity of zanidatamab monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers (BTC)	• Confirmed objective response rate (ORR) by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), assessed by independent central review (ICR)
Secondary: • To further evaluate the anti-tumor activity of zanidatamab monotherapy in subjects with advanced or metastatic HER2-amplified BTC	• Duration of response (DOR) by RECIST 1.1 assessed by ICR • Proportion of subjects with a DOR ≥ 16 weeks by RECIST 1.1 assessed by ICR • Disease control rate (DCR) by RECIST 1.1 assessed by ICR • Progression-free survival (PFS) by RECIST 1.1 assessed by ICR • ORR by RECIST 1.1 assessed by investigator • DOR by RECIST 1.1 assessed by investigator • Proportion of subjects with a DOR ≥ 16 weeks by RECIST 1.1 assessed by investigator • DCR by RECIST 1.1 assessed by investigator • PFS by RECIST 1.1 assessed by investigator • Overall survival (OS)

Study Objectives and Endpoints	
Objectives	**Endpoints**
Secondary (Cont.):	
• To evaluate the safety and tolerability of zanidatamab monotherapy in subjects with advanced or metastatic HER2-amplified BTC	• Frequency and severity of adverse events (AEs) • Frequency of serious adverse events (SAEs) and deaths • Frequency and severity of clinical laboratory abnormalities • Frequency of dose modifications of zanidatamab
• To evaluate the pharmacokinetics (PK) of zanidatamab	• Serum concentrations of zanidatamab as a function of time post-dosing • PK parameters for single (first) dose and multiple doses
• To evaluate the immunogenicity of zanidatamab	• Frequency, duration, and time of onset of anti-drug antibodies (ADA) and neutralizing antibodies, if applicable
[redacted]	

Study Design

This pivotal, multicenter, open-label, single-arm trial will evaluate the anti-tumor activity of zanidatamab monotherapy in subjects with HER2-amplified, inoperable and advanced or metastatic BTC, including intra-hepatic cholangiocarcinoma (ICC), extra-hepatic cholangiocarcinoma (ECC), and gallbladder cancer (GBC). Subjects must have received at least 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, and have experienced disease progression after or developed intolerance to the most recent prior therapy.

New or archival tumor tissue is required from all subjects for HER2 amplification and HER2 protein expression testing at a central lab using in situ hybridization (ISH) and immunohistochemistry (IHC) assays. Subjects may be tested for HER2 status at the central lab any time after diagnosis of advanced or metastatic disease and before study enrollment. Subjects who elect to be pre-screened for HER2 status must sign a separate informed consent for collection, storage, and analysis of the tumor tissue. Once a prospective subject experiences disease

progression or develops intolerance to his/her most recent prior therapy, the main consent for the remaining screening assessments must be signed.

Two cohorts of subjects will be enrolled:

- Cohort 1, comprising subjects with HER2 amplification by ISH and HER2 overexpression by IHC; i.e., IHC 2+ or 3+
- Cohort 2, comprising subjects with HER2 amplification by ISH and HER2 IHC 0 or 1+

Enrolled subjects will receive zanidatamab, 20 mg/kg given intravenously (IV) every 2 weeks (Q2W) until 1 of the treatment discontinuation criteria is met. The primary endpoint of confirmed ORR per RECIST 1.1 will be evaluated by ICR. Disease response will be evaluated every 8 weeks (Q8W) using computed tomography (CT) or magnetic resonance imaging (MRI) scans.

Number of Planned Subjects

Cohort 1: approximately 75 subjects.

Cohort 2: approximately 25 subjects.

Study Population

Subjects must meet the below enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a Good Clinical Practice (GCP) audit and/or health regulatory authority inspection.

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 subjects 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 will be considered as having received 1 prior line of therapy for advanced disease.
4. Subjects must have at least 1 measurable target lesion by RECIST 1.1. Subjects who have received prior local therapy (embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or is within the treatment field and has shown ≥ 20% growth in size since post-treatment assessments.
5. Subjects must test positive for HER2 amplification by in situ hybridization (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 are not acceptable. Testing may occur at any time after diagnosis of advanced or metastatic disease and before study enrollment.
6. Male or female, ≥ 18 years of age (or the legal age of adulthood per country-specific regulations).
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1.

8. Adequate hematologic function, defined as absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 75 x 10^9/L (not requiring transfusion support), and hemoglobin (Hgb) ≥ 9 g/dL (subjects with chronic anemia that is supported by intermittent red blood cell [RBC] transfusions are eligible).
9. Liver function: serum bilirubin ≤1.5 x the upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease, aspartate aminotransferase (AST) ≤ 3 x ULN, and alanine aminotransferase (ALT) ≤ 3 x ULN. For subjects with liver involvement, AST, and ALT ≤ 5.0 x ULN is acceptable.
10. Adequate cardiac function, as defined by left ventricular ejection fraction (LVEF) ≥ 50%.
11. Kidney function: glomerular filtration rate (GFR) ≥ 30 mL/min as estimated by the Modification of Diet in Renal Disease (MDRD) equation (see Section 7.8.3).
12. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 3 days prior to the first dose of zanidatamab. Females with false positive urine test results can be enrolled if subsequent serum testing is negative (see Section 4.3).
13. For female subjects of childbearing potential and for male subjects with a partner of child-bearing 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 (see Section 4.3).
14. Male subjects must agree to not donate sperm and female subjects must agree to not donate oocytes starting at screening and throughout the study period, and for at least 12 months after the last dose of zanidatamab (see Section 4.3).
15. The subject or subject's legally acceptable representative must provide written informed consent. Subjects who elect to be pre-screened for HER2 status must provide a separate written informed consent for collection, storage, and analysis of the tumor tissue.

Exclusion Criteria

1. Received systemic anti-cancer 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 central nervous system (CNS) metastases, symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks of start of study treatment. Stable, treated brain metastases are allowed (defined as subjects who are off steroids and anticonvulsants and are neurologically stable with no evidence of radiographic progression for at least 4 weeks at the time of screening).
5. Known leptomeningeal disease (LMD). If LMD has been reported radiographically on baseline MRI, but is not suspected clinically by the investigator, the subject 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 be resolved more than 2 weeks prior to the first dose of zanidatamab.

7. Prior or concurrent malignancy whose natural history or treatment has, 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 have not stabilized with treatment.
9. Active hepatitis, including the following:
    a. Acute or chronic hepatitis B (Exception: subjects who are hepatitis B surface antigen positive are eligible if they have HBV DNA less than 500 IU/mL)
    b. Infection with hepatitis C (Exception [i] subjects who have no history of curative viral treatment and are documented to be viral load negative are eligible; [ii] subjects who have completed curative viral therapy ≥ 12 weeks prior to enrollment, and viral load is negative are eligible)
10. Infection with human immunodeficiency virus (HIV)-1 or HIV-2 (Exception: subjects with well-controlled HIV [e.g., CD4 > 350/mm^3 and undetectable viral load] are eligible).
11. Females who are 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/m^2 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 are permitted.
15. Ongoing, clinically significant toxicity (Grade 2 or higher) associated with prior cancer therapies, with the following exceptions:
    a. Alopecia
    b. Congestive heart failure (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. QTc Fridericia (QTcF) > 470 ms.
17. History of myocardial infarction or unstable angina within 6 months prior to enrollment, 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 impact safety or compliance with study procedures.

Test Product, Dose, and Mode of Administration

Zanidatamab (ZW25), 20 mg/kg, given IV Q2W (Days 1 and 15 of each 28-day cycle).

Reference or Combination Products, Dose, and Mode of Administration

N/A.

Required Premedication

All subjects must receive mandatory prophylactic treatment for potential infusion reactions 30 to 60 minutes before the start of each zanidatamab infusion. Pretreatment should include corticosteroids, antihistamines, and acetaminophen at the following recommended doses:

- Corticosteroids - either hydrocortisone 100 mg IV or dexamethasone 10 mg IV
- Antihistamines - diphenhydramine 50 mg per oral (PO) or IV
- Acetaminophen - 650 to 1000 mg PO

If an alternative premedication regimen is thought to be required, the investigator must seek sponsor approval. Sponsor approval is required before implementation.

For subjects who experience an infusion reaction despite the above premedications, other medication(s) as needed per the investigator or per institutional standards including histamine-2 receptor antagonists (H2 blockers) may be given in addition to the mandatory premedication.

Duration of Treatment

Subjects may continue on treatment with zanidatamab until investigator-determined radiographic disease progression per RECIST 1.1, unequivocal clinical progression, unacceptable toxicity, consent withdrawal, physician decision, pregnancy, start of a subsequent anticancer therapy, or study termination by the sponsor. Unequivocal clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers (e.g., increase in disease-related pain), or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. A marked deterioration in ECOG performance status may also indicate unequivocal clinical progression. Every effort should be made to confirm disease progression radiographically. Only in instances where subjects appear to have unequivocal clinical progression and it is not possible or feasible for the subject to undergo radiologic assessment should investigators remove the subject from study treatment. Subjects who discontinue treatment with zanidatamab for any reason should enter the 30-day safety follow-up period, and will continue with efficacy follow-up (if treatment discontinuation was due to reasons other than progressive disease or start of subsequent anticancer therapy) as well as survival follow-up.

Efficacy Assessments

CT and/or MRI scans will be performed at baseline and Q8W during treatment (timed from Cycle 1 Day 1) and will continue after treatment discontinuation every 8 weeks until disease progression or start of subsequent anticancer therapy. Disease response will be assessed according to RECIST 1.1 by ICR (primary endpoint) and investigator (secondary endpoint); responses are to be confirmed 4 weeks following initial documentation of objective response by the investigator.

Pharmacokinetic and Immunogenicity Assessments

Blood samples will be collected at protocol-specified timepoints for evaluation of serum concentrations (PK) of zanidatamab and for evaluation of ADA (immunogenicity).

Serum concentrations of zanidatamab will be measured as a function of time post-dosing. PK parameters to be estimated include the following: 1) for single (first) dose: maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the serum concentration-time curve from zero to the last measurable concentration (AUC_{0-t}), terminal elimination rate constant (λ_z), half-life ($t_{1/2}$), area under the serum concentration-time curve from zero to infinity ($AUC_{0-\infty}$), serum clearance (CL), volume of distribution (V_d), etc. and 2) for multiple doses: area under the serum concentration-time curve from zero to the end of dosing interval (AUC_{tau}), average concentration (C_{ave}) for Dose 1, C_{max} and minimum concentration (C_{min}) (trough) for subsequent doses, accumulation index, fluctuation ratio, steady state concentration (C_{ss}), and attainment of steady state. ADAs to zanidatamab and possibly neutralizing antibodies will be measured, including frequency, time of onset, and duration of immunogenicity response.

At least 30 subjects (the first 10 subjects enrolled in China and first 20 suitable subjects enrolled in the rest of world) will be assigned to an extensive PK schedule (suitability determined by the medical monitor). Further subjects will then be assigned to the sparse PK schedule (peak-trough measurements only). Thirty subjects (the first 10 suitable subjects in China who reach Cycle 4 and first 20 suitable subjects in the rest of the world who reach Cycle 4, with suitability determined by the medical monitor) will also be assigned to an extensive PK schedule for 1 cycle at steady state (Cycle 4 or later).

Biomarker Assessments

Blood and tumor tissue samples will be collected at the specified timepoints for assessment of biomarkers. Biomarkers may include but are not limited to circulating tumor DNA (ctDNA), tumor tissue DNA and RNA, HER2 extracellular domain (ECD), carbohydrate antigen 19-9 (CA19-9), and post-treatment HER2 tumor status. Biomarkers will be investigated as an exploratory endpoint and will not be used to guide subject selection for the study. Only the biomarkers specified above will be tested on samples collected in Mainland China.

Safety Assessments

Safety will be monitored by recording the type, frequency, and severity of AEs, including the following:

- Adverse events of special interest (AESIs): infusion-related reactions, non-infectious pulmonary toxicities, and cardiac events of absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value < 50%, and/or grade ≥ 2 heart failure
- SAEs and deaths

The following safety parameters will also be assessed:

- Clinical laboratory values (including hematology, coagulation, serum chemistry, and urinalysis)
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- ECOG PS
- Concomitant medications, including opioids
- Electrocardiograms (ECGs)

Cardiac function will be monitored via echocardiogram or multigated acquisition (MUGA) scans. The same modality (echocardiogram or MUGA scan) must be used throughout the study period. AEs will be collected from Cycle 1 Day 1 predose through 30 days after last dose of study drug. Study protocol-related SAEs will be collected from the time of signing the pre-screening or main informed consent for the study. Investigators should follow subjects with AEs until the event returns to baseline, stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies, is lost to follow-up, or withdraws consent, or study closure.

Safety and study conduct will be monitored throughout the study by an independent data monitoring committee (IDMC). The committee is tasked with monitoring the safety of participants in this study through regular and/or ad hoc meetings. An IDMC meeting will be held after the first 25 subjects enrolled have received at least 1 dose of zanidatamab. After the first IDMC meeting, subsequent meetings will be held quarterly to review cumulative safety data to identify any potential new safety signals. An additional IDMC meeting will be held at least 28 days after the tenth subject enrolled in China has received 1 dose of zanidatamab to review safety. The IDMC will be responsible for making recommendations to the sponsor as to appropriate study direction; further details will be provided in the IDMC charter.

Quality of Life and Disease-Related Pain Assessments

The EQ-5D-5L questionnaire will be used to obtain QOL information and the BPI short form will be used to assess disease-related pain at protocol-specified timepoints.

Statistical Methods

This is a single-arm, open-label study that will enroll approximately 100 subjects: 75 subjects in Cohort 1, and 25 subjects in Cohort 2. The primary endpoint is the confirmed ORR by ICR. The primary efficacy analysis will evaluate this endpoint for the Cohort 1 Primary Efficacy Analysis Set, defined as all safety evaluable subjects in Cohort 1. The 2-sided Clopper-Pearson exact binomial 95% confidence intervals (CIs) that could be observed with a sample size of 75 subjects are listed in the table below. The primary analysis of efficacy will be performed approximately 6 months after the last subject has been enrolled in Cohort 1 of the study.

Clopper-Pearson 95% Confidence Intervals for N = 75 Subjects

Confirmed ORR		95% CI	
Percent	**Responses**	**Lower**	**Upper**
20.0%	15	11.7%	30.8%
25.3%	19	16.0%	36.7%
30.7%	23	20.5%	42.4%
36.0%	27	25.2%	47.9%
40.0%	30	28.9%	52.0%
45.3%	34	33.8%	57.3%
50.7%	38	38.9%	62.4%

With a sample size of 100 subjects (Cohorts 1 and 2 combined), the binomial probabilities of detecting 1 or more treatment-emergent adverse events (TEAEs) with a frequency of 5%, 1%, and 0.1% are approximately 0.99, 0.63, and 0.10, respectively.

Summaries of subject disposition, demographics, disease characteristics, and exposure will be provided. Safety and efficacy endpoints will be summarized using descriptive statistics (e.g., mean, median, standard deviation, minimum, maximum) for continuous variables, and frequencies and percentages for categorical variables. In addition, the PK parameters of zanidatamab will be estimated and summarized with descriptive statistics.

Table 1: Schedule of Events

Assessment	Optional HER2 Pre-Screening	Screening (≤ 28 days)	Evaluation Cycles (8 weeks)							Subsequent 28-Day Cycles		Q8W	Q12W	EOT[m]	Safety Follow-up (30 Days Post-Last Dose)	Efficacy Follow-up (Q8W)	Survival Follow-up (Q3 mos)[q]
			Cycle 1				Cycle 2										
			D1	D2	D5	D15 (±2d)	D1 (±2d)	D15 (±2d)	D28 (±7d)	D1 (±2d)	D15 (±2d)	(±7d)	(±7d)	(+7d)	(+7d)	(±7d)	(±14d)
Zanidatamab [a]			X			X	X	X		X	X						
Informed consent	X[t]	X															
Medical history		X															
Eligibility		X	X														
Demographics		X															
New tumor biopsy or archived tissue	X[g]	X[g]												X[k]			
Disease assessment (CT/MRI)[b]		X							X			X[b,w]		X[n]	X[o]	X[cc]	
Brain scan [bb]		X										X[bb]				X[bb, cc]	
Height		X															
Weight[h]		X	X			X	X	X		X	X						
Physical exam[c, h]		X	X				X			X				X	X		
ECOG PS[c, h]		X	X				X			X				X	X		
Vital signs[f]		X	X			X	X	X		X	X			X	X		
Hematology[c, h, v]		X	X			X	X	X		X	X			X	X		
Coagulation[d, h, v]		X[d]															
Serum chemistry[c, h, v]		X	X			X	X	X		X	X			X	X		
Urinalysis[d, h]		X[d]															
Pregnancy test[c, h, r] or question [r]		X	X				X			X				X	X		
12-lead ECG		X[d]												X			
Echo/MUGA[h, l]		X	First post-baseline scan at Cycle 3 Day 1 predose[l], then every 12 weeks											X			
Hepatitis B and C and HIV[x]		X															
EQ-5D-5L and BPI questionnaires		X							X			X[w]		X			
Assessment of opioid use		X							X			X[w]		X			
ADA[h, u]			X			X	X	X		X[j]				X	X[p]		
ctDNA[h]			X						X					X[k]			
HER2 ECD[h]			X			X		X		X[s]				X[k]			

Assessment	**Optional HER2 Pre-Screening**	**Screening (≤ 28 days)**	**Evaluation Cycles (8 weeks)**							**Subsequent 28-Day Cycles**		**Q8W**	**Q12W**	**EOT[m]**	**Safety Follow-up (30 Days Post-Last Dose)**	**Efficacy Follow-up (Q8W)**	**Survival Follow-up (Q3 mos)[q]**
			Cycle 1				**Cycle 2**										
			D1	**D2**	**D5**	**D15** (±2d)	**D1** (±2d)	**D15** (±2d)	**D28** (±7d)	**D1** (±2d)	**D15** (±2d)	(±7d)	(±7d)	(+7d)	(+7d)	(±7d)	(±14d)
CA19-9		X							X			X[w]		X		X[cc]	
PK samples[e, f, u]			X	X[i]	X[i]	X	X	X		X[z,dd]	X[dd]			X[aa]			
AEs[y]		AEs and concomitant medications are recorded from Day 1 pre-dose through the end of the safety reporting period (30 days after the last dose of study treatment). Any study protocol-related SAE and concomitant medications given for treatment of the SAE, should be recorded from the time of signing the pre-screening or main informed consent for the study.															
Concomitant medications																	
Subsequent anti-cancer therapies																	X

Schedule of Events Footnotes

Ab = antibody; ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; Ag = antigen; BPI = brief pain inventory; CA19-9 = carbohydrate antigen 19-9; CR = complete response; CT = computed tomography; D or d = day; ECD = extracellular domain; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of treatment; EQ-5D-5L = European Quality of Life 5-Dimensions 5-level questionnaire; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan;
PK = pharmacokinetics; PR = partial response; PRO = patient-reported outcomes; Q3 mos = every 3 months; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event

a See Section 5 for zanidatamab dosing and administration.

b After screening, all subsequent radiographic scans for disease assessments may be done within a ± 7-day window and based on 8-week intervals timed from Cycle 1 Day 1. Objective responses (CR or PR) must be confirmed 4 weeks (+7 days) following initial documentation of the response by the investigator.

c Does not need to be repeated on Cycle 1 Day 1 if assessment completed for screening within the previous 3 days.

d Repeated at subsequent cycles if medically indicated.

e See Table 2 for extensive sampling timepoints, Table 3 for sparse sampling timepoints, and Table 4 for extensive sampling timepoints at steady state.

f On applicable dosing days, the assessment should be performed pre-dose and post-dose.

g See Section 7.1 for details. Only done at screening if not previously done as part of pre-screening.

h On applicable dosing days, the assessment should be performed pre-dose.

i Not required for subjects on sparse PK sampling schedule.

j Pre-dose on Day 1 of Cycles 4, 6, 8, 10, 12, 18, 24, and 36.

k Only at disease progression. Tumor biopsy is optional and requires additional consent.

l After screening, an echocardiogram/MUGA should be done predose within a -7-day window from Cycle 3 Day 1, then all subsequent scans should be done pre-dose every 3 cycles (Q12W) thereafter within a -7 day time window. An echocardiogram/MUGA is not required at EOT if ≤3 months since the previous scan.

m Should take place as soon as possible after a subject permanently stops study treatment (within 7 days after treatment discontinuation).

n Not required if ≤ 4 weeks since previous scan.

o Only required if feasible, and last scan showed unconfirmed PR/CR and performed ≥4 weeks prior.

p Not required if ≤ 2 weeks since last sample.

q Every 3 months until death, lost to follow-up, withdrawal of consent, study completion, or study termination by the sponsor.

r Urine pregnancy tests will be performed for women of childbearing potential on Day 1 of each cycle prior to dosing. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead. Male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant.

s Pre-dose on Day 1 of Cycles 4, 8, and 12 only.

t For subjects who opt to be prescreened for HER2 amplification status.

u A blood sample for measurement of zanidatamab PK and ADA should be taken for any subject who experiences an AE that results in an unscheduled visit or meets SAE criteria, if less than 24 hours have elapsed since the last dose of zanidatamab.

v Refer to Section 7.8.3 for specific parameters.

w Timed from Cycle 1 Day 1.

x HIV 1/2 Ag/Ab combination immunoassay.

y All AEs should be followed until the event returns to baseline, stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies, is lost to follow-up, withdraws consent, or study closure.

z Day 1 of Cycles 4, 6, 8, 10, and 12 only.

aa Only required if subject has completed less than 6 months of treatment.

bb MRI or CT if MRI not feasible (CT with contrast unless medically contraindicated). For subjects with history or clinical suspicion of brain metastases, brain MRI or CT must be repeated at time of all tumor restaging.

cc Until disease progression or start of subsequent anticancer therapy.

dd For extensive PK sampling at steady state (Cycle 4 or later); see Table 4.

Table 2: Pharmacokinetic Extensive Sampling Timepoints

Time	Cycle 1 (4 Weeks)									Cycle 2 (4 Weeks)		Additional Even-Numbered Cycles[a]		EOT
	D1					D2	D5	D15		D1 and D15		D1		
	Pre-dose	End of ZW25 Infusion	2 h Post-dose	4 h Post-dose	8 h Post-dose	24 h Post-dose	96 h Post-dose	Pre-dose	End of ZW25 Infusion	Pre- dose	End of ZW25 Infusion	Pre- dose	End of ZW25 Infusion	
Allowed time window		+15 min	± 15 min	± 15 min	± 3 h	±4 h	± 4 h	– 4 h	+15 min	– 4 h	+15 min	– 4 h	+15 min	
PK serum sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]

D = day; EOT = end of treatment; h = hour; min = minute; PK = pharmacokinetics; ZW25 = zanidatamab
Extensive sampling will be performed for the first 10 subjects enrolled in China and first 20 suitable subjects enrolled in the rest of world (suitability determined by medical monitor).
a Day 1 of Cycles 4, 6, 8, 10, and 12.
b Only required if subject has completed less than 6 months of treatment.

Table 3: Pharmacokinetic Sparse Sampling Timepoints

Time	Cycle 1 (4 Weeks)				Cycle 2 (4 Weeks)		Additional Even-Numbered Cycles[a]		EOT
	D1		D15		D1 and D15		D1		
	Pre-dose	End of ZW25 Infusion	Pre-dose	End of ZW25 Infusion	Pre-dose	End of ZW25 Infusion	Pre-dose	End of ZW25 Infusion	
Allowed time window		+15 min	– 4 h	+15 min	– 4 h	+15 min	– 4 h	+15 min	
PK serum sample	X	X	X	X	X	X	X	X	X[b]

D = day; EOT = end of treatment; h = hour; min = minute; PK = pharmacokinetics; ZW25 = zanidatamab
a Day 1 of Cycles 4, 6, 8, 10, and 12.
b Only required if subject has completed less than 6 months of treatment.

Table 4: Steady-State Extensive Pharmacokinetic Sampling Schedule

Time	Cycle 4 or any Subsequent Cycle							
	D1					D3	D5	D15
	Pre-dose[a]	End of ZW25 infusion	2 h post-dose	4 h post-dose	8 h post-dose	48 h post-dose	96 h post-dose	336 h post-dose
Allowed time window		+15 min	± 15 min	± 30 min	± 3 hr	± 1 day	± 1 day	± 3 days
PK serum sample	X	X	X	X	X	X	X	X

D=day; h=hour; min=minutes; PK=pharmacokinetic
Extensive sampling at steady state will be performed for the first 10 suitable subjects in China who reach Cycle 4 and the first 20 suitable subjects in the rest of world who reach Cycle 4 (suitability determined by medical monitor).
a Relative to start of zanidatamab administration.
Note: Dates and times of the start and end of zanidatamab infusions and dates and times of the PK samples must be recorded.
Note: The sampling specified here is to be performed in addition to the sampling specified in Table 2 and Table 3.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
λ_z	terminal elimination rate constant
5-FU	5-fluorouracil
5-HT3	5-hydroxytryptamine
ADA	anti-drug antibody
ADC	antibody-drug conjugate
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASC	active symptom control
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the serum concentration-time curve from zero to infinity
AUC_{0-t}	area under the serum concentration-time curve from zero to the last measurable concentration
AUC_{tau}	area under the serum concentration-time curve from zero to the end of dosing interval
ß-hCG	beta-human chorionic gonadotropin
BOR	best overall response
BPI	Brief Pain Inventory
BTC	biliary tract cancer
BUN	blood urea nitrogen
C_{ave}	average concentration
CA19-9	carbohydrate antigen 19-9
CC	cholangiocarcinoma
CD4	cluster of differentiation 4
CDx	companion diagnostics
CFR	Code of Federal Regulations
CH	constant heavy chain
CHF	congestive heart failure
CisGem	cisplatin and gemcitabine
CI	confidence interval
CL	serum clearance
CLIA	Clinical Laboratory Improvements Amendment
C_{max}	maximum concentration
C_{min}	minimum concentration
CNS	central nervous system
CR	complete response
CRF	case report form
C_{SS}	steady state concentration
CT	computed tomography
ctDNA	circulating tumor DNA

CTFG	Clinical Trial Facilitation Group
DCR	disease control rate
DOR	duration of response
DLT	dose-limiting toxicity
ECC	extrahepatic cholangiocarcinoma
ECD	extracellular domain
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR/ErbB	epidermal growth factor receptor
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-Dimensions 5-level questionnaire
ESMO	European Society for Medical Oncology
Fab	fragment antigen-binding
Fc	fragment crystallizable
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FGFR2	fibroblast growth factor receptor 2
FISH	fluorescence in situ hybridization
FNAs	fine needle aspirates
FSH	follicle stimulating hormone
GBC	gallbladder cancer
GCP	Good Clinical Practice
GEA	gastroesophageal adenocarcinoma
GFR	glomerular filtration rate
H2	histamine-2 receptor antagonist
HER2	human epidermal growth factor receptor 2
Hgb	hemoglobin
hIgG	human immunoglobulin
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
ICC	intrahepatic cholangiocarcinoma
ICF	informed consent form
ICH	International Council for Harmonisation
ICR	independent central review
IDH	isocitrate dehydrogenase
IDMC	independent data monitoring committee
IEC	independent ethics committee
IgG	immunoglobulin G
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IRR	infusion-related reaction
ISH	in situ hybridization
IUO	investigational use only

IV	intravenous(ly)
LMD	leptomeningeal disease
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX	modified FOLFOX (folinic acid [leucovorin], 5-FU, and oxaliplatin)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MUGA	multigated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK-1	neurokinin-1
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PO	per oral (orally)
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
QxH	every x hours
Qx mos	every x months
QxW	every x weeks
QOL	quality of life
QTcF	QTc Fridericia
RBC	red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RD	recommended dose
SAE	serious adverse event
SAP	statistical analysis plan
scFv	single-chain variable fragment
Scr	serum creatinine
SD	stable disease
SOC	system organ class
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
$t_{1/2}$	half-life
t_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
Vd	volume of distribution

VH	variable heavy
VL	variable light
WBC	white blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Biliary Tract Cancers

Biliary tract cancers (BTCs), including gallbladder cancer (GBC) and cholangiocarcinoma (CC) (both intrahepatic cholangiocarcinoma [ICC] and extrahepatic cholangiocarcinoma [ECC]), are poor prognosis cancers that account for approximately 3% of all adult cancers (Valle 2017). BTCs represent a heterogeneous group of diseases that are associated with distinct risk factors, molecular characteristics, and symptoms at presentation. For example, the liver fluke *Opistorchis viverrini* infection is a risk factor for ICC and ECC but not GBC, while patients with GBC are less likely to present with jaundice compared to patients with ICC or ECC (Valle 2017). Mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) and fibroblast growth factor receptor 2 (FGFR2) are more prevalent in patients with ICC (Valle 2017); (Arai 2014). Recent studies with small molecule inhibitors of IDH1 or FGFR2 have demonstrated clinical activity in patients with advanced CC containing these respective gene mutations (A. Vogel 2019, Abou-Alfa 2019). Human epidermal growth factor receptor 2 (HER2) amplification, which is more frequent in GBC, represents another potential molecular treatment target (Valle 2017).

The incidence and mortality rates of BTCs are increasing, mostly due to a rise in the incidence of ICC. More than 65% of patients with BTC are diagnosed with non-resectable disease and the relapse rate is high among patients who undergo potentially curative surgery. The 5-year survival rate is approximately 5 to 15% for all patients; the estimated 5-year survival rate varies by stage of disease: 50% for American Joint Committee on Cancer (AJCC) Stage I, 30% for Stage II, 10% for Stage III, and 0% for Stage IV (Valle 2017).

1.2. Standard of Care Therapies for Advanced or Metastatic BTC

The most active cytotoxic chemotherapeutics for advanced BTCs are gemcitabine- and platinum-containing regimens (Tsavaris 2004, Eckel 2007). In a randomized, multicenter,

Phase 3 trial of 410 subjects (the ABC-02 Study), cisplatin combined with gemcitabine (CisGem) was associated with superior overall survival (OS) and progression-free survival (PFS) compared to gemcitabine alone in the first-line setting of advanced or metastatic BTC (Valle 2010). These results were replicated in a randomized Phase 2 trial conducted in Japan (the BT22 Study) (Okusaka 2010). Based on these results, CisGem has become the recognized standard regimen for first-line treatment of patients with advanced BTC. In the second-line setting, the most robust data comes from a recent Phase 3 trial (the ABC-06 Study), in which 162 subjects were randomized 1:1 to receive either mFOLFOX (folinic acid [leucovorin], 5-fluorouracil [5-FU], and oxaliplatin) plus active symptom control (ASC), versus ASC alone. The median OS for subjects treated with mFOLFOX plus ASC was 6.2 months versus 5.3 months for subjects who received ASC alone (hazard ratio [HR] 0.69, 95% CI: 0.50, 0.97, p = 0.031). The PFS and objective response rate (ORR) with mFOLFOX + ASC was 4 months and 5%, respectively; the PFS and ORR with ASC alone was not reported (Lamarca 2019). Other than the ABC-06 trial, there are no other published randomized data in the second-line and later BTC setting.

Given the lack of second-line systemic treatments showing clinically meaningful benefit for patients with advanced BTC, there remains a need for new treatment approaches, including

molecularly targeted therapies. Several targeted agents have entered clinical development with encouraging results, including HER2-directed therapies. Pemigatinib (PEMAZYRE™), a small molecule kinase inhibitor, was recently approved for the treatment of patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement.

1.3. HER2 Expression in BTC

HER2 is a member of the epidermal growth factor receptor (EGFR/ErbB) family comprising 4 structurally related receptors: HER1 (EGFR), HER2, HER3, and HER4. HER receptors are normally activated by binding to specific ligands, resulting in a conformational change that allows formation of receptor homodimers and heterodimers. Receptor dimerization triggers autophosphorylation of specific tyrosine residues and activation of intracellular signaling pathways. Over-expression and amplification drive tumorigenesis through the creation of spontaneous receptor homodimers or heterodimers with other ErbB family members, resulting in activated oncogenic downstream signaling such as phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK), which in turn promote cellular proliferation, survival and angiogenesis (Moasser 2007). HER2 is a well-described predictive biomarker for anti-HER2 therapy in breast and gastric cancer (Slamon 2001, Bang 2010) and many other solid tumors also harbor HER2 gene amplification or over-expression (Meric-Bernstam 2019). However, data from published series of HER2 expression across solid tumors vary both in terms of methodology and reporting, and their utility is consequently limited.

A systematic literature review and meta-analysis of published data in BTC showed that among 38 studies (a total of 3839 patients) that reported HER2 positivity assessed by immunohistochemistry (IHC), the mean prevalence of HER2 overexpression was 26.5% (95% CI: 18.9, 34.1%) (Galdy 2017). There was no statistically significant difference in HER2 overexpression between regions; the mean prevalence of HER2 overexpression in Asia was 28.4% (95% CI: 14.5, 42.3%) versus 19.7% (95% CI: 10.1, 29.2%) for Western countries, *P* value = 0.49. When all 38 studies were considered, no differences in the mean prevalence of HER2 overexpression were found between BTC tumor subtypes. However, when only studies that defined HER2 overexpression as the presence of moderate/strong staining were considered, the mean prevalence of HER2 overexpression was highest for GBC (19.1%), followed by ECC (17.4%), and ICC (4.8%). HER2 amplification analysis was performed in 16 of the 38 studies and showed a mean prevalence of 30.1%. The mean prevalence of HER2 amplification for ECC was 22.5% and 17.6 % for ICC; the prevalence was not reported for GBC (not all of the 16 studies reported the prevalence of HER2 amplification by BTC subtype). A separate study of 221 patients with BTC showed good correlation between HER2 overexpression and gene amplification (78% concordance rate) (Nakazawa 2005).

Similar to breast and gastric cancers, a number of studies have suggested that HER2 overexpression or gene amplification has biologic importance or clinical relevance in BTCs. Constitutive expression of HER2 in gallbladder epithelium led to the development of adenocarcinoma in transgenic mice (Kiguchi 2001) and high HER2 expression in a cholangiocarcinoma cell line resulted in enhanced invasiveness, motility, and proliferation via AKT/p70S6K pathway activation, compared with cell lines without HER2 overexpression

(Treekitkarnmongkol 2010). Furthermore, in a HER2-amplified GBC cell line, SNU-2670, trastuzumab demonstrated anti-tumor effects as monotherapy and in combination with gemcitabine, promoting increased apoptosis compared to cell lines without HER2 amplification (Nam 2016).

1.4. Approved HER2-Targeted Therapies

The introduction of HER2-targeted therapy into the clinic has led to marked improvements in disease-free survival, PFS, and OS for patients with HER2-high breast cancer (Schramm 2015). In the United States (US), there are multiple approved HER2-targeted agents, all of which are indicated for the treatment of HER2-high breast cancer. These include the antibody-based therapies trastuzumab (HERCEPTIN® and biosimilars), pertuzumab (PERJETA®), and margetuximab (MARGENZA™), the antibody-drug conjugates (ADCs) ado-trastuzumab emantasine (KADCYLA®; also referred to as T-DM1) and fam-trastuzumab deruxtecan-nxki (ENHERTU®; also referred to as DS-8201a); the oral small molecule dual EGFR/HER2 inhibitor lapatinib (TYKERB®); the irreversible oral small molecule EGFR/HER2/HER4 inhibitor neratinib (NERLYNX®); and the tyrosine kinase inhibitor tucatinib (TUKYSA™). Trastuzumab is also approved for advanced HER2-overexpressing gastric/gastroesophageal junction cancer. There are no approved HER2 agents for any other HER2-high expressing cancers, or for cancers with lower levels of HER2 expression and absence of gene amplification.

1.5. HER2-targeted Therapies in BTC

Of the HER2-targeted agents, lapatinib has been evaluated in both the first- and second-line setting in an unselected population of subjects with advanced BTC (Ramanathan 2009, Peck 2012). Results of these studies were unremarkable and showed no significant evidence of anti-tumor activity. However, in a separate case series of 9 GBC and 5 CC subjects treated with trastuzumab, lapatinib, or pertuzumab monotherapy, 4/9 GBC subjects (44.4%) had partial responses (PR) and 1/9 GBC subject (11.1%) had a complete response (CR), equating to an ORR of 55.6% (Javle 2015). An additional 3 GBC subjects had stable disease (SD). The duration of response (DOR) ranged from 8+ to 168 weeks (median 40 weeks). All 5 GBC subjects with objective responses had HER2 overexpression or amplification. The clinical benefit of HER2-targeted agents may therefore be associated with HER2 amplification or over-expression, and a biomarker-based strategy is needed to select patients for HER2-directed therapies.

1.6. Zanidatamab

Zanidatamab (formerly referred to as ZW25) is a novel humanized, bispecific antibody that binds to the same 2 extracellular domains of HER2 as trastuzumab (ECD4) and pertuzumab (ECD2). Binding of zanidatamab results in blockade of ligand-dependent and independent growth and potent activation of antibody-dependent cellular cytotoxicity (ADCC). The unique binding geometry of zanidatamab also leads to increased tumor cell binding, receptor clustering, and receptor internalization relative to trastuzumab, including in settings of lower HER2 expression.

A brief summary of zanidatamab nonclinical and clinical data is provided below; additional data are presented in the Investigator's Brochure. Planned and ongoing clinical studies are also summarized in the Investigator's Brochure.

In preclinical studies in tumor cell lines and xenograft tumor models, zanidatamab demonstrated anti-tumor activity that was superior to trastuzumab across a range of tumors and HER2 expression levels. Zanidatamab treatment of mice bearing HER2 1+ patient-derived breast cancer xenografts (ST1337B) significantly improved host survival compared with trastuzumab or human immunoglobulin (hIgG). Zanidatamab was also efficacious in nude mice bearing established tumors with a human non-small cell lung cancer (NSCLC) or head and neck squamous cell carcinoma (HNSCC) cell lines (A549 and FaDu cell lines, both HER2 < 3+, respectively). In addition, zanidatamab was efficacious in nude mice bearing established tumors with the human SKOV- 3 ovarian epithelial adenocarcinoma cell line that has a 3+ level of HER2 expression.

An ongoing first-in-human study of zanidatamab, a multi-part Phase 1 trial (ZWI-ZW25-101; NCT02892123), is evaluating the safety, pharmacokinetics (PK), immunogenicity, and potential anti-tumor activity of zanidatamab as a single agent and in combination with selected chemotherapy agents in subjects with locally advanced (unresectable) and/or metastatic HER2-expressing tumors. Part 1 of the study used a standard 3+3 dose-escalation design to determine the maximum-tolerated dose (MTD), optimal biological dose, or recommended dosage (RD) of zanidatamab monotherapy administered every week (QW), once every 2 weeks (Q2W), or once every 3 weeks (Q3W) to subjects with any HER2-expressing cancer that had progressed after receipt of all therapies known to confer clinical benefit. The QW or Q2W dosing cohorts completed enrollment with no dose-limiting toxicities (DLTs) and the MTD was not reached. The single agent RD for further study was identified as 10 mg/kg QW or 20 mg/kg Q2W. Part 2 of Study ZWI-ZW25-101 is evaluating the safety, tolerability, and preliminary anti-tumor activity of zanidatamab monotherapy administered at a Part 1 RD in subjects with selected HER2-expressing locally advanced and/or metastatic cancers in up to 5 disease-specific cohorts, including HER2-high breast cancer (IHC 3+, or IHC 2+/ fluorescence in situ hybridization [FISH+]), HER2-intermediate breast cancer (IHC 2+/FISH-negative [FISH-]), HER2-high gastroesophageal adenocarcinoma (GEA), HER2-intermediate GEA, and other HER2-high solid tumors. Subjects eligible for Part 2 must have central confirmation of HER2 status based on new biopsies or archival tissues obtained ≤6 months without intervening HER2-directed agents. Part 3 of the study is evaluating the safety, tolerability, and preliminary anti-tumor activity of zanidatamab administered in combination with selected chemotherapy agents, including paclitaxel, capecitabine, and vinorelbine, in subjects with HER2-expressing breast and gastric cancers.

Safety and anti-tumor activity data of zanidatamab monotherapy in GEA and other solid tumors was presented at the European Society for Medical Oncology (ESMO) 2019 annual meeting (Meric-Bernstam 2019). Among the 58 subjects enrolled in Part 1 and 2, the median age was 61 years (range 26–81); 60% were male and 86% had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1. The median number of prior cancer regimens was 4 (range 1–10), and 55% had received prior HER2 therapy. A total of 20/23 GEA subjects (87%) had received prior trastuzumab and 1 subject each (4%) had received T-DM1 and neratinib. Only 2/9 BTC subjects (22%) had received prior trastuzumab; none of the remaining BTC subjects had received prior HER2-targeted agents.

All treatment-related adverse events (AEs) were Grade 1 or 2. The most common treatment-related AEs were diarrhea (26 subjects, 45%) and infusion reaction (16 subjects, 28%). There were no treatment-related left ventricular ejection fraction (LVEF) decreases ≥ 10% during

treatment. A single subject had a treatment-related serious adverse event (SAE), which was Grade 2 fatigue. Analyses of 10 mg/kg QW and 20 mg/kg Q2W dosing showed dose-proportional and non-linear PK, with steady state reached by the end of Cycle 2. The half-life ($t_{1/2}$) of 10 mg/kg QW was approximately 123 hours, and the $t_{1/2}$ of 20 mg/kg Q2W was approximately 150 hours. The overall exposure was similar for 10 mg/kg QW and 20 mg/kg Q2W. The trough values were maintained above the minimum predicted efficacious level.

Among all 46 response-evaluable subjects, the ORR (all PRs) was 35% (16/46 subjects). The disease control rate (DCR) was 72% (33/46). The median time on treatment for responding subjects was 5.1 months (range, 3.3 to 14.2). With the exception of 2 subjects, all responding subjects had HER2 amplification confirmed by central review.

The ORR for response-evaluable subjects with BTC was 67% (4/6 subjects); all responses were confirmed. Among the 4 BTC subjects with confirmed objective responses, 3 had GBC and 1 had ICC. Three of the 4 responding subjects with BTC had HER2 amplification confirmed by central review.

Based on the above safety and efficacy results, zanidatamab monotherapy was generally well tolerated and has shown promising clinical activity across a range of advanced solid tumors; in particular, the ORR was high in subjects with BTCs with HER2 overexpression and amplification.

1.7. Rationale for Zanidatamab in Recurrent/Relapsed BTC

Due to the lack of treatment options for patients with recurrent/relapsed BTC after frontline CisGem, targeted therapies are attractive options for patients with specific genomic alterations. To date, studies have shown that HER2 is a relevant target in BTC. Similar to breast cancer or GEA, there is evidence to suggest that HER2 genomic alterations may drive or promote oncogenesis, and HER2-targeted agents have clinical activity in tumors that harbor HER2 over-expression or amplification. In the ZWI-ZW25-101 Phase 1 trial, zanidatamab monotherapy is associated with promising clinical benefit in heavily pre-treated BTC subjects. The current Phase 2b trial is therefore designed to confirm the anti-tumor activity of zanidatamab in subjects with relapsed/refractory, HER2-amplified BTC in the second-line and later setting.

2. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	
• To evaluate the anti-tumor activity of zanidatamab monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers (BTC)	• Confirmed objective response rate (ORR) by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), assessed by independent central review (ICR)
Secondary:	
• To further evaluate the anti-tumor activity of zanidatamab monotherapy in subjects with advanced or metastatic HER2-amplified BTC	• Duration of response (DOR) by RECIST 1.1 assessed by ICR • Proportion of subjects with a DOR ≥16 weeks by RECIST 1.1 assessed by ICR • Disease control rate (DCR) by RECIST 1.1 assessed by ICR • Progression-free survival (PFS) by RECIST 1.1 assessed by ICR • ORR by RECIST 1.1 assessed by investigator • DOR by RECIST 1.1 assessed by investigator • Proportion of subjects with a DOR ≥16 weeks by RECIST 1.1 assessed by investigator • DCR by RECIST 1.1 assessed by investigator • PFS by RECIST 1.1 assessed by investigator • Overall survival (OS)
• To evaluate the safety and tolerability of zanidatamab monotherapy in subjects with advanced or metastatic HER2-amplified BTC	• Frequency and severity of adverse events (AEs) • Frequency of serious adverse events (SAEs) and deaths • Frequency and severity of clinical laboratory abnormalities • Frequency of dose modifications of zanidatamab
• To evaluate the pharmacokinetics (PK) of zanidatamab	• Serum concentrations of zanidatamab as a function of time post-dosing • PK parameters for single (first) dose and multiple doses
• To evaluate the immunogenicity of zanidatamab	• Frequency, duration, and time of onset of anti-drug antibodies (ADA) and neutralizing antibodies, if applicable

Objectives	Endpoints
[redacted]	

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This pivotal, multicenter, open-label, single-arm trial will evaluate the anti-tumor activity of zanidatamab monotherapy in subjects with HER2-amplified, inoperable and advanced or metastatic BTC, including ICC, ECC, and GBC. Subjects must have received at least 1 prior gemcitabine-containing systemic chemotherapy regimen for advanced disease, and have experienced disease progression after or developed intolerance to the most recent prior therapy.

New or archival tumor tissue is required from all subjects for HER2 amplification and HER2 protein expression testing at a central lab using in situ hybridization (ISH) and immunohistochemistry (IHC) assays. Subjects may be tested for HER2 status at the central lab any time after diagnosis of advanced or metastatic disease and before study enrollment. Subjects who elect to be pre-screened for HER2 status must sign a separate informed consent for collection, storage, and analysis of the tumor tissue. Once a prospective subject experiences disease progression or develops intolerance to their most recent prior therapy, the main consent for the remaining screening assessments must be signed.

Two cohorts of subjects will be enrolled:

- Cohort 1, comprising approximately 75 subjects with HER2 amplification by ISH and HER2 overexpression by IHC; i.e., IHC 2+ or 3+
- Cohort 2, comprising approximately 25 subjects with HER2 amplification by ISH and HER2 IHC 0 or 1+

Enrolled subjects will receive zanidatamab, 20 mg/kg given intravenously (IV) Q2W until 1 of the treatment discontinuation criteria is met (see Section 4.4.1). Unequivocal clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers (e.g., increase in disease-related pain), or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. A marked deterioration in ECOG PS may also indicate unequivocal clinical progression. Subjects who discontinue treatment with zanidatamab for reasons other than progressive disease or start of subsequent anticancer therapy will continue in follow-up with disease assessments approximately every 8 weeks after the previous scan until disease progression or start of subsequent anticancer therapy. Responses that are initially observed during this follow-up period should be confirmed with disease assessment 4 weeks later. Following progression or start of subsequent anticancer therapy, disease assessments will be discontinued, and subjects will enter long-term follow-up for survival status. Data on survival will be collected via clinic visits (if feasible) or via telephone calls every 3 months after the last follow-up visit. Subjects may be discontinued from the study due to death, lost to follow-up, consent withdrawal, or study termination by sponsor.

Computed tomography (CT) and/or magnetic resonance imaging (MRI) scans will be performed at baseline and every 8 weeks (Q8W) during treatment timed from Cycle 1 Day 1 and will continue after treatment discontinuation every 8 weeks until disease progression or start of subsequent anticancer therapy. Disease response will be assessed according to RECIST 1.1 by ICR (primary endpoint) and investigator (secondary endpoint); responses are to be confirmed 4 weeks following initial documentation of objective response by the investigator.

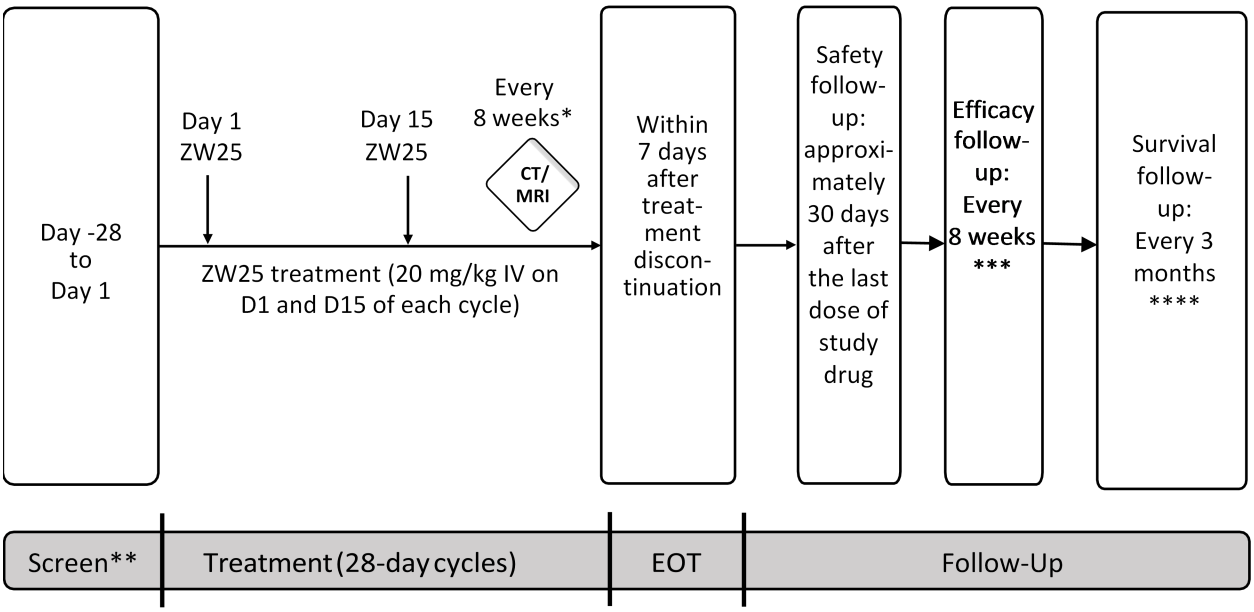
Safety will be monitored by recording the type, frequency, and severity of AEs graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 (27 November 2017). Safety assessments will include monitoring for SAEs, adverse events of special interest (AESIs; infusion-related reactions [IRRs], non-infectious pulmonary toxicities, and cardiac events of absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value < 50%, and/or grade ≥ 2 heart failure), deaths, clinical laboratory values, physical examinations, cardiac function, vital signs, body weight, and ECOG PS. Safety and study conduct will be monitored by an independent data monitoring committee (IDMC), which will be tasked with monitoring the safety of participants through regular and/or ad hoc meetings (see Section 9.4.12).

Blood samples will be collected at protocol-specified timepoints for evaluation of zanidatamab PK and ADA. [redacted]

Tumor biopsies will be collected from all subjects at either pre-screening or screening and processed as formalin-fixed, paraffin-embedded (FFPE) tissues to assess HER2 amplification, protein expression, and exploratory biomarkers of response. Archival tumor tissue may also be used. If possible, an additional optional tumor biopsy is to be obtained at the time of disease progression from an accessible site to allow for assessment of changes in HER2 expression as well as the presence of other exploratory biomarkers. Biomarkers of response may be evaluated. Only the biomarkers specified above will be tested on samples collected in Mainland China.

A study schema is presented in Figure 1. The schedule of assessments is presented in Table 1.

Figure 1: Study Design



CT = computed tomography; EOT = end of treatment; IV = intravenous; MRI = magnetic resonance imaging; ZW25 = zanidatamab
* Timed from Cycle 1 Day 1.
** Subjects may be tested for HER2 status any time after diagnosis of advanced or metastatic disease and before study enrollment. Subjects who elect to be pre-screened for HER2 status must sign a separate informed consent for collection, storage, and analysis of the tumor 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.

3.2. Discussion and Rationale for Study Design

The prognosis for patients with advanced BTC is very poor, with an estimated 5-year survival rate of approximately 5 to 15% for all patients (Valle 2017). Gemcitabine combined with a platinum agent has become the recognized standard regimen for first-line treatment of patients with advanced BTC (Okusaka 2010, Valle 2010). In the second-line setting, results of a recent Phase 3 trial (the ABC-06 Study) showed a median OS benefit of 0.9 months for subjects treated with mFOLFOX plus ASC compared with those who received ASC alone (HR 0.69, 95% CI: 0.50, 0.97, p = 0.031). However, mFOLFOX treatment was associated with a higher rate of Grade 3/4 AEs (59% vs. 39%) and 3 of 81 treated subjects died from chemotherapy-related toxicities (Lamarca 2019). Other than the ABC-06 trial, there are no other published randomized data in the second-line and later BTC setting. Pemigatinib was granted approval for the treatment of patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma based on ORR and DOR. In the FIGHT-202 trial, 107 subjects were treated in the open-label, single-arm study. The ORR was 36% (95% confidence interval [CI]: 27, 45), with a median DOR of 9.1 months (95% CI: 6.0, 14.5) (PEMAZYRE™).

Studies have shown that HER2 is over-expressed in BTC, and HER2-targeted agents demonstrate clinical activity in tumors that harbor HER2 over-expression or amplification (Kiguchi 2001, Nakazawa 2005, Treekitkarnmongkol 2010, Galdy 2017) and (Nam 2016). However, no HER2-targeted agents are approved for treatment of patients with BTC. Given the high unmet medical need for this patient population and the promising anti-tumor activity and tolerability of zanidatamab monotherapy in BTC, a single-arm study design is considered appropriate.

Data from studies in other pathologies indicate that antibody targeting of HER2 is most effective in disease that is HER2 amplified and shows intermediate-to-high levels of protein expression by IHC. In the ToGA study 22.4% of enrolled subjects had FISH positive/IHC 0 or FISH positive/IHC 1+ disease (Bang 2010). A post-hoc exploratory survival analysis failed to show a trend for benefit from the addition of trastuzumab to frontline chemotherapy (Bang 2010). The recently reported results of the colorectal cohort of the MyPathway study that treated 57 subjects with HER2 amplified disease demonstrated an overall ORR of 32% (18/57 subjects). However, no objective responses were observed in the 8 subjects who did not have high levels of protein expression by IHC (Meric-Bernstam 2019). The primary efficacy population for the current study will therefore comprise subjects with disease that is HER2 amplified by ISH and IHC 2+ or 3+ (Cohort 1, N = 75; see Section 3.1). To evaluate the activity of zanidatamab in subjects with lower levels of HER2 expression, subjects with disease that is HER2 amplified by ISH and IHC 0 or 1+ will also be enrolled (Cohort 2, N = 25; see Section 3.1).

The primary endpoint of this study, confirmed ORR, is a direct measure of antitumor activity and is an acceptable endpoint that may be evaluated in a single-arm study according to the FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" (December 2018).

Standardized RECIST 1.1 criteria (Eisenhauer 2009) will be employed to evaluate disease responses during the study, and all imaging assessments will be submitted to an independent third-party imaging core laboratory to ensure consistent unbiased application of the RECIST 1.1 criteria. Investigator-determined responses will be confirmed by repeat scans performed 4 weeks after initial documentation of response. Every effort should be made to confirm disease progression radiographically whenever possible. Only in instances where subjects appear to have unequivocal clinical progression and it is not possible or feasible for the subject to undergo radiologic assessment should investigators remove the subject from study treatment. Local assessment of disease response will be used for subject management and treatment decisions. To further assess the clinical significance of ORR in this study, DOR will be evaluated as a secondary endpoint.

3.2.1. Method of Assigning Subjects to Treatment Groups

This is a single-arm study that will enroll subjects into 2 separate cohorts.

3.2.2. Rationale for Selection of Doses

All subjects in the study will receive 20 mg/kg zanidatamab given IV Q2W. This dose was a recommended dose from the monotherapy part of the Phase 1, dose-escalation study of zanidatamab (ZWI-ZW25-101).

3.2.3. Blinding

This is an open-label study.

4. STUDY POPULATION

Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a Good Clinical Practice (GCP) audit and/or health regulatory authority inspection.

4.1. 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 subjects 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 will be considered as having received 1 prior line of therapy for advanced disease.
4. Subjects must have at least 1 measurable target lesion by RECIST 1.1. Subjects who have received prior local therapy (embolization, chemoembolization, radiofrequency ablation, or radiation therapy) are eligible provided measurable disease falls outside of the treatment field or is within the treatment field and has shown ≥ 20% growth in size since post-treatment assessments.
5. Subjects must test positive for HER2 amplification by in situ hybridization (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 are not acceptable. Testing may occur at any time after diagnosis of advanced or metastatic disease and before study enrollment.
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 absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 75 x 10^9/L (not requiring transfusion support), and hemoglobin (Hgb) ≥ 9 g/dL (subjects with chronic anemia that is supported by intermittent red blood cell [RBC] transfusions are eligible).
9. Liver function: serum bilirubin ≤1.5 x the upper limit of normal (ULN) or ≤ 3 x ULN for subjects with Gilbert's disease, aspartate aminotransferase (AST) ≤ 3 x ULN, and alanine aminotransferase (ALT) ≤ 3 x ULN. For subjects with liver involvement, AST, and ALT ≤ 5.0 x ULN is acceptable.
10. Adequate cardiac function, as defined by LVEF ≥ 50%.

11. Kidney function: glomerular filtration rate (GFR) ≥ 30 mL/min as estimated by the Modification of Diet in Renal Disease (MDRD) equation (see Section 7.8.3).
12. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotropin (β-hCG) pregnancy test result within 3 days prior to the first dose of zanidatamab. Females with false positive urine test results can be enrolled if subsequent serum testing is negative (see Section 4.3).
13. For female subjects of childbearing potential and for male subjects with a partner of child-bearing 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 (see Section 4.3).
14. Male subjects must agree to not donate sperm and female subjects must agree to not donate oocytes starting at screening and throughout the study period, and for at least 12 months after the last dose of zanidatamab (see Section 4.3).
15. The subject or subject's legally acceptable representative must provide written informed consent. Subjects who elect to be pre-screened for HER2 status must sign a separate written informed consent for collection, storage, and analysis of the tumor tissue.

4.2. Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Received systemic anti-cancer 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 central nervous system (CNS) metastases, symptomatic CNS metastases, or radiation treatment for CNS metastases within 4 weeks of start of study treatment. Stable, treated brain metastases are allowed (defined as subjects who are off steroids and anticonvulsants and are neurologically stable with no evidence of radiographic progression for at least 4 weeks at the time of screening).
5. Known leptomeningeal disease (LMD). If LMD has been reported radiographically on baseline MRI, but is not suspected clinically by the investigator, the subject 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 be resolved more than 2 weeks prior to the first dose of zanidatamab.
7. Prior or concurrent malignancy whose natural history or treatment has, 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 have not stabilized with treatment.
9. Active hepatitis, including the following criteria:

a Acute or chronic hepatitis B (Exception: subjects who are hepatitis B surface antigen positive are eligible if they have HBV DNA less than 500 IU/mL)

b Infection with hepatitis C (Exception [i] subjects who have no history of curative viral treatment and are documented to be viral load negative are eligible; [ii] subjects who have completed curative viral therapy ≥ 12 weeks prior to enrollment, and viral load is negative are eligible)

10. Infection with human immunodeficiency virus (HIV)-1 or HIV-2 (Exception: subjects with well-controlled HIV [e.g., CD4 > 350/mm^3 and undetectable viral load] are eligible).
11. Females who are 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/m^2 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 are permitted.
15. Ongoing, clinically significant toxicity (Grade 2 or higher) associated with prior cancer therapies, with the following exceptions:
    a Alopecia
    b Congestive heart failure (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. QTc Fridericia (QTcF) > 470 ms.
17. History of myocardial infarction or unstable angina within 6 months prior to enrollment, 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 impact safety or compliance with study procedures.

4.3. Childbearing Potential and Contraception

4.3.1. Definitions

A person of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone

(FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

According to the inclusion and exclusion criteria, pregnant or breastfeeding subjects cannot be included in the study, and adequate contraceptive measures should be taken to prevent female subjects of childbearing potential or female partners of male subjects (either of whom are of childbearing potential) from getting pregnant from the time of signing informed consent, during study participation and for at least 12 months after the last dose of study drug (see Section 4.3.2). Subjects will be instructed that known or suspected pregnancy occurring during this same period of time should be reported to the investigator, regardless of when the pregnancy was confirmed. If a female subject is pregnant, the investigator will immediately discontinue the subject from the study. Upon discontinuation, only those procedures that would not expose the subject to undue risk will be performed.

In the event that a female subject or female partner of a male subject is found to be pregnant after inclusion in the study, the pregnancy will be followed to term with subject/partner consent, and the status of the mother and child will be reported to the sponsor after delivery.

Details of the pregnancy will be recorded on the withdrawal page of the case report form (CRF), and a Pregnancy Report Form will be completed.

4.3.2. Methods of Contraception

The contraceptive standards and acceptable combinations of contraception methods that are associated with a failure rate of < 1% per year when used consistently and correctly are considered highly effective birth control methods per the Clinical Trial Facilitation Group (CTFG) 2014 guidance document: "*Recommendations related to contraception and pregnancy in clinical trials"*. These methods are detailed in Table 5.

Table 5: Acceptable Methods of Highly Effective Birth Control

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - oral
  - injectable
  - implantable[b]
- intrauterine device (IUD)[b]
- intrauterine hormone-releasing system (IUS)[b]
- bilateral tubal occlusion[b]
- vasectomised partner[b,c]
- sexual abstinence[d]

a Subjects should not simultaneously use more than one form of hormonal contraception associated with inhibition of ovulation (e.g., if subject is taking oral combined estrogen and progestogen containing hormonal contraception, they should not use another combined estrogen and progestogen or progestogen-only hormonal contraception).
b Contraception methods that are considered to have low user dependency per the CTFG guidance document.
c Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical confirmation of the surgical success.
d Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Unacceptable methods of contraception for this clinical trial (either because they have a failure rate of > 1% per year or because they are considered unacceptable methods in clinical trials per the CTFG guidance document) are listed in Table 6.

Table 6: Unacceptable Methods of Birth Control

• Progestin-only hormonal contraception	• Male or female condom with or without spermicide
• Cap, diaphragm, or sponge with spermicide	• Periodic abstinence
• Withdrawal	• Spermicides only
• Lactational amenorrhea method (LAM)	• Concomitant use of female and male condoms

4.4. Removal of Subjects From Therapy or Assessment

Jazz Pharmaceuticals or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and CRF.

4.4.1. Treatment Discontinuation

Study treatment may be discontinued for any of the following reasons:

- AE
- Death

- Lost to follow-up
- Withdrawal by subject
- Physician decision (non-AE, non-progressive disease [PD])
- Pregnancy
- PD (either radiographic or unequivocal clinical progression; see Section 7.2)
- Study termination by sponsor
- Other, non-AE

If a subject has not received zanidatamab for more than 4 weeks due to an AE, the investigator should contact the medical monitor to discuss whether the subject should continue to receive study treatment.

If a subject starts subsequent non-study anti-cancer therapy, study treatment must be discontinued before the start of the new therapy.

At a minimum, all efforts should be made for subjects to complete the End of Treatment (EOT) visit (Section 6.4) and the safety follow-up visit (Section 6.5).

Subjects who discontinue treatment with zanidatamab for reasons other than progressive disease or start of subsequent anticancer therapy will continue in follow-up with disease assessments approximately every 8 weeks after the previous scan until disease progression or start of subsequent anticancer therapy. Following progression or start of subsequent anticancer therapy, disease assessments will be discontinued, and subjects will enter long-term follow-up for survival status.

4.4.2. Subject Withdrawal from Study

Subjects may be discontinued from the study for any of the following reasons:

- Lost to follow-up
- Death
- Withdrawal of consent
- Study termination by sponsor

5. TREATMENTS

5.1. Treatments Administered

Subjects will be treated with zanidatamab administered as monotherapy.

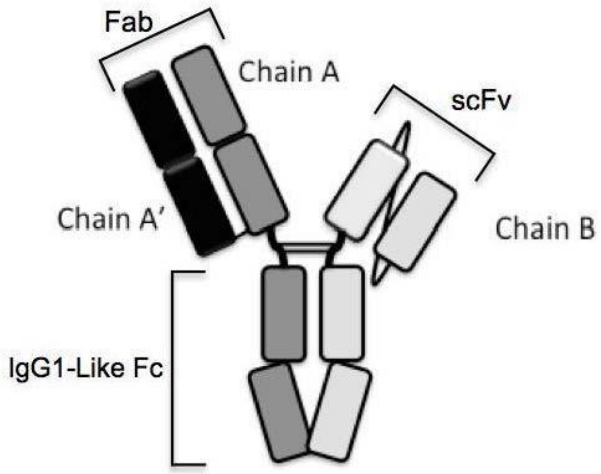
5.2. Investigational Study Drug (Zanidatamab)

Detailed information describing the preparation, administration, and storage of zanidatamab is located in the Pharmacy Manual.

5.2.1. Description

Zanidatamab is a humanized bispecific antibody recognizing 2 non-overlapping epitopes of the ECD of the human HER2 antigen. A schematic representation of zanidatamab is shown in Figure 2. The IgG1-like fragment crystallizable (Fc) region of zanidatamab contains complementary mutations in each constant heavy chain (CH) 3 domain that impart preferential pairing to generate a heterodimeric molecule and correspondingly disfavor formation of homodimers. Chain A is otherwise a normal IgG1 heavy chain and forms a fragment antigen-binding (Fab) arm through pairing with immunoglobulin G (IgG) Kappa light Chain A'. Chain A/A' binds to ECD2 of HER2. Chain B has an IgG1-like hinge and CH2 and CH3 domains, but contains a single-chain variable fragment (scFv) antibody rather than a Fab arm. Chain B binds to ECD4 of HER2. In place of the CH1 domain it has a variable light (VL) domain, an unstructured 20 amino acid linker of glycine and serine residues, followed by a variable heavy (VH) domain to form an scFv domain. Zanidatamab is being developed as a treatment for locally advanced (unresectable) and/or metastatic HER2-expressing cancers.

Figure 2: Structure of Zanidatamab



Fab = fragment antigen-binding; Fc = fragment crystallizable; IgG1 = immunoglobulin G 1; scFv = single-chain variable fragment

5.2.2. Dose and Administration

All subjects must receive prophylactic treatment for potential infusion reactions prior to zanidatamab dosing as outlined in Section 5.2.7.1.

Dosing for zanidatamab will be given as follows:

- 20 mg/kg IV zanidatamab; dosing Q2W on Days 1 and 15 of each 28-day cycle (see Section 5.2.3 for information regarding dose modifications)

Zanidatamab will be administered by IV infusion given over approximately 120 to 150 minutes. If the first 2 doses are well tolerated by a given subject, the infusion duration for that subject may

be decreased to 90 minutes. If the next 2 doses are well tolerated, the infusion duration may be decreased to less than 90 minutes, **however, the infusion rate should not exceed 250 mL/hour.** Refer to the Pharmacy Manual for specific details. Zanidatamab must not be administered as an IV push or bolus. Zanidatamab should not be mixed with other medications. See Section 5.4 for guidelines for management of infusion reactions.

Dosing is based on the subject's actual body weight at baseline. Doses must be adjusted for subjects who experience a ≥ 10% change in weight from baseline. Other dose adjustments for changes in body weight are permitted per institutional standard. Detailed instructions for dose preparation are provided in the Pharmacy Manual.

5.2.3. Dose Modifications

Recommendations for management of and potential dose modifications for zanidatamab-associated toxicity are provided in Table 7. Guidelines for management of zanidatamab-associated left ventricular dysfunction are provided in Table 8. Guidelines for managing pulmonary toxicity are provided following Table 8.

Note that there must be a minimum of 12 days between doses. Cycles will not be skipped. If a cycle is delayed for any reason, once the subject resumes treatment the next dose delivered will be considered Day 1 of the cycle that was delayed. If the Day 15 dose of a cycle is delayed by ≥ 12 days, then that dose will be considered skipped. The next dose delivered will be Day 1 of the subsequent cycle.

Table 7: Recommended Management and Potential Dose Modifications for Zanidatamab-Associated Toxicity

Adverse Event Related to Zanidatamab	Grade	Action for Zanidatamab
Nausea and/or vomiting	Grade 1/2	• Suggest a 5HT3 receptor antagonist until resolution of symptoms. • No dose modification of zanidatamab is required. • For breakthrough nausea or vomiting, consider adding olanzapine 5 or 10 mg daily for three days. For subjects already receiving olanzapine, prochlorperazine may be used.
	Grade 3	• Suggest a 5HT3 receptor antagonist plus a glucocorticoid (e. g., dexamethasone); consider adding a NK-1 receptor antagonist to a 5HT3 receptor antagonist and glucocorticoids if the latter combination is not sufficient for symptom relief. Treatment until resolution of symptoms to ≤ Grade 1. • Hold zanidatamab until severity ≤ Grade 1 or pretreatment level, then resume zanidatamab at the same dose level

Table 7: Recommended Management and Potential Dose Modifications for Zanidatamab-Associated Toxicity (Cont.)

Adverse Event Related to Zanidatamab	Grade	Action for Zanidatamab
Vomiting	Grade 4	• Suggest a 5HT3 receptor antagonist plus a glucocorticoid (e. g., dexamethasone); consider adding a NK-1 receptor antagonist to a 5HT3 receptor antagonist and glucocorticoids if the latter combination is not sufficient for symptom relief. Treatment until resolution of symptoms to ≤ Grade 1. • Hold zanidatamab until severity ≤ Grade 1 or pretreatment level. • For Grade 4 vomiting that improves to ≤ Grade 2 within 72 hours with supportive management, resume at the same dose level. • For Grade 4 vomiting lasting longer than 72 hours, permanently discontinue zanidatamab. • For recurrent Grade 4 vomiting, permanently discontinue zanidatamab.
Diarrhea	Grade 1/2	• Oral hydration with fluid that contains water, salt, and glucose, such as broth or Gatorade. • Suggest loperamide 4 mg PO followed by 2 mg Q4H or with each loose stool until no diarrhea. • No dose modification of zanidatamab is required.
Diarrhea	Grade 3	• Aggressive fluid hydration and clear liquid diet. • Loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider Lomotil alternating with loperamide and/or octreotide 100 or 150 mcg subcutaneously Q8H for subjects with persistent diarrhea despite 48 hours of loperamide. If subjects are refractory to loperamide, Lomotil, and octreotide, gastroenterology should be consulted. • Hold zanidatamab until severity ≤ Grade 1 or pretreatment level. • When symptoms improve to ≤ Grade 1 or pretreatment level, resume zanidatamab at the same dose level or consider dose reduction after discussion with the medical monitor. • For recurrent Grade 3 symptoms despite maximum use of loperamide, Lomotil, and octreotide, zanidatamab dose reduction is mandatory. • For recurrent Grade 3 diarrhea lasting longer than 72 hr despite dose reduction of zanidatamab and maximum use of loperamide, Lomotil, and octreotide, or non-compliance with maximum antidiarrheal therapy, permanently discontinue zanidatamab.
	Grade 4	• Aggressive fluid hydration and clear liquid diet. • Loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider Lomotil alternating with loperamide and/or octreotide 100 or 150 mcg subcutaneously Q8H for subjects with persistent diarrhea despite 48 hours of loperamide. If subjects are refractory to loperamide, Lomotil, and octreotide, gastroenterology should be consulted. • Hold zanidatamab until severity ≤ Grade 1 or pretreatment level. • For Grade 4 diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management, resume upon improvement to ≤ Grade 1 or pretreatment level. zanidatamab dose reduction is mandatory. • For Grade 4 diarrhea lasting longer than 72 hours, permanently discontinue zanidatamab. • For recurrent Grade 4 diarrhea, permanently discontinue zanidatamab.

Table 7: Recommended Management and Potential Dose Modifications for Zanidatamab-Associated Toxicity (Cont.)

Adverse Event Related to Zanidatamab	Grade	Action for Zanidatamab
Rash	Grade 1/2	• Suggest topical steroid as needed. • No dose modification of zanidatamab is required.
	Grade 3	• Suggest initiation of topical steroid; if response insufficient, consider oral corticosteroids. Suggest wound care for skin erosions and ulcerations and to prevent infection. • Suggest analgesics for pain control if necessary. • If not limiting self-care activities and not associated with infection requiring systemic antibiotics, follow guidelines for Grades 1–2 severity. • If limiting self-care activities or associated with infection requiring systemic antibiotics, hold zanidatamab until severity ≤ Grade 1 or pretreatment level, then resume at the same dose. • For recurrence of Grade 3 symptoms limiting self-care activities or associated with infection requiring systemic antibiotics, despite optimal management with topical and/or oral corticosteroids, zanidatamab dose reduction is mandatory.
	Grade 4	• Permanently discontinue zanidatamab.
Other zanidatamab-related AEs (other than IRR)[a]	Grade 1/2	• No dose modification of zanidatamab is required
	Grade 3	• Hold zanidatamab until severity ≤ Grade 1 or pretreatment level. • When symptoms improve to ≤ Grade 1 or pretreatment level, resume zanidatamab at the same dose level.
	Grade 4	• Grade 4 electrolyte imbalances/laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset (e.g., Grade 4 hyponatremia) do not require zanidatamab discontinuation. • For other Grade 4 AEs, permanently discontinue zanidatamab.

AE = adverse event; IRR = infusion-related reaction; PO = by mouth; Q2H = every 2 hours; Q4H = every 4 hours; Q8H = every 8 hours.

a Guidance for management of infusion-related reactions is provided in Section 5.2.3.1.

Table 8: Management of Left Ventricular Dysfunction

Left Ventricular Dysfunction (Regardless of Causality)	Action for Zanidatamab
• Absolute decrease in LVEF of ≥ 16 percentage points from pre-treatment baseline, or • LVEF below institutional limits of normal and absolute decrease of ≥ 10 percentage points below pretreatment baseline	• Suspend dosing for at least 4 weeks • Repeat LVEF assessment within 4 weeks • Dosing may be resumed within 4 to 8 weeks if LVEF returns to normal limits and the absolute decrease is ≤ 15 percentage points from baseline; otherwise, permanently discontinue
• Grade ≥ 2 (symptomatic) heart failure	• Hold zanidatamab. Referral to a cardiologist is recommended. If symptomatic CHF is confirmed, permanently discontinue.

CHF = congestive heart failure; LVEF = left ventricular ejection fraction.

Pulmonary Toxicity

Dosing with zanidatamab should be held for subjects with symptoms or findings consistent with Grade 2 or higher pneumonitis or interstitial lung disease (ILD) pending evaluation per institutional standards including radiographic imaging and pulmonary function tests as indicated. Zanidatamab treatment should be permanently discontinued in the event of confirmed treatment-related Grade 2 or higher ILD. Subjects who experience any of the above-mentioned pulmonary toxicities should be evaluated for alternative infectious etiology and should receive prompt treatment per local standard of care.

5.2.3.1. Infusion Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Subjects should be closely monitored for such reactions. Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions. Management of zanidatamab-related infusion reactions are based on the grade of symptoms as outlined in Table 9.

Table 9: Zanidatamab Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Zanidatamab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for worsening symptoms. Institute medical management as described in the text following this table. Subsequent infusions should be given at the reduced infusion rate[a]. Consider additional premedications (e.g., H2 blockers) for subsequent infusions.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of the previous rate once infusion-related reaction has resolved. Closely monitor for worsening symptoms. Proper medical management should be instituted as described in the text accompanying this table. Subsequent infusions should be given after premedication and at the reduced infusion rate[a] Consider additional premedications (e.g., H2 blockers) for subsequent infusions.
Grade 3 – severe Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described in the text accompanying this table. Infusion should not be restarted even if signs and symptoms completely resolve. With medical monitor approval the subject may be dosed at the next scheduled treatment[a]. Consider additional premedications (e.g., H2 blockers for subsequent infusions).

	For recurrent Grade 3 reactions, permanently discontinue.
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The subject should be withdrawn from study drug treatment. Hospitalization is recommended.

NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

a Once the zanidatamab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it may only be increased for subsequent infusions with medical monitor approval; premedication for subsequent infusions must be administered per Section 5.2.7 and may be supplemented per institutional standards. If the subject has a second infusion-related reaction (≥ Grade 3) on the slower infusion rate, the infusion should be discontinued, and the subject should be withdrawn from zanidatamab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), antipyretic (e.g., acetaminophen or equivalent), and, if considered indicated, oral (PO) or IV glucocorticoids, bronchodilators, and oxygen.

NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to PO or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

If feasible, blood samples for evaluation of tryptase, PK and/or ADA should be drawn during or as soon as possible after an infusion reaction.

5.2.4. Storage and Handling

Zanidatamab must be stored in a controlled location, where access is limited to only designated site staff. Refer to the Pharmacy Manual for detailed drug storage information. Drug accountability procedures are also provided in the Pharmacy Manual.

5.2.5. Packaging and Labeling

Refer to the Pharmacy Manual for packaging and labeling.

5.2.6. Preparation

Detailed drug preparation and administration instructions are provided in the Pharmacy Manual.

5.2.7. Concomitant Therapy

All prior systemic anti-cancer therapies taken from the time of diagnosis will be captured in the CRF.

All medications being taken at the time of study entry should be continued as necessary and at a stable dose level and frequency, if possible, unless prohibited for study entry.

For additional guidance on required and concomitant medications, investigators should refer to region-specific prescribing information for each agent.

5.2.7.1. Required Concomitant Therapy

All subjects must receive mandatory prophylactic treatment for potential infusion reactions 30 to 60 minutes before the start of each zanidatamab infusion. Pretreatment should include corticosteroids, antihistamines, and acetaminophen at the following recommended doses:

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

If an alternative premedication regimen is thought to be required, the investigator must seek sponsor approval. Sponsor approval is required before implementation.

For subjects who experience an infusion reaction despite the above premedication, other medication as needed per the investigator or per institutional standards including histamine-2 receptor antagonists (H2 blockers) may be given in addition to the mandatory premedication.

5.2.7.2. Allowed Concomitant Therapy

Supportive therapy, including transfusions and bisphosphonates (e.g., Zometa®), is allowed on study. Supportive care treatments, including growth factors and colony-stimulating factors, are also allowed. Corticosteroid treatment is permitted only as follows:

- Topical, ocular, intra-articular, intranasal, and/or inhalational corticosteroids
- Physiologic replacement doses of systemic corticosteroids (i.e., < 15 mg/day prednisone)
- As part of premedication for zanidatamab
- For prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed hypersensitivity reaction caused by a contact allergen
- For acute medical conditions (higher doses permitted with medical monitor approval, but not to exceed 4 weeks)

Routine prophylaxis with vaccines is generally permitted; however, live vaccines are prohibited. All other therapies not specifically listed in the exclusion criteria or in prohibited therapy are allowed.

5.2.7.3. Prohibited Concomitant Therapy

Subjects may not receive cancer-related surgery, radiotherapy, other investigational, or systemic anti-neoplastic therapy during the study. Chinese or other herbal medicines for the treatment of cancer are also prohibited. Radiation therapy under certain circumstances (e.g., palliative radiation therapy to certain sites [non-target sites]) may be allowed with sponsor approval. Use of alternative supplemental therapies is discouraged and use of any such product must be recorded.

5.3. Duration of Study Treatment

Subjects may continue on study treatment until investigator-determined radiographic disease progression per RECIST 1.1, unequivocal clinical progression, unacceptable toxicity, consent withdrawal, physician decision, pregnancy, start of a subsequent anticancer therapy, or study termination by the sponsor. Every effort should be made to confirm disease progression radiographically. Only in instances where subjects appear to have unequivocal clinical progression and it is not possible or feasible for the subject to undergo radiologic assessment may investigators remove the subject from study treatment.

Subjects who discontinue treatment with zanidatamab for any reason should enter the 30-day follow-up period, as well as survival follow-up.

5.4. Management of Infusion Reactions and Other Adverse Reactions

Management of infusion reactions and other toxicities related to or associated with zanidatamab is described in Section 5.2.3. Required premedications as prophylaxis for zanidatamab infusion reactions are described in Section 5.2.7.1.

5.5. Treatment Compliance

Zanidatamab administration will be performed by study site staff and documented in source documents and the CRF.

6. STUDY ACTIVITIES

AEs and concomitant medications will be recorded from Day 1 (pre-dose) through the safety reporting period (see Section 7.8.1.3). Any study protocol-related SAE (defined in Section 7.8.1.1) as well as any concomitant medications given for treatment of the SAE, should be recorded from the time of signing the pre-screening or main informed consent for the study. A schedule of events is provided in Table 1. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

Guidance regarding the potential impact of COVID-19 on study enrollment and conduct is provided in the study manual.

6.1. Optional HER2 Pre-screening Visit (After Diagnosis and Prior to Screening Visit)

Subjects may be tested for HER2 status any time after diagnosis of advanced or metastatic disease and before study enrollment. The following assessments will be done at this optional visit:

- Informed consent for collection, storage, and analysis of the tumor tissue
- New tumor biopsy or archived tissue. Either an FFPE tissue block or a minimum of 10 freshly cut slides are required (see the Laboratory Manual for details). FNAs (cytology samples) and biopsies from sites of bone metastases are not acceptable. If there is enough biopsy tissue to provide at least 10 additional tissue slides, next

generation sequencing (NGS) testing can be performed, and the results shared (not applicable in China).

Once a prospective subject experiences disease progression or develops intolerance to their most recent prior therapy, the main consent for the remaining screening assessments listed below must be signed.

6.2. Screening Visit (Day –28 to 1)

The screening procedures listed below will be completed within 28 days before first administration of study treatment (C1D1). In case a subject cannot receive their first treatment within the required time windows for the screening assessments, rescreening should be performed.

Procedures done as part of standard of care within the 28-day window and meeting study requirements may be used for study purposes.

- Informed consent
- Medical history
- Eligibility (per the inclusion and exclusion criteria)
- Demographic data
- EQ-5D-5L and BPI questionnaires; administered prior to any other assessments
- Assessment of opioid use
- New tumor biopsy or archived tissue (only required if not done as part of pre-screening). Either an FFPE tissue block or a minimum of 10 freshly cut slides are required (see the Laboratory Manual for details). FNAs (cytology samples) and biopsies from sites of bone metastases are not acceptable. If there is enough biopsy tissue to provide at least 10 additional tissue slides, NGS testing can be performed and the results shared (not applicable in China).
- Disease assessment per RECIST 1.1 (CT/MRI scans)
- Brain scan (MRI or CT if MRI not feasible [CT with contrast unless medically contraindicated])
- Height
- Body weight
- Physical examination
- ECOG PS
- Vital signs
- Hematology, coagulation, and serum chemistry panels (including tryptase). The coagulation panel must be repeated at subsequent cycles if indicated.
- Urinalysis; must be repeated at subsequent cycles if indicated.

- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.
- Male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant.
- 12-lead ECG; must be repeated at subsequent cycles if indicated
- Echocardiogram/multigated acquisition scan (MUGA)
- Hepatitis B surface antigen, hepatitis C antibody, and HIV tests (HIV 1/2 Ag/Ab combination immunoassay)

6.3. Treatment Period

6.3.1. Cycle 1

6.3.1.1. Cycle 1 Day 1

Prior to dosing:

- Confirm subject eligibility per inclusion/exclusion criteria
- Body weight
- Physical exam (does not need to be repeated if completed for screening within the previous 3 days)
- ECOG PS (does not need to be repeated if completed for screening within the previous 3 days)
- Vital signs
- Hematology (does not need to be repeated if completed for screening within the previous 3 days)
- Serum chemistry (does not need to be repeated if completed for screening within the previous 3 days)
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead. Test does not need to be repeated if completed for screening within the previous 3 days.
- Male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant.
- Samples for:
  - ADA
  - ctDNA

- HER2 ECD
- PK

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

- Vital signs (within 30 minutes of the end of the infusion)
- Samples for PK as applicable

6.3.1.2. Cycle 1 Day 2

- Samples for PK (subjects undergoing extensive PK sampling only)

6.3.1.3. Cycle 1 Day 5

- Samples for PK (subjects undergoing extensive PK sampling only)

6.3.1.4. Cycle 1 Day 15 (±2 days)

Prior to dosing:

- Body weight
- Vital signs
- Hematology
- Serum chemistry
- Samples for:
  - ADA
  - HER2 ECD
  - PK

Administer study treatment:

- Zanidatamab administration

Post-dose activities

- Vital signs (within 30 minutes of the end of the infusion)
- Samples for PK

6.3.2. Cycle 2

6.3.2.1. Cycle 2 Day 1 (±2 days)

Prior to dosing:

- Body weight

- Physical exam
- ECOG PS
- Vital signs
- Hematology
- Serum chemistry
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.
- Male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant.
- Samples for:
  - ADA
  - PK

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

- Vital signs (within 30 minutes of the end of the infusion)
- Samples for PK

6.3.2.2. Cycle 2 Day 15 (±2 days)

Prior to dosing:

- Body weight
- Vital signs
- Hematology
- Serum chemistry
- Samples for:
  - ADA
  - HER2 ECD
  - PK

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

- Vital signs (within 30 minutes of the end of the infusion)
- Samples for PK

6.3.2.3. Cycle 2 Day 28 (±7 days)

- EQ-5D-5L and BPI questionnaires; administered prior to any other assessments
- Assessment of opioid use
- Disease assessment per RECIST 1.1 (CT/MRI scans)
- Samples for ctDNA

6.3.3. Each Subsequent 28-Day Cycle

6.3.3.1. Cycle 3 and Subsequent Cycles: Day 1 (±2 days)

Prior to dosing:

- Body weight
- Physical exam
- ECOG PS
- Vital signs
- Hematology
- Serum chemistry
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.
- Male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant.
- Echocardiogram/MUGA (within 7 days prior to Cycle 3 Day 1 and every 3 cycles thereafter [i.e., Day 1 of Cycle 6, 9, 12, etc. - 7 days])
- Samples for:
  - ADA (Cycles 4, 6, 8, 10, 12, 18, 24, and 36 only)
  - HER2 ECD (Cycles 4, 8, and 12 only)
  - PK (Cycles 4, 6, 8, 10, and 12 only; extensive PK sampling for 1 cycle for subjects participating in extensive steady-state PK schedule)

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

- Vital signs (within 30 minutes of the end of the infusion)
- Samples for PK (Cycles 4, 6, 8, 10, and 12 only)

6.3.3.2. Cycle 3 and Subsequent Cycles: Day 15 (±2 days)

Prior to dosing:

- Body weight
- Vital signs
- Hematology
- Serum chemistry
- Samples for PK (for 1 cycle at Cycle 4 or later, only for subjects participating in extensive steady-state PK schedule)

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

- Vital signs (within 30 minutes of the end of the infusion)

6.3.4. Every 8 Weeks (±7 days); Timed from Cycle 1 Day 1

- EQ-5D-5L and BPI questionnaires; administered prior to any other assessments
- Assessment of opioid use
- Disease assessment per RECIST 1.1 (CT/MRI scans; include brain scan for subjects with history or clinical suspicion of brain metastases; CT with contrast unless medically contraindicated).

6.4. End of Treatment Visit

The EOT visit will be performed for subjects who are withdrawn from treatment for any reason and will take place as soon as possible after a subject permanently stops study treatment (within 7 days after treatment discontinuation) unless delayed due to an AE. EOT evaluations must be performed before initiation of a new therapy. The date the subject met criteria for study treatment discontinuation and the reason for study treatment discontinuation will be recorded.

The following procedures will be performed at the EOT visit:

- Optional tumor biopsy at disease progression for subjects who provide additional consent
- EQ-5D-5L and BPI questionnaires; administered prior to any other assessments
- Assessment of opioid use
- Disease assessment per RECIST 1.1 (CT/MRI scans; not required if ≤4 weeks since previous scan; include brain scan for subjects with history or clinical suspicion of brain metastases; CT with contrast unless medically contraindicated)

- Physical examination
- ECOG PS
- Vital signs
- Hematology
- Serum chemistry
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.
- Male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant.
- 12-lead ECG
- Echocardiogram/MUGA (not required if ≤3 months since last scan)
- Samples for:
  - ADA
  - ctDNA (only at time of disease progression, if applicable)
  - HER2 ECD (only at time of disease progression, if applicable)
  - PK (only required if subject has completed less than 6 months of treatment)

6.5. Safety Follow-up (Approximately 30 Days After the Last Dose of Study Drug)

Approximately 30 days after the last dose of study drug, all subjects will have a follow-up visit, which will include the following assessments:

- Disease assessment per RECIST 1.1 (CT/MRI scans; only required if feasible, and last scan showed unconfirmed PR/CR and performed ≥4 weeks prior; include brain scan for subjects with history or clinical suspicion of brain metastases; CT with contrast unless medically contraindicated)
- Physical examination
- ECOG PS
- Vital signs
- Hematology
- Serum chemistry
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In

the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.

- Male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant.
- ADA samples (not required if ≤ 2 weeks since last sample)

Additionally, all AEs should continue to be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies, is lost to follow-up, or withdraws consent, or study closure.

6.6. Efficacy Follow-up (Every 8 Weeks)

Subjects who discontinue treatment with zanidatamab for reasons other than progressive disease or start of subsequent anticancer therapy will continue in follow-up with disease assessments (per RECIST 1.1 [CT/MRI scans; include brain scan for subjects with history or clinical suspicion of brain metastases; CT with contrast unless medically contraindicated]) approximately every 8 weeks (±7 days) after the previous scan until disease progression or start of subsequent anticancer therapy. Responses that are initially observed during this follow-up period should be confirmed with disease assessment 4 weeks (+7 days) later. Following progression or start of subsequent anticancer therapy, disease assessments will be discontinued, and subjects will enter long-term follow-up for survival status.

6.7. Survival Follow-Up

Subjects will be followed for survival after discontinuation of study treatment via telephone calls, medical records, and/or clinic visits approximately every 3 months (± 14 days; month = 30 days) after the last follow-up visit or as directed by the sponsor until death, lost to follow-up, withdrawal of consent, study completion, or study termination by the sponsor. Subsequent anti-cancer therapies initiated during follow-up will also be collected, if available.

7. STUDY ASSESSMENTS

A schedule of events is provided in Table 1.

7.1. Screening/Baseline Assessments

Only subjects who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Subject medical history includes a thorough review of significant past medical history, current conditions, and any treatment for prior malignancies and response to prior treatment.

Tumor biopsies will be collected from all subjects at either pre-screening or screening and processed as FFPE tissues to assess HER2 amplification, protein expression by IHC, and exploratory biomarkers of response. Archival tumor tissue may also be used. Subjects may be tested for HER2 status any time after diagnosis of advanced or metastatic disease and before study enrollment. An ISH assay is being developed as an investigational use only (IUO) reagent

for determining eligibility. An IHC assay is being developed an IUO reagent for assigning subjects to Cohort 1 or 2.

All samples will be run in a central laboratory under Clinical Laboratory Improvement Amendments (CLIA) guidelines. DNA and RNA may be isolated from tissue biopsies for characterizing gene expression and somatic mutations associated with response.

Tests for hepatitis B surface antigen, hepatitis C antibody, and HIV will be performed at screening. For female subjects of childbearing potential, screening for pregnancy will be performed at screening. These tests may be done using the blood samples taken for clinical chemistry. A urine pregnancy test is also acceptable.

7.2. Response/Efficacy Assessments

Tumor response will be evaluated at the visits outlined in the schedule of assessments (Table 1) based on CT and/or MRI scans (using the same methodology for each scan of the same subject; CT with contrast unless medically contraindicated) of the chest, abdomen, and pelvis plus additional areas of known or suspected tumor involvement including the brain for subjects with history or clinical suspicion of brain metastases. All CT and MRI imaging will be performed locally and submitted for centralized independent review. Additional imaging, such as nuclear bone scans, may be done as appropriate at the discretion of the investigator.

Disease response will be assessed according to RECIST 1.1 (Eisenhauer 2009) by ICR (primary endpoint) and investigator (secondary endpoint); responses are to be confirmed 4 weeks following initial documentation of objective response by investigator. Investigator assessment of response will be used for all treatment-related decisions.

Unequivocal clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers (e.g., increase in disease-related pain), or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. A marked deterioration in ECOG performance status may also indicate unequivocal clinical progression.

Every effort should be made to confirm disease progression radiographically. Only in instances where subjects appear to have unequivocal clinical progression and it is not possible or feasible for the subject to undergo radiologic assessment should investigators remove the subject from study treatment.

Subjects who discontinue treatment with zanidatamab for reasons other than progressive disease or start of subsequent anticancer therapy will continue in follow-up with disease assessments approximately every 8 weeks after the previous scan until disease progression or start of subsequent anticancer therapy. Responses that are initially observed during this follow-up period should be confirmed with disease assessment 4 weeks later. Following progression or start of subsequent anticancer therapy, disease assessments will be discontinued, and subjects will enter long-term follow-up for survival status.

Subjects' clinical data must be available for CRF source verification.

7.3. Pharmacokinetic Assessments

Venous blood samples for measurement of serum concentrations of zanidatamab will be drawn at selected timepoints as specified in the PK assessment schedules. The actual date and time

(24-hour clock time) of each sampling will be recorded in the subject's source document at the site.

The first 10 subjects enrolled in China and first 20 suitable subjects enrolled in the rest of world (suitability determined by the medical monitor) will be assigned to the more extensive PK schedule (Table 2). Further subjects will be then assigned to the sparse PK schedule (peak-trough, Table 3). Extensive PK for 1 cycle at steady state (Cycle 4 or later; Table 4) will be done for the first 10 suitable subjects in China who reach Cycle 4 and the first 20 suitable subjects in the rest of the world who reach Cycle 4 (suitability determined by the medical monitor).

The sampling window for each timepoint is presented in Table 2, Table 3, and Table 4. Deviations from planned sampling windows will be assessed before database lock for the impact on PK and may be excluded from timepoint summaries of PK concentrations. Actual time will be used for derivation of PK parameters.

Serum concentrations of zanidatamab will be measured as a function of time post-dosing. PK parameters to be estimated include the following: 1) for single (first) dose: maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the serum concentration-time curve from zero to the last measurable concentration (AUC_{0-t}), terminal elimination rate constant (λ_z), half-life ($t_{1/2}$), area under the serum concentration-time curve from zero to infinity ($AUC_{0-\infty}$), serum clearance (C_L), volume of distribution (V_d), etc.; and 2) for multiple doses: area under the serum concentration-time curve from zero to the end of dosing interval (AUC_{tau}), average concentration (C_{ave}) for Dose 1, C_{max} and minimum concentration (C_{min}) (trough) for subsequent doses, accumulation index, fluctuation ratio, steady state concentration (C_{ss}), and attainment of steady state.

Complete instructions for PK sample collection, processing, handling, and shipment will be provided in the Laboratory Manual.

If a subject experiences an AE that results in an unscheduled visit or meets SAE criteria, a blood sample for the measurement of serum concentrations of zanidatamab should be collected if less than 24 hours have elapsed since the last dose of zanidatamab, if possible. The sample will be recorded as unscheduled timepoint and may be also used in PK parameters derivation using actual time. An additional sample may also be drawn in the event of an infusion reaction.

7.4. Biomarker Studies

Blood and tumor tissue samples will be taken at selected timepoints specified in the assessment schedule (Table 1) for assessment of biomarkers. Biomarkers may include but are not limited to ctDNA, tumor tissue DNA and RNA, HER2 ECD, CA19-9, and post-treatment HER2 tumor status.

Tumor biopsies or archival tissues will be assessed for HER2 amplification, protein expression by IHC, and exploratory biomarkers of response. DNA and RNA may be isolated from tissue biopsies for characterizing gene expression and somatic mutations associated with response.

Tumor samples will also be used for developing candidate companion diagnostics (CDx) for this study, including but not limited to CDx bridging assays.

Only the biomarkers specified above will be tested on samples collected in Mainland China.

Complete instructions for biomarker sample collection, processing, handling, and shipment will be provided in the Laboratory Manual.

7.5. Immunogenicity Assessments

Blood samples to test for antibodies to zanidatamab will be obtained at selected timepoints specified in the assessment schedule (Table 1). Blood samples for ADAs will be taken before the start of the zanidatamab infusion. All ADA blood sample collection timepoints during the first 2 treatment cycles coincide with a pre-dose PK sample timepoint. If a subject terminates early from the clinical trial, all efforts will be made to collect blood samples to test for antibodies to zanidatamab unless consent has been withdrawn.

If a subject experiences an AE that results in an unscheduled visit or meets SAE criteria, a blood sample to test for antibodies to zanidatamab should be collected if less than 24 hours have elapsed since the last dose of zanidatamab, if possible. The sample will be recorded as unscheduled timepoint. An additional sample may also be drawn in the event of an infusion reaction.

The immunogenicity testing will be performed in 3 steps as follows: screening assay (Tier 1), confirmation assay (Tier 2), and titration (Tier 3). Only samples positive in the screening assay will be tested in confirmation and only samples positive in the confirmation assay will be further titrated to determine the titer of ADA.

For any samples that are confirmed positive for anti-zanidatamab antibody, there may be additional testing done to characterize domain specificity (T2a) and possibly neutralizing activity.

Complete instructions for ADA sample collection, processing, handling, and shipment will be provided in the Laboratory Manual.

Additional sample handling, processing, storage, labeling, and shipping instructions will be provided to the site in the Laboratory Manual.

7.6. Biospecimen Repository

For subjects who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by the sponsor and used for future research (not applicable in China), including but not limited to the evaluation of targets for novel therapeutic agents. No germ-line DNA testing will be performed. Blood and tissue samples donated for future research will be retained for a period of up to 5 years after study closure, or as permitted by local regulations. If additional consent is not provided, any remaining biological samples will be destroyed following study completion.

7.7. Quality of Life and Disease-Related Pain Assessments

The EQ-5D 5-L questionnaire will be used to assess overall quality of life. If possible, the questionnaire should be completed before any other procedures at the study visits noted in the schedule of events (see Table 1). The EQ-5D-5L consists of a visual assessment scale to assess overall health status and the 5-dimensional score assesses health status in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response

levels: no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems.

The Brief Pain Inventory (BPI) short form will be used to assess disease-related pain. The BPI rapidly assesses the severity of pain and its impact on functioning and is widely used in clinical trials. The BPI pain items assess worst pain in the last 24 hours, least pain in the last 24 hours, pain on average, and pain right now. The BPI interference items include general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.

7.8. Safety Assessments

Assessment of safety during the course of this study will consist of the surveillance and recording of AEs including AESIs, SAEs, clinical laboratory tests, concomitant medications, including opioids, over-the-counter medications, and herbal therapies, and physical examination findings. Other safety assessments include evaluation of ECOG PS, vital signs, ECGs, and echocardiogram/MUGA.

Safety and study conduct will be monitored by an IDMC, who will be tasked with monitoring the safety of participants through regular and/or ad hoc meetings (see Section 9.4.12).

7.8.1. Adverse Events

7.8.1.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, IND Safety Reporting, an AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events CRF:

- From the time of signing the pre-screening or main informed consent for the study through Cycle 1 Day 1 pre-dose, only study protocol-related SAEs should be recorded. A protocol-related SAE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All AEs (regardless of relationship to study drug) should be recorded from Cycle 1 Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.8.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE,

or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets 1 of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing in-patient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Important medical event:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent 1 of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

Adverse Event Severity

AE severity should be graded using the NCI-CTCAE, version 5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. "Severity" characterizes the intensity of an AE. "Serious" is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to the study drug should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture) There is a reasonable possibility of a relationship based on facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible.

7.8.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

The investigator should use precise medical terminology when recording AEs or SAEs. Avoid colloquialisms and abbreviations.

Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE. However, medically important events that may be linked and/or separated in time should be recorded as independent events on the eCRF. For example, if severe hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such an event should be recorded only once unless its severity increases or decreases (in which case it should be recorded again).

A recurrent AE is one that occurs and resolves between subject evaluation time points, but then subsequently recurs. All recurrences of the AE should be recorded as separate events.

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form. The following should be considered when recording SAEs:

- Death is an outcome of an event. The primary cause of death as assessed by the investigator should be recorded and reported as the SAE term on both an SAE form and CRF. If the cause of death is truly unknown, then “Death of Unknown Cause” can be used as the SAE term for the initial report. Once the cause of death is known, the event term should be updated on a follow-up report.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Cancer

Clinical manifestations of disease progression that meet the criteria for a SAE must be reported. Do not use the term ‘disease progression’ alone when reporting SAEs, because it is too nonspecific. Symptoms of disease progression that meet the criteria for an SAE must be reported. When possible, report the specific disease (clinical) manifestation of the progression (e.g., ‘malignant pleural effusion’, ‘spinal bone metastases’, ‘lymphadenopathy’, ‘brain metastases’).

Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 12 months after the last dose of study drug including any pregnancies that occur in the partner of a male study subject. Only report pregnancies that occur in a male subject's partner if the estimated date of conception is after the male subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 24 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported.

Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug will also be recorded on the Adverse Events CRF.

Abortion, whether therapeutic or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the "serious" criterion above (see definitions Section 7.8.1.1) should be reported as SAEs.

7.8.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from the start of study drug dosing on Cycle 1 Day 1 to 30 days after the last dose of study drug. However, all study protocol-related SAEs are to be recorded from the time of signing the pre-screening or main informed consent for the study. All SAEs that occur after the safety reporting period and are considered related to prior zanidatamab study drug treatment in the opinion of the investigator should also be reported to the sponsor.

All AEs (including SAEs and AESIs) will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies, is lost to follow-up, or withdraws consent, or study closure.

7.8.1.4. Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Investigator assessment of causality
- Study treatment

The completed SAE form is to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form).

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.8.1.5. Sponsor Safety Reporting to Regulatory Authorities

The sponsor will report all SAEs to regulatory authorities as required per local regulatory reporting requirements.

7.8.2. Adverse Events of Special Interest

AESIs are infusion-related reactions, non-infectious pulmonary toxicities, and cardiac events of absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value < 50%, and/or grade ≥ 2 heart failure. AESIs should be recorded as AEs and reported as SAEs when appropriate.

Additional data related to AESIs may be collected in the CRF.

7.8.3. Clinical Laboratory Tests

Samples for clinical laboratory tests will be obtained at selected timepoints specified in the assessment schedule (Table 1).

Clinical laboratory analyses will be performed at local laboratories. Any abnormalities in any of the laboratory parameters will be judged in relation to the reference ranges from the laboratory and to the clinical relevance assessed by the investigator.

The following hematology parameters will be determined:

- Hemoglobin
- Hematocrit
- White blood cell (WBC) count (total and differential)
- RBC count
- Platelet count
- Mean corpuscular volume
- Mean cell hemoglobin (MCH)
- MCH concentration

Coagulation parameters such as prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) will also be required at specified timepoints.

The following clinical chemistry parameters will be measured:

- Creatinine, urea (or blood urea nitrogen [BUN])
- AST
- ALT
- Alkaline phosphatase
- Lactate dehydrogenase
- Total bilirubin
- Albumin

- Total protein
- Sodium
- Potassium
- Chloride
- Glucose
- Uric acid
- Calcium
- Magnesium
- Tryptase (if test is available, only at screening and within 24 hours of an infusion reaction)

The estimated GFR should be calculated using the MDRD equation as applicable, with serum creatinine (Scr) reported in mg/dL as follows:

- GFR (mL/min/1.73 m^2) = 175 x $(Scr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

Urine will be screened for pH, glucose, ketones, blood, protein, and microscopy (if indicated).

For female subjects of childbearing potential, pregnancy tests will be performed at screening and at predetermined timepoints specified in the assessment schedule (see Table 1). These tests may be done using the blood samples taken for clinical chemistry. A urine pregnancy test is also acceptable.

7.8.4. Vital Signs

Vital signs measurements include heart rate, blood pressure, respiratory rate, and temperature. Vital signs will be recorded at selected timepoints specified in the assessment schedule (Table 1) and performed in a standardized manner (i.e., after the subject has rested in the sitting position for 5 minutes). Post-dose assessments should be done within approximately 30 minutes after the end of the zanidatamab infusion.

7.8.5. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Height will only be measured at screening.

7.8.6. ECOG Performance Status

ECOG PS will be assessed at selected timepoints specified in the assessment schedule (Table 1). ECOG PS scores are described in Appendix A.

7.8.7. Electrocardiogram

12-lead ECGs will be recorded at selected timepoints specified in the assessment schedule (Table 1) and as clinically indicated. The ECG will be recorded after at least a 10-minute rest.

The date and an overall interpretation of the ECG will be recorded in the CRF. The interpretation of the ECG will be assessed as normal or abnormal, and if abnormal as clinically significant or not. If the ECG is considered abnormal and clinically significant, the abnormality must be recorded in the CRF. At least the following parameters should be assessed: heart rate, PR interval, QRS complex, and QTcF. See Appendix C for the equation to calculate QTcF.

7.8.8. Echocardiogram/MUGA

Echocardiograms or MUGA scans are recorded at selected timepoints specified in the assessment schedule (Table 1). Echocardiograms or MUGAs will be recorded locally and will be assessed for an estimate of the ejection fraction. The same method must be used throughout the study. Management of left ventricular dysfunction is described in Section 5.2.3.

7.9. Appropriateness of Measurements

The RECIST 1.1 criteria used to assess efficacy in this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Pharmacokinetic assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to zanidatamab.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audits during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities or the institutional review board (IRB)/independent ethics committee (IEC) at their discretion.

The investigator must permit the IRB/IEC, the sponsor's auditors, and representatives from regulatory authorities to have direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs. Subject confidentiality will be protected at all times.

8.2. Monitoring

Data for each subject will be recorded on a CRF. Data collection must be completed for each subject who signs an ICF and undergoes any screening assessment.

In accordance with GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

A clinical monitoring plan will detail the tasks to be completed at each monitoring visit. This will include the following at a minimum:

- Site monitoring procedures including review of the ICF, source document review, source data verification, and review of CRF data
- AE and SAE reporting
- Investigational product receipt, ordering, preparation and administration, storage, documentation, accountability, dosing compliance, and return/destruction

The monitoring visits also provide the sponsor with the opportunity to ensure the investigator's obligations and all applicable ICH or health authority regulation requirements are being fulfilled.

The investigator must permit the monitor direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs. Subject confidentiality will be protected at all times.

8.3. Data Management and Coding

Study centers will enter data directly into an electronic data capture system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Changes to data previously entered into the electronic data capture system will be recorded in the audit trail and will be FDA 21 CFR Part 11 compliant and/or meet other region-specific electronic records regulatory requirements.

Adverse events and pre-existing conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and medications will be coded using the World Health Organization (WHO) Drug Dictionary. Missing or inconsistent data will be queried in the electronic database to the investigator for clarification. Subsequent modifications to the database will be documented.

8.4. Drug Accountability

Each site will verify their inventory of study drug supplies throughout the study and verify that study drug is received intact and in the correct amounts. The monitor may check the study supplies at each study center at any time during the study.

The study monitor will ensure that the site has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log. A full drug accountability log will be maintained at the study center at all times. All discrepancies must be accounted for and documented.

9. DATA ANALYSIS METHODS

9.1. Statistical Hypotheses

This is a single-arm, open-label study. No statistical hypotheses will be tested.

9.2. Determination of Sample Size

This study will enroll approximately 100 subjects: approximately 75 subjects in Cohort 1 and approximately 25 subjects in Cohort 2. No formal sample size calculations were performed.

Approximately 75 subjects will be enrolled in Cohort 1 to evaluate the primary endpoint of confirmed ORR for the primary analysis of efficacy. The 2-sided Clopper-Pearson exact binomial 95% confidence intervals (CIs) that could be observed with this sample size are listed in Table 10.

Table 10: Clopper-Pearson 95% Confidence Intervals for N = 75 Subjects

Confirmed ORR		95% CI	
Percent	Responses	Lower	Upper
20.0%	15	11.7%	30.8%
25.3%	19	16.0%	36.7%
30.7%	23	20.5%	42.4%
36.0%	27	25.2%	47.9%
40.0%	30	28.9%	52.0%
45.3%	34	33.8%	57.3%
50.7%	38	38.9%	62.4%

Approximately 25 subjects will be enrolled in Cohort 2 to evaluate the primary endpoint of confirmed ORR as a secondary analysis of efficacy. The 2-sided Clopper-Pearson exact binomial 95% CIs that could be observed with a sample size of 25 subjects are listed in Table 11.

Table 11: Clopper-Pearson 95% Confidence Intervals for N=25 Subjects

Confirmed ORR		95% CI	
Percent	Responses	Lower	Upper
20.0%	5	6.8%	40.7%
24.0%	6	9.4%	45.1%
28.0%	7	12.1%	49.4%
32.0%	8	15.0%	53.5%
36.0%	9	18.0%	57.5%
40.0%	10	21.1%	61.3%
44.0%	11	24.4%	65.1%
48.0%	12	27.8%	68.7%

With a sample size of 100 subjects (Cohorts 1 and 2 combined), the probabilities of detecting 1 or more treatment-emergent adverse events (TEAEs) for various frequencies of occurrence in this population are listed in Table 12.

Table 12: Probabilities of Detecting ≥ 1 Adverse Event

Frequency of Adverse Event	Binomial Probability
0.1%	0.10
1%	0.63
5%	0.99

9.3. Analysis Sets

For the purposes of analysis, the subject analysis sets are defined in Table 13.

Table 13: Subject Analysis Sets

Analysis Set	Description
Enrolled	All participants who sign the main study informed consent, were eligible for the study, and received approval to enroll at the end of Screening.
Safety	All safety evaluable subjects enrolled in Cohorts 1 and 2. A subject is considered safety evaluable if they received any amount of zanidatamab.
Efficacy	The following Efficacy Analysis Sets will be evaluated for this study: • Cohort 1 (Primary) - Includes all safety evaluable subjects enrolled in Cohort 1. The primary analysis of efficacy will be performed using this analysis set. • Cohort 2 - Includes all safety evaluable subjects enrolled in Cohort 2.
Response Evaluable	The following Response Evaluable Analysis Sets will be evaluated for this study: • Cohort 1 - Includes all response evaluable subjects enrolled in Cohort 1 • Cohort 2 - Includes all response evaluable subjects enrolled in Cohort 2 Response Evaluable includes all subjects in the safety analysis set with measurable disease and at least 1 evaluable post-baseline disease assessment (per RECIST 1.1) or who discontinued study treatment due to death or unequivocal clinical progression. In the event of significant discordance between the set of subjects identified as response evaluable by the investigator and ICR, the following 2 Response Evaluable Analysis Sets may be evaluated for each of the above cohorts: • ICR Response Evaluable • Investigator Response Evaluable

9.4. Statistical and Analytical Plans

The statistical analysis plan (SAP) will be written and finalized prior to database lock and will provide additional details regarding the statistical methods, endpoints, and analyses to be performed, and deviations from the statistical analysis methods described in the protocol. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.4.1. General Considerations

The final analysis of the study will be conducted after the final database lock for the study.

9.4.1.1. Randomization and Blinding

This is a single-arm, open-label study; therefore, no randomization or blinding will be performed.

9.4.1.2. Adjustments for Covariates

No adjustments for covariates will be performed.

9.4.1.3. Handling of Dropouts and Missing Data

For the purpose of cohort assignment, subjects missing IHC results will be assigned to Cohort 1. Further details for the handling of missing, unused, or spurious data will be described in the SAP.

9.4.1.4. Multicenter Studies

No formal comparisons between sites will be performed.

9.4.1.5. Multiple Comparisons and Multiplicity

No adjustments for multiple comparisons will be performed.

9.4.1.6. Data Transformations and Derivations

Data transformations, conventions, and derivations will be detailed in the SAP.

9.4.1.7. Examination of Subgroups

Subgroup analysis of the primary endpoint by BTC histology type will be performed. Selected secondary efficacy endpoints may also be evaluated by this subgroup.

9.4.2. Subject Disposition

An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.4.3. Subject Characteristics

Baseline demographic and disease characteristics will be summarized using counts and percentages for categorical variables and summary statistics (e.g., mean, quartiles, standard deviation, and range) for continuous variables.

9.4.4. Treatment Compliance

Not applicable.

9.4.5. Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Version 2009 or higher, and listed and summarized by preferred term using counts and percentages. Multiple occurrences of the same medication within a subject will be summarized only once.

The change from baseline in opioid use will be summarized over time and at the time of a subject's best overall response.

9.4.6. Efficacy Analyses

The endpoints listed below will be evaluated based on both the ICR and the investigator RECIST 1.1 response assessments.

The primary analysis of efficacy will evaluate these endpoints and the primary endpoint, confirmed ORR, for subjects in the Cohort 1 Primary Efficacy Analysis Set. Secondary analyses of these endpoints will evaluate these endpoints for the Cohort 2 Efficacy Analysis Set (see Section 9.3). If a meaningful treatment effect is observed in Cohort 2, a pooled efficacy analysis of Cohort 1 + 2 may be performed.

9.4.6.1. Best Overall Response

Best overall response (BOR) is defined as the BOR per RECIST 1.1 prior to any of the following occurring for a subject:

- Receipt of non-protocol specified anticancer therapy
- Documented disease progression
- Death from any cause
- Subject withdrawal of consent

Confirmed BOR requires confirmation of CR or PR a minimum of 4 weeks from the initial response.

BOR and confirmed BOR will be summarized using counts and percentages.

9.4.6.2. Objective Response Rate

Objective response is defined as achieving a BOR of CR or PR per RECIST 1.1. The proportion of subjects with an objective response and the corresponding exact binomial 95% CI will be calculated.

Confirmed objective response is defined as achieving a confirmed BOR of CR or PR per RECIST 1.1. The primary endpoint for this study is the confirmed ORR based on the ICR response assessments evaluated for the Cohort 1 Primary Efficacy Analysis Set. A secondary endpoint of confirmed ORR will also be computed based on the investigator response assessments. For each endpoint, the proportion of subjects with a confirmed objective response and the corresponding exact binomial 95% CI will be calculated.

9.4.6.3. Progression-free Survival

PFS is defined as the time from the first dose of study treatment to the date of documented disease progression (per RECIST 1.1), clinical progression, or death from any cause.

Unequivocal clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers (e.g., increase in disease-related pain), or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. A marked deterioration in ECOG performance status may also indicate unequivocal clinical progression. Subjects who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment that was a CR, PR, or SD. Details of the censoring scheme for this analysis will be described in the SAP.

Kaplan-Meier plots and estimates of the quartiles and their corresponding 95% CI will be computed.

9.4.6.4. Disease Control Rate

Disease control is defined as a best response of CR, PR, or SD per RECIST 1.1. The proportion of subjects who achieve disease control and the corresponding exact binomial 95% CI will be calculated.

9.4.6.5. Duration of Response

DOR is defined as the time from the first objective response (CR or PR) to documented PD per RECIST 1.1, clinical progression, or death from any cause. Only subjects who achieve a confirmed response in the Safety Analysis Set will be included in the analysis. Details of the censoring scheme for this analysis will be described in the SAP.

Kaplan-Meier plots and estimates of the quartiles and their corresponding 95% CI will be computed.

In addition, the proportion of subjects with a DOR ≥ 16 weeks and the corresponding exact binomial 95% CI will be calculated.

9.4.6.6. Overall Survival

OS is defined as the time from the first dose of study treatment until the date of death from any cause. Subjects who are alive at the time of analysis or were lost to follow-up will be censored at the date they were last known to be alive (i.e., right censored). Details of the censoring scheme for the analysis of OS and imputation methods for partial or missing dates of death or last contact will be described in the SAP.

Kaplan-Meier plots and estimates of the quartiles and their corresponding 95% CI will be computed.

9.4.7. Pharmacokinetic Analyses

Serum concentrations of zanidatamab will be measured as a function of time post-dosing. PK parameters to be estimated include the following: 1) for single (first) dose: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t_{1/2}$, $AUC_{0-\infty}$, CL, V_d, etc.; and 2) for multiple doses: AUC_{tau}, C_{ave} for Dose 1, C_{max} and C_{min} (trough) for subsequent doses, accumulation index, fluctuation ratio, C_{ss}, and attainment of steady state.

The following PK parameters will be determined for steady-state extensive PK sampling: $AUC_{tau,ss}$, $C_{ave,ss}$, $C_{min,ss}$, $C_{max,ss}$, λ_z, $t_{1/2}$, and V_z.

9.4.8. Immunogenicity Analyses

If applicable, the occurrence of ADAs will be summarized using counts and percentages by zanidatamab dose level and nominal timepoint. Titers for confirmed positive ADA will be summarized using descriptive statistics (n, arithmetic mean, geometric mean, median, standard deviation, range, coefficient of variance). The duration and time of onset of anti-drug antibodies may also be summarized using descriptive methods.

All immunogenicity analyses will be based on the Safety Analysis Set.

9.4.9. Biomarker Analyses

Potential biomarkers will be summarized using descriptive statistics (i.e., n, arithmetic mean, geometric mean, median, standard deviation, range, coefficient of variance). Details will be described separately in the SAP.

9.4.10. Safety Analyses

The endpoints listed below will be evaluated for the Safety Analysis Set.

9.4.10.1. Extent of Exposure

Zanidatamab exposure will be summarized using counts and percentages for categorical variables and summary statistics (mean, median, standard deviation, and range) for continuous variables.

Information to be summarized includes duration of exposure, relative dose intensity (%), the total frequency of and reasons for delayed and prematurely discontinued infusions, and the number treatment cycles initiated.

9.4.10.2. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. All AEs will be coded by the Sponsor to standard "preferred terms" and system organ classifications (SOC) using MedDRA. Severity will be graded by study investigators using NCI-CTCAE v5.0.

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 frequency of TEAEs will be summarized by preferred term and SOC using counts and percentages. Multiple occurrences of the same AE within a subject will be summarized only once at the most severe grade level for the time frame under consideration. For summaries by severity, only the worst grade for an AE will be counted for a particular subject. AEs occurring prior to the first dose of zanidatamab or more than 30 days after the last dose of zanidatamab will be excluded from summaries but included in data listings. In addition, treatment-related AEs and AEs which lead to premature discontinuation of study treatment will summarized.

9.4.10.3. Deaths and Serious Adverse Events

The frequency of deaths will be summarized using counts and percentages. By-subject listings of deaths will also be produced.

The frequency of SAEs will be summarized by SOC and preferred term using counts and percentages. Treatment-related SAEs will also be summarized.

9.4.10.4. Clinical Laboratory Results

Laboratory results will be graded using NCI-CTCAE v5.0 and summarized by laboratory test and toxicity grade using counts and percentages. For each laboratory test, only the worst (i.e.,

highest) toxicity grade will be counted for subjects with multiple toxicities within a time period (including scheduled and unscheduled assessments).

9.4.10.5. Cardiac Function

The frequency of ECG abnormalities (e.g., heart rate, PR interval, QRS complex, and QTcF) will be summarized using counts and percentages. In addition, the percentage of subjects with LVEF < 50% and ≥ 50% and with an absolute decrease ≥ 10 percentage points from baseline LVEF will be summarized.

The frequency of QTc interval increases from baseline (< 30 msec, 30–60 msec, and > 60 msec) and the frequency of QTc interval prolongations ≥ 470 msec during the treatment period will each be summarized using counts and percentages. For both endpoints, the worst value for each subject during the treatment period will be summarized.

9.4.10.6. Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be summarized using descriptive statistics (i.e., mean, median, standard deviation, and range).

9.4.10.7. ECOG Performance Status

ECOG PS over time will be listed by subject. The baseline status, worst status post-baseline, and status at EOT will be summarized using counts and percentages.

9.4.10.8. Quality of Life and Disease-Related Pain Analyses

PRO based on the EQ-5D-5L will be summarized over time with descriptive statistics by visit, using the Safety Analysis Set. In addition, the change from baseline in BPI domain scores will be summarized over time and at the time of a subject's best overall response.

9.4.11. Timing of Analyses

The primary analysis of efficacy will be performed approximately 6 months after the last subject has been enrolled in Cohort 1 of the study.

9.4.11.1. Interim Analyses

No interim analyses will be performed.

9.4.12. Independent Data Monitoring Committee

Safety and study conduct will be monitored throughout the study by an IDMC. The committee is tasked with monitoring the safety of participants in this study through regular and/or ad hoc meetings. An IDMC meeting will be held after the first 25 subjects have received at least 1 dose of zanidatamab. After the first IDMC meeting, subsequent meetings will be held quarterly to review cumulative safety data to identify any potential new safety signals. An additional IDMC meeting will be held at least 28 days after the tenth subject enrolled in China has received 1 dose of zanidatamab to review safety. The IDMC will be responsible for making recommendations to the sponsor as to appropriate study direction; further details will be provided in the IDMC charter.

10. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

10.1. Institutional Review Board/Independent Ethics Committee

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval or favorable opinion of the study and all relevant study information must be obtained before the study center can be initiated. Any necessary extensions or renewals of IRB/IEC approval/favorable opinion must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IRB/IEC together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IRB/IEC as required. On completion of the study, the IRB/IEC will be notified that the study has ended.

10.2. Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended, as required.

10.3. Ethical Conduct of the Study

The investigator(s) and all parties involved in this study must conduct the study in accordance with the protocol, and in adherence to the ethical principles based on the Declaration of Helsinki and GCP, the applicable ICH guidelines, and the applicable national, regional, and local laws and regulatory requirements.

10.4. Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has been presented with the risks and benefits and given written informed consent to participate in the study, unless the procedure was done as part of standard of care. Pre-screening of HER2 status, after the subject consents to allow the central laboratory analysis/review of HER2 status, is allowed before written informed consent for all other study procedures is given.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study in simple terms, using the IRB/IEC-approved ICF. The subject will be given every opportunity to ask for clarification of any points he or she does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects who

choose to participate will be required to sign and date the ICF. After dated signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their legally authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be submitted to the IRB(s)/IEC(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

10.4.1. Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRB(s)/IEC(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA 1996) and applicable national and/or local laws and regulations on personal data protection and consistent with the ICFs or authorizations from the study subjects. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding, de-identification, or pseudonymization of subject identities.

10.5. Study Documentation and Records Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives.

Essential documents should be retained for whichever is the longest of the following:

- Two years after the final marketing approval
- At least 2 years since the discontinuation of clinical development of the investigational product
- The time period required by the applicable law or regulatory requirements.

It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-

related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

10.6. Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the study, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the Clinical Trial Agreement.

11. REFERENCES

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APPENDIX A. ECOG PERFORMANCE STATUS SCALE

ECOG	
Score	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B. INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled A Phase 2b, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers.

I, the undersigned, have read and understood the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement.

Investigator Signature Date

Investigator Name, Printed

APPENDIX C. QTCF EQUATION

QTcF (duration of QT interval using Fridericia's correction) should be calculated using the following equation:

$$QTc_F = \frac{QT}{\sqrt[3]{\frac{RR}{1\ s}}}$$

Where QT = duration of QT interval, RR = duration of RR interval, and s=seconds

APPENDIX D. DOCUMENT HISTORY

Version	Date
Original	13-Feb-2020
Amendment 1	26-Apr-2020
China-specific Amendment 1	23-Jul-2020
Amendment 2 (including changes in China-specific Amendment 1)	21-Apr-2021
Amendment 3	08-Sep-2023

Summary of Changes in Amendment 3		
Section(s)	**Change**	**Rationale**
Global	• Updated name and organizational affiliation of medical monitor • Changed name and address of Sponsor (Rest of World) from Zymeworks Inc. to Jazz Pharmaceuticals, Inc. • Added information for Sponsor's US Representative • Added JZP598 as a synonym for zanidatamab • Added EU CT number	Administrative changes. Incorporated the most current Sponsor and Medical Monitor information, which has changed since the last amendment as a result of Jazz Pharmaceuticals, Inc's acquisition of zanidatamab from Zymeworks, Inc.

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Title page and page headers	Updated date and amendment number	To update the information for Amendment 2
Title page	Updated medical monitor information	Administrative change
Throughout protocol	Minor clarifications/corrections	To provide clarity and consistency
Throughout	Changed “ZW25” to “zanidatamab”	Administrative change
Section 1.2 Section 1.4 Section 3.2	Added information on a recently approved therapy for bile duct cancer and recently approved HER2-targeted therapies	To provide current information
Synopsis Section 3.1 Section 4.1	Revised Inclusion Criterion 3 pertaining to prior chemotherapy regimens	Clarification
Synopsis Section 4.1	Revised description of women of childbearing potential in Inclusion Criterion 13, and replaced list of contraception methods with reference to appropriate section of protocol	To make language consistent with Inclusion Criterion 12, at the request of a health authority To avoid duplication
Synopsis Section 4.2	Revised Exclusion Criterion 6 to specify exclusion of subjects with infected biloma rather than any biloma	To ensure subjects are not excluded unnecessarily
Synopsis Section 4.2	Revised Exclusion Criterion 7 to apply to any malignancy, not just invasive malignancy	To make the criterion more straightforward
Synopsis Section 4.2	Revised Exclusion Criterion 15 so that Grade 2 peripheral sensory neuropathy is an exception to the exclusion of clinically significant toxicity (Grade 2 or higher) associated with prior cancer therapies	To ensure subjects are not excluded unnecessarily, as many subjects would have received prior treatment with cisplatin or oxaliplatin and may have neuropathy associated with that treatment

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Synopsis Table 1 Section 3.1 Figure 1 Section 4.4.1 Section 6.6 Section 7.2	Radiographic efficacy assessments are to continue for subjects who discontinue treatment with zanidatamab for reasons other than progressive disease or start of subsequent anticancer therapy. These assessments will continue in follow-up with disease assessments approximately every 8 weeks (±7 days) after the previous scan until disease progression or start of subsequent anticancer therapy. Responses that are initially observed should be confirmed with disease assessment 4 weeks (+7 days) later. Following disease progression or start of subsequent anticancer therapy, disease assessments will be discontinued, and subjects will enter long-term follow-up for survival status.	To enable accurate determination of duration of response
Table 1 Section 6.2 Section 6.3.4 Section 6.4 Section 6.5 Section 6.6 Section 7.2	Added option for screening brain scan by CT if MRI not feasible, and specified that subjects with history or clinical suspicion of brain metastases should have repeat MRI or CT at time of all tumor restaging. CT is to be performed with contrast unless medically contraindicated.	To allow flexibility for assessments and obtain information on possible brain metastases

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Synopsis Section 3.1 Section 7.8.2	Adverse events of special interest are modified to include: infusion-related reactions, non-infectious 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	For consistency across the zanidatamab program
Section 5.2.7.1	Added that any alternative premedication regimen must be approved by Sponsor before implementation	For consistency with synopsis
Table 1 Section 6.3.3.1	Clarified that MUGA/echocardiogram should be performed every 3 cycles, within 7 days prior to Day 1 of the cycle	Clarification of timing
Table 1 Section 6.2 Section 6.3.1.1 Section 6.3.2.1 Section 6.3.3.1 Section 6.4 Section 6.5	For visits at which female subjects of childbearing potential have a pregnancy test, male subjects with partners of childbearing potential will be asked to confirm their partner is not pregnant	To ensure reporting of any pregnancy in partners of male study subjects
Table 2, Table 3	PK assessment windows are widened for certain timepoints	For the convenience of study subjects
Synopsis Table 2 Section 7.3	Increased the total number of subjects to undergo initial extensive PK sampling from 16 to 30	To ensure adequate data is obtained to characterize PK

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Synopsis Table 1 Table 4 Section 6 Section 7.3 Section 9.4.7	Added extensive PK sampling at steady state (Cycle 4 or later) for the first 10 suitable subjects in China who reach Cycle 4 and first 20 suitable subjects in the rest of the world who reach Cycle 4 (suitability determined by the medical monitor)	To enable collection of additional extensive PK data in subjects who have received at least 4 cycles of zanidatamab plus combination chemotherapy to provide information on steady-state PK
Synopsis Section 3.1 Section 7.4	Post-treatment HER2 tumor status is added as a biomarker assessment	To provide information about the effect of treatment on HER2 tumor status
Synopsis Table 1 Section 3.1 Section 7.4	[redacted]	[redacted]
Synopsis Section 3.1 Section 7.4	Only specified biomarkers will be tested on samples collected in Mainland China	To comply with health authority guidelines
Section 4.3.1	Removed follow-up for any baby born to a female subject or female partner of a male subject who became pregnant during the study	There is no mechanism for collecting and storing this information
Section 4.3.2 Table 5	Clarified that subjects should not simultaneously use more than one form of hormonal contraception associated with inhibition of ovulation	At the request of a health authority
Section 5.2.2	Removed option for 60-minute infusion, but added option for infusion duration of less than 90 minutes provided maximum infusion rate is not exceeded	Maximum infusion rate is 250 mL/hour, and it is unlikely that infusion volume would be less than 250 mL

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Section 5.2.3 Table 7	Revised guidance for management of potential zanidatamab-associated toxicities, including dose modifications for nausea/vomiting, diarrhea, rash, and other toxicities	To clarify guidance for managing potential zanidatamab-related AEs, including recommended zanidatamab dose modifications for severe AEs of vomiting, diarrhea, rash, and other toxicities
Section 5.2.3, Table 8 Section 5.2.3.1, Table 9	Revised guidance for management of LVEF dysfunction and infusion-related reactions	To align with program-level assessment of cardiac risk and infusion reactions
Section 5.2.3	Provided guidance for management of pulmonary toxicity	To provide guidance to the investigator in the event of pulmonary toxicity
Section 5.2.3.1 Section 6.2 Section 7.8.3	Added assessment of tryptase at screening and within 24 hours of an infusion-related reaction, if the test is available	To obtain information on the nature of the infusion-related reaction
Section 5.2.7	Added statement referring investigators to region-specific prescribing information for additional guidance on required and concomitant medications	To support compliance with prescribing information
Section 5.2.7.2	Added the following statement: “Routine prophylaxis with vaccines is generally permitted; however, live vaccines are prohibited.”	To provide further guidance to sites about vaccines
Section 6	Added statement that guidelines to follow regarding the effect of COVID-19 on study conduct and enrollment are provided in the study manual	COVID-19 may affect study enrollment and conduct, and these effects vary by region and country, so specific COVID-19 guidelines are provided in the study manual
Section 6.1, Section 6.2	Added option for next generation sequencing and sharing of those results if an additional 10 tissue slides are provided (not applicable in China)	Results of next generation sequencing may provide information that would inform treatment decisions, which would provide a benefit to the subject

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Table 1 Section 6.4	The timing of the end-of-treatment visit is changed from within 7 days after the last dose to within 7 days after treatment discontinuation (unless delayed due to an AE)	Due to the timing of disease assessments, a decision to discontinue treatment could occur at a point in the cycle at which it would not be possible to perform the end-of-treatment visit within 7 days of the last dose
Section 7.1	Removed collection of current medications during screening	The only concomitant medications to be collected during screening are those used to treat study protocol-related SAEs, if applicable
Section 7.5	Specified that only samples positive in the confirmation assay would be further titrated to determine titer of ADA	Clarification
Section 7.6	Specified that the future use of remaining blood and/or tissue samples for subjects who provided additional consent would not be applicable in China	To comply with health authority guidelines
Section 7.8	Specified that over-the-counter medications and herbal remedies would be collected as concomitant medications	To ensure complete collection of all concomitant medications taken by subjects
Section 7.8.1	Removed the time requirement of ≥ 24 hours hospitalization for an AE to be classified an SAE	The 24-hour period is not a requirement, and it is more conservative to classify any AE resulting in hospitalization as an SAE
Section 7.8.1	Changed descriptor of SAE criteria category from “medically significant” to “important medical event”	To align terminology

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Section 7.8.1.2	Clarified reporting of SAEs associated with disease progression and death of unknown cause, and added instructions for reporting AEs occurring secondarily to other events and for reporting persistent and recurring AEs	To encourage sufficient detail when reporting of AEs related to progression of the underlying malignancy To ensure consistent AE reporting across study sites
Section 7.8.1.2	Removed reference to "accidental" abortion	It is redundant to include both accidental and spontaneous abortion
Synopsis Table 1 Section 6.5 Section 7.8.1.3	Follow-up will be the same for all AEs, i.e., SAEs, AESIs, and non-serious AEs will all be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies, is lost to follow-up, or withdraws consent, or study closure	To obtain accurate information on the duration, reversibility, and resolution of AEs
Synopsis Section 7.8.1.3	The safety reporting period is changed to from the start of study drug dosing to 30 days after the last dose of study drug regardless of subsequent anticancer therapy	To ensure full collection of safety information
Synopsis Table 1 Section 6 Section 7.8.1.1 Section 7.8.1.3	During the screening period (from time of signing the pre-screening or main informed consent form), rather than collect all protocol-related AEs, only protocol-related SAEs will be collected	To ensure reporting of AEs during the screening period is focused on significant events
Section 7.8.1.4	Investigator assessment of causality is added to the information required in the initial SAE report	If causality is not provided with the initial report, it is conservatively handled as a SUSAR until causality is obtained

Summary of Changes in Amendment 2		
Section(s)	**Change**	**Rationale**
Section 7.8.1.5	The following statement is removed: "Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor (see Section 7.8.1.4)."	Investigator reporting requirements are already covered in Section 7.8.1.4
Section 7.8.7 Appendix C	Provided equation to calculate QTcF	For the convenience of study sites
Section 9.3, Table 13	Clarified definition of enrolled analysis set	To be consistent with CRF
Section 9.3, Table 13	Revised definition of Response Evaluable Analysis Set to include all subjects in the safety analysis set with measurable disease and at least 1 evaluable post-baseline disease assessment (per RECIST 1.1) or who discontinued study treatment due to death or unequivocal clinical progression	To clarify that the Response Evaluable Analysis Set includes subjects with measurable disease
Title Page, Synopsis, Section 7.3 Section 9.4.12	Incorporated changes described in China-specific amendment 1 (see summary below)	To create a single protocol for all regions

Summary of Changes in China-Specific Amendment 1		
Section(s)	**Change**	**Rationale**
Title Page	Updated the Medical Monitor to reflect the respective roles and responsibilities of Zymeworks Inc. and BeiGene, Ltd in China.	Administrative change.
Synopsis, Section 7.3 and 9.4.13	Included a requirement for extensive PK in the first 10 subjects enrolled in China. Updated IDMC schedule to include additional IDMC meetings for safety in these subjects.	To confirm ZW25 dose in Chinese population

Summary of Changes in Amendment 1		
Section(s)	**Change**	**Rationale**
Title Page	The Sponsor information has been updated to reflect the respective roles and responsibilities of Zymeworks Inc. and BeiGene, Ltd.	Administrative change.
Synopsis, Schedule of Assessments, and Sections 2, 6.2 , 6.3.2.3, 6.3.4, 6.4, 7.7, and 9.4.11	The EORTC QLQ-C30 and QLQ-BIL21 QOL questionnaires have been removed. Disease-related pain will now be assessed using the BPI short form rather than the QLQ-BIL21 pain score.	For patient convenience and to use a more sensitive instrument, the BPI, to measure disease-related pain.
Synopsis and Sections 2 and 9.4.5	To change the timeframe over which opioid use will be analyzed.	To align with use of the BPI to measure disease-related pain.
Synopsis and Sections 3.1 and 7.8.2	To specify that absolute decreases of ≥ 10 percentage points below baseline LVEF will be considered AESI.	Clarification.

Summary of Changes in Amendment 1		
Section(s)	**Change**	**Rationale**
Section 5.2.2	The text has been revised as follows: ZW25 will be administered by IV infusion given over approximately 120–150 minutes. If the first 2 doses are well tolerated by a given subject, the infusion duration for that subject may be decreased to 90 minutes. If the next 2 doses are well tolerated, the infusion duration may be decreased to 60 minutes. However, the infusion rate should not exceed 250 mL/hour. Refer to the Pharmacy Manual for specific details. ZW25 must not be administered as an IV push or bolus. ZW25 should not be mixed with other medications. See Section 5.4 for guidelines for management of infusion reactions.	To align with current instructions for ZW25 dosing.
Section 5.2.2.1	The following language has been added: Note that there must be a minimum of 12 days between doses. Cycles will not be skipped. If a cycle is delayed for any reason, once the subject resumes treatment the next dose delivered will be considered Day 1 of the cycle that was delayed. If the Day 15 dose of a cycle is delayed by ≥12 days, then that dose will be considered skipped. The next dose delivered will be Day 1 of the subsequent cycle.	Clarification.
Section 6.3.1.1	Text has been added to state that the Cycle 1 Day 1 physical exam does not need to be repeated if completed for screening within the previous 3 days.	Clarification.

Summary of Changes in Amendment 1		
Section(s)	**Change**	**Rationale**
Section 7.8.1.2	The text has been revised as follows: **Diagnosis vs. Signs or Symptoms** In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE. ~~Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion reactions, do not use the NCI-CTCAE terms of "cytokine release syndrome," "acute infusion reaction," or "allergic or hypersensitivity reaction." Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.~~	To correctly reflect the procedure for reporting IRRs as AEs. Similar to other AEs, IRRs should be reported as diagnoses and not individual symptoms.
Section 9.4.6.4	The text has been revised as follows: Disease control is defined as a best response of CR, PR ~~non-CR/non-PD (for subjects who have only non-target lesions),~~ or SD per RECIST 1.1. The proportion of subjects who achieve disease control and the corresponding exact binomial 95% CI will be calculated.	For consistency with the eligibility criteria, which only allows enrollment of subjects with target lesions.
Throughout protocol	Minor clarifications/corrections	To provide clarity and consistency.

PROTOCOL APPROVAL SIGNATURE

Protocol Title: A Phase 2b, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2-amplified biliary tract cancers

Protocol Number: ZWI-ZW25-203

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

[redacted] MD, PhD
Sr. Medical Director
Jazz Pharmaceuticals, Inc.

See Document Approval page for eSignature and date of approval

Signature Page for ZW25-203-03 Protocol Amendment
VV-CLIN-019723

Approval Task - Approval of Document Signing Verdict/Reason: I Approved This Document	[redacted] Clinical 13-Sep-2023 20:53:16 GMT+0000

Signature Page for ZW25-203-03 Protocol Amendment
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