

# CLINICAL STUDY PROTOCOL

**Protocol Number:** ZWI-ZW25-102

**Version:** Amendment 4; 03 October 2023

**Protocol Title:** Phase 1 Zanidatamab Monotherapy Trial in Japanese Subjects with Locally Advanced (Unresectable) and/or Metastatic HER2-expressing Cancers

**Investigational Product:** Zanidatamab (ZW25; JZP598)

**Phase:** Phase 1

**Sponsor:** Jazz Pharmaceuticals Ireland Limited  
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## PROTOCOL SYNOPSIS

<p><b>Protocol Number</b> ZWI-ZW25-102</p> <p><b>Version</b> Amendment 4; 03 October 2023</p> <p><b>Phase</b> 1</p>	<p><b>Product Name</b> Zanidatamab (also known as ZW25; JZP598)</p> <p><b>Sponsor</b> Jazz Pharmaceuticals Ireland Limited Waterloo Exchange, Waterloo Road Dublin 4, Ireland D04 E5W7</p>
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**Protocol Title:**

Phase 1 Zanidatamab Monotherapy Trial in Japanese Subjects with Locally Advanced (Unresectable) and/or Metastatic HER2-expressing Cancers

Study Objectives and Endpoints	
Objectives	Endpoints
<b>Primary:</b>	
<ul style="list-style-type: none"> <li>• To characterize the safety and tolerability of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>• Frequency of dose-limiting toxicities (DLTs)</li> <li>• Frequency and severity of adverse events (AEs)</li> <li>• Frequency of serious adverse events (SAEs) and deaths</li> <li>• Frequency and severity of adverse events of special interest (AESIs)</li> <li>• Frequency and severity of clinical laboratory abnormalities</li> <li>• Frequency of electrocardiogram (ECG) abnormalities</li> <li>• Frequency of left ventricular ejection fraction (LVEF) abnormalities</li> <li>• Eastern Cooperative Oncology Group Performance Status (ECOG PS)</li> <li>• Frequency of dose reductions of zanidatamab</li> </ul>
<b>Secondary:</b>	
<ul style="list-style-type: none"> <li>• To evaluate the pharmacokinetic (PK) profile of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>• Serum concentrations of zanidatamab as a function of time post-dosing</li> <li>• PK parameters for single (first) dose and multiple doses</li> </ul>
<ul style="list-style-type: none"> <li>• To explore the potential antitumor effects of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>• Objective response rate (ORR) assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria</li> <li>• Duration of response (DOR)</li> <li>• Disease control rate (DCR)</li> <li>• Clinical benefit rate (CBR)</li> <li>• Progression-free survival (PFS)</li> </ul>
<ul style="list-style-type: none"> <li>• To characterize the immunogenicity of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>• Frequency, duration, and time of onset of anti-drug antibodies (ADA), neutralizing antibodies, and HER2 extracellular domain (ECD)</li> </ul>

**Study Design:**

This is a Phase 1, multicenter, open-label, dose escalation and dose expansion study to evaluate the safety and tolerability of zanidatamab in Japanese subjects and to establish the PK profile of zanidatamab in Japanese subjects. The study will consist of a dose escalation with 2 planned weight-based dose levels and evaluation of 2-tiered flat dosing to establish the safety profile of zanidatamab. Following dose escalation, dose expansion will be opened at each weight-based dose level to establish the PK profiles of subjects with gastroesophageal adenocarcinoma (GEA) or non-GEA cancers. Eligible subjects include those with locally advanced (unresectable) or metastatic HER2-expressing cancers. Subjects will have either HER2-expressing GEA or another HER2-expressing solid tumor (i.e., non-GEA).

For GEA, gastric cancer-specific guidelines ([Bartley 2017](#)) will be used to assess HER2 expression levels. For non-GEA cancers, American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for assessing HER2 expression in breast cancer ([Wolff 2018](#)) will be used.

The study will be conducted in 2 parts:

- Part A (Dose escalation and evaluation of 2-tiered flat dosing): First, at least 8 subjects will be treated following the modified toxicity probability interval (mTPI) method ([Ji 2010](#)) to evaluate the safety, tolerability, and PK of zanidatamab and to identify the highest tested safe dose (HSD). Zanidatamab dosing will be evaluated for the following weight-based dose levels:
  - Dose Level 1: 20 mg/kg Q2W on Days 1 and 15 of a 28-day cycle
  - Dose Level 2: 30 mg/kg Q3W on Day 1 of a 21-day cycle

The HSD is defined as the highest dose level tested during dose escalation that has enrolled at least 6 subjects and has a DLT rate of < 25%. If the evaluation is completed by reaching the maximum number of subjects (30) and the dose level being evaluated has a DLT rate  $\geq$  25% and/or fewer than 6 subjects have been evaluated, the dose level will be considered as “not-tolerable”. If the mTPI method indicates that evaluating a dose lower than 20 mg/kg Q2W is warranted, a lower dose level (Dose Level –1 [i.e., 15 mg/kg Q2W]) is included.

If the HSD established per the mTPI method is 30 mg/kg Q3W, an additional 6 to 9 subjects with GEA and 6 to 9 subjects with non-GEA cancers will be enrolled to receive zanidatamab at the following flat dose level, which approximates the exposure of subjects treated at 30 mg/kg Q3W:

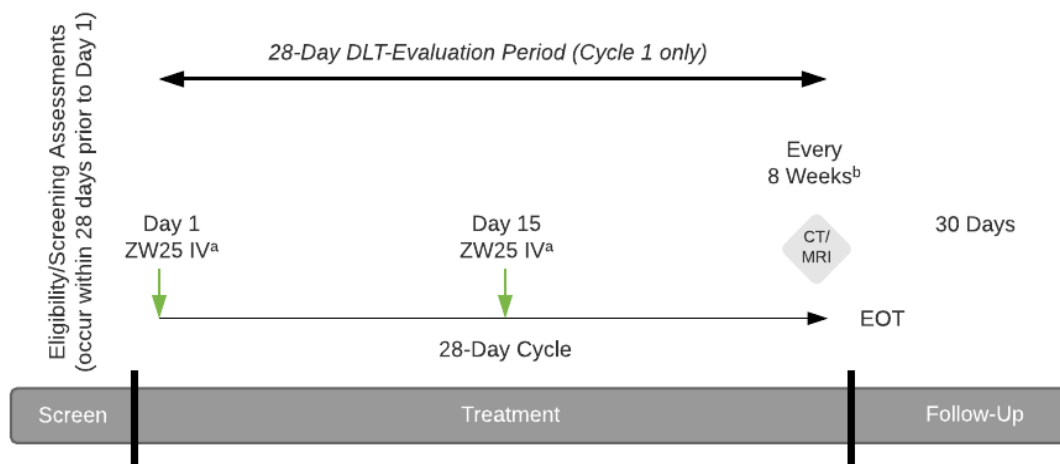
- Flat Dose Level: 1,800 mg (for subjects < 70 kg) or 2,400 mg (for subjects  $\geq$  70 kg) Q3W on Day 1 of a 21-day cycle.

All subjects enrolled in Part A will be dosed at least 24 hours apart on Cycle 1 Day 1 and be assessed for DLTs. Study drug administration, DLT evaluation, and safety observation during the DLT period will be carried out in the hospital setting and subjects will be under hospitalization management in principle. Subjects will be monitored per institutional standards during hospitalization, and AEs and concomitant medications will be recorded throughout this period. Discharge will be permitted for subjects with no safety concerns following study drug administration and observation for at least 24 hours. Subjects who are determined by the investigator to be manageable in the outpatient setting can be discharged. The investigator’s decision to discharge a subject will be based on clinical evaluation of the subject and any laboratory and/or radiological tests deemed necessary by the investigator. All subjects will be followed up via phone 24 hours after their discharge to evaluate their health status.

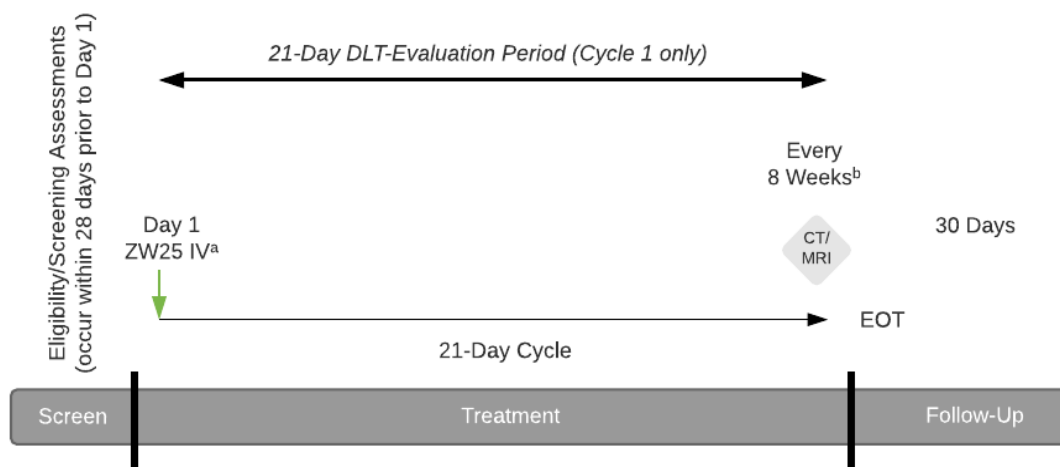
- Part B (Dose expansion): To further characterize the safety, PK, and antitumor activity of zanidatamab, a sufficient number of subjects will be treated at the 2 highest weight-based doses determined to be safe such that there are at least 6 PK-evaluable GEA subjects and 6 PK-evaluable non-GEA subjects per dose level across both parts of the study. Part B will be opened for enrollment only if the total number of PK-evaluable subjects enrolled in Part A has not reached at least 6 GEA subjects and 6 non-GEA subjects at each weight-based dose level.

The overall study design is presented in the following figures.

### **Study Design for Dose Level 1 and Dose Level -1**



### **Study Design for Dose Level 2 and Flat Dosing**



CT = computed tomography; DLT = dose-limiting toxicity; EOT = end of treatment; IV = intravenously; MRI = magnetic resonance imaging; ZW25 = zanidatamab

a Planned weight-based dose levels are Dose Level -1 = 15 mg/kg every 2 weeks; Dose Level 1 (starting dose) = 20 mg/kg every 2 weeks (Q2W); and Dose Level 2 = 30 mg/kg every 3 weeks (Q3W). Planned flat dosing is 1,800 mg Q3W (for subjects < 70 kg) or 2,400 mg Q3W (for subjects ≥ 70 kg).

b Timed from Cycle 1 Day 1.

Note: Despite the depiction of only 1 cycle in this diagram, the CT/MRI disease assessments are performed every 8 weeks during treatment (timed from Cycle 1 Day 1). Dose Level -1 is the de-escalation dose if de-escalation from Dose Level 1 is required.

### **Part A Dose Escalation Enrollment**

Enrollment into the study will begin with Part A Dose Level 1. During dose escalation, at least half of the subjects enrolled to each 2-3 subject cohort will be non-GEA.

Initially, 2 subjects will be enrolled into Dose Level 1. Further enrollment will hold until the second subject has completed the DLT period.

In the absence of DLTs, the enrollment will proceed in cohorts of 2 subjects each, as follows:

1. The next 2 subjects will be enrolled into Part A Dose Level 2. Further enrollment will hold until both subjects complete the DLT period.
2. Four more subjects will then be enrolled in Dose Level 2, two subjects at a time, and waiting for each group to complete the DLT period before the next group begins.

When 8 subjects (2 at Dose Level 1 and 6 at Dose Level 2) have completed the DLT evaluation period without observation of any DLT, Dose Level 2 will be considered the HSD.

When a DLT first occurs, subjects will be enrolled in cohorts of 3 subjects each with the dose level assignment for each cohort according to the mTPI method (see [Table 5](#)); however, the Safety Monitoring Committee (SMC) may override the mTPI dose assignment if warranted. As defined previously, the HSD will be the highest dose level tested during dose escalation that has enrolled at least 6 subjects and has a DLT rate of < 25%.

At the completion of Part A dose escalation, if the HSD is 30 mg/kg, enrollment may begin to evaluate Part A Flat Dosing. Enrollment into Part B may begin concurrently.

### **Part A Flat Dosing Enrollment**

Subjects will be enrolled into two separate Part A Flat Dosing groups (GEA and non-GEA). These subjects will be enrolled into Part A Flat Dose slots prior to Part B slots, unless otherwise approved by the Jazz Pharmaceuticals Medical Monitor. If Part A Flat Dosing is still enrolling, but a slot is not available during a DLT-evaluation period, subjects may enroll into Part B.

DLT evaluation of flat dosing in GEA subjects and non-GEA subjects will occur in parallel. Enrollment into each of the GEA and non-GEA flat dosing groups will proceed as follows:

1. Three subjects will be enrolled into the first cohort of subjects.
2. If there is no more than 1 DLT within the first cohort of subjects, an additional cohort of 3 subjects will enroll; however, if there is more than 1 DLT observed within the first cohort of subjects, evaluation of flat dosing will stop, and all further subjects will be enrolled to available slots in Part B.
3. If there is no more than 1 DLT in the first 2 cohorts of subjects (6 subjects total enrolled), Part A Flat Dosing will be complete, and all further subjects will be enrolled to available slots in Part B.
4. If there are 2 DLTs within the first 2 cohorts of subjects, an additional cohort of 3 subjects will enroll; however, if there are more than 2 DLTs observed within the first 2 cohorts of subjects, evaluation of flat dosing will stop, and all further subjects will be enrolled to available slots in Part B.

No more than 9 subjects total are planned to be enrolled into each flat dosing group of GEA and non-GEA cancers; however, subjects may be replaced if they are deemed not evaluable for DLTs and/or PK. The 2-tiered flat dosing will be determined to be safe if there is no more than one DLT among the first 6 subjects enrolled or no more than 2 DLTs among 9 total subjects in each group (GEA and non-GEA).

### **Part B Enrollment**

At the completion of dose escalation, dose expansion (Part B) may be activated by the sponsor to reach approximately 12 subjects per dose level, inclusive of subjects in Part A. Dose expansion will enroll subjects with GEA and non-GEA cancers such that, across the entire study (Parts A and B combined), there will be at least 6 PK-evaluable GEA subjects and at least 6 PK-evaluable non-GEA subjects at each of the 2 weight-based dose levels. There will be no dose expansion of the flat dosing groups (GEA and non-GEA) in Part B.

Enrollment into the higher dose level will be prioritized first, unless otherwise approved by the Jazz Pharmaceuticals Medical Monitor. Part B will enroll GEA and non-GEA subjects distributed as necessary so that a total of 6 GEA and 6 non-GEA subjects are enrolled into each of the two highest dose levels considered safe. If no DLTs occur in Part A and all subjects are PK-evaluable, final enrollment into the weight-based dose levels will be as shown in the following table:

**Part B Enrollment Schema**

Dose Level	Study Part		
	Part A	Part B	Total
Dose Level 1	2 subjects	10 subjects	12 subjects
Dose Level 2	6 subjects	6 subjects	12 subjects

The final enrollment number for the entire study will depend on DLT and PK evaluability. Subjects who are not PK-evaluable will be replaced to ensure there are at least 6 PK-evaluable GEA and 6 PK-evaluable non-GEA subjects per dose level at each weight-based dose level, and at least 6 PK-evaluable GEA and 6 PK-evaluable non-GEA subjects enrolled to flat dosing.

Subjects will be followed until death or approximately 30 days after discontinuation of study treatment, whichever occurs first.

**Number of Subjects:**

Up to approximately 48 subjects may be enrolled in this study. Up to 30 subjects may be enrolled in Part A Dose Escalation to determine the HSD for weight-based dosing and up to 18 subjects may be enrolled in Part A Flat Dosing. Across the entire study (Parts A and B combined), there will be at least 6 PK-evaluable GEA subjects and at least 6 PK-evaluable non-GEA subjects at each weight-based dose level, and at least 6 PK-evaluable GEA and 6 PK-evaluable non-GEA subjects enrolled to flat dosing.

**Study Population:**

Male or female Japanese subjects  $\geq 20$  years of age with any locally advanced (unresectable) and/or metastatic HER2-expressing cancer and ECOG performance status of 0 or 1 and a life expectancy of at least 3 months in the opinion of the investigator.

**Inclusion Criteria**

1. Disease Diagnosis: Any locally advanced (unresectable) and/or metastatic HER2-expressing (HER2 1+, 2+, or 3+ by IHC) cancer (including but not limited to GEA, biliary tract, breast, ovarian, colorectal, and non-small cell lung) that has progressed after receipt of all therapies known to confer clinical benefit (unless ineligible to receive a specific therapy).
2. Male or female Japanese subjects,  $\geq 20$  years of age at the time of signing informed consent.
3. ECOG performance status 0 or 1
4. Adequate hepatic function, as follows:
  - a. Aspartate aminotransferase (AST)  $\leq 2.5 \times$  the upper limit of normal (ULN) per institutional values (if liver or bone metastases are present,  $\leq 5 \times$  ULN)
  - b. Alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN per institutional values (if liver or bone metastases are present,  $\leq 5 \times$  ULN)
  - c. Total bilirubin  $\leq 1.5 \times$  ULN per institutional values
5. Adequate renal function (serum creatinine  $\leq 1.5 \times$  ULN or calculated glomerular filtration rate  $> 50$  mL/min)
6. Hematological function, as follows:
  - a. Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$
  - b. Platelet count  $\geq 75 \times 10^9/L$
  - c. Hemoglobin  $\geq 9$  g/dL

- d. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) < 1.5 × ULN
7. LVEF ≥ 50% as determined by either echocardiogram or multiple gated acquisition scan (MUGA)
  8. Evaluable disease (target or non-target lesions per RECIST version 1.1)
  9. Able to provide a fresh formalin-fixed, paraffin-embedded (FFPE) tumor sample for retrospective central evaluation of HER2 status; archival tumor specimens may be used if it is collected ≤ 6 months prior to enrollment and there is no intervening HER2 targeted treatment, unless otherwise approved by the medical monitor. Study eligibility may be based on local or central read (using ASCO/CAP guidelines) of fresh or archived tumor biopsy; if local read is used for eligibility, archived or fresh FFPE biopsy must be provided for retrospective centralized review unless otherwise approved by the sponsor.
  10. Female subjects of childbearing potential and male subjects with a partner of childbearing potential must be willing to use 2 methods of birth control with a failure rate of less than 1% per year during the study and for 7 months after the last dose of study drug. These include, but are not limited to, established use of oral contraceptives, or placement of intra-uterine device or intra-uterine system (as described in Section 4.3.2).  
  
In addition, female subjects must agree not to donate oocytes, and male subjects must avoid sperm donation for the duration of the study and for 7 months after the last dose of study drug.
  11. Signed informed consent prior to any study procedures, except pre-screening for HER2 status.

#### Exclusion Criteria

1. Treatment with experimental therapies within 4 weeks before first zanidatamab dosing
2. Treatment with other cancer therapy not otherwise specified within 4 weeks before zanidatamab dosing
3. Treatment with anthracyclines within 90 days before first zanidatamab dosing or total lifetime dose exceeding 300 mg/m<sup>2</sup> adriamycin or equivalent
4. Treatment with trastuzumab, pertuzumab, lapatinib, or T-DM1 within 3 weeks before the first zanidatamab dose
5. Untreated brain metastases, unless approved by the medical monitor (subjects with treated brain metastases who are off steroids and anticonvulsants and are stable for at least 1 month at the time of screening are eligible). All breast cancer and GEA subjects should undergo screening for brain metastases prior to starting treatment. Those subjects found to have untreated brain metastases may be rescreened following appropriate therapy.
6. History of or ongoing leptomeningeal disease (LMD). If LMD has been reported radiographically on baseline MRI but is not suspected clinically by the investigator, the subject is eligible if he or she is free of neurological symptoms of LMD as documented by the investigator
7. Major surgery or radiotherapy within 3 weeks before the first zanidatamab dose
8. Pregnant or breastfeeding women. Women who are breastfeeding may be enrolled in the study if they cease breastfeeding for the duration of the study and for 7 months after completion of study treatment.
9. History of life-threatening hypersensitivity to monoclonal antibodies or to recombinant proteins or excipients in drug formulation

10. Any other cancer within 3 years before the first zanidatamab dose with the exception of contralateral breast cancer, adequately treated cervical carcinoma in situ, or adequately treated basal or squamous cell carcinoma of the skin, or any other cancer that has undergone curative treatment, with approval from the sponsor medical monitor.
11. Acute or chronic uncontrolled renal disease, pancreatitis, or liver disease (with exception of subjects with Gilbert's Syndrome, asymptomatic gall stones, liver metastases, or stable chronic liver disease per investigator assessment)
12. Peripheral neuropathy: > Grade 2 NCI-CTCAE version 4.03
13. Prior history of interstitial lung disease
14. History of noncompliance to medical regimens
15. Known active hepatitis B or C or known infection with human immunodeficiency virus (HIV). Subjects who are hepatitis B surface antigen [HBsAg] positive are eligible if they have hepatitis B virus (HBV) DNA less than 500 IU/mL or 2,500 copies/mL with monitoring and/or antiviral prophylaxis as appropriate.
16. Known SARS-CoV-2 infection; subjects with prior infection that has resolved per local institutions' requirements and screening guidance are eligible
17. 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 study medical monitor.
18. QTc Fridericia (QTcF) > 470 ms. Note: For subjects with longer QTcF on initial ECG, follow-up ECG may be performed in triplicate and the mean of the 3 values will be used to determine eligibility.
19. Any toxicity related to prior cancer therapies that has not resolved to  $\leq$  Grade 1, with the following exceptions: alopecia; neuropathy (which must have resolved to  $\leq$  Grade 2); and congestive heart failure (CHF), which must have been  $\leq$  Grade 1 in severity at the time of occurrence and must have resolved completely; and Grade 2 hypothyroidism or panhypopituitarism related to treatment with immunotherapy (subject must be on a stable dose of hormone replacement therapy).
20. Clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic CHF.
21. Known myocardial infarction or unstable angina within 6 months before the first zanidatamab dose.

**Test Product, Dose, and Mode of Administration**

Zanidatamab is a liquid for IV infusion administered as a single agent (monotherapy). Zanidatamab planned dose levels are the following:

**Weight-based dosing:**

- Dose Level 1: 20 mg/kg Q2W on Days 1 and 15 of a 28-day cycle
- Dose Level 2: 30 mg/kg Q3W on Day 1 of a 21-day cycle
- Dose Level -1 (to be used only if dose de-escalation from Dose Level 1 is needed): 15 mg/kg Q2W on Days 1 and 15 of a 28-day cycle

**Flat dosing:**

- 1,800 mg (for subjects < 70 kg) or 2,400 mg (for subjects  $\geq$  70 kg) Q3W on Day 1 of a 21-day cycle

**Reference Product, Dose, and Mode of Administration**

Not applicable

**Required Premedication**

Prior to dosing with zanidatamab, all subjects must receive prophylactic treatment for potential infusion-related reactions that includes a corticosteroid. The mandated regimen includes acetaminophen orally, diphenhydramine (or equivalent) orally or IV, and a corticosteroid (recommended dose of either hydrocortisone 100 mg IV or dexamethasone 10 mg IV) 30 to 60 minutes prior to infusion of zanidatamab. If an alternative premedication regimen is thought to be required, sponsor approval should be sought. For subjects who experience an infusion-related reaction despite initial premedication, additional prophylactic treatment as needed per the investigator or per institutional standards including histamine-2 receptor antagonists (H<sub>2</sub> blockers) may be given in addition to the mandatory premedication prior to subsequent doses.

At any time during the study, the SMC may recommend/modify premedications/supportive medications and the sponsor may implement these recommendations without amending the protocol.

**Duration of Treatment:**

Treatment may be continued as long as there is no evidence of clinical progression, unacceptable toxicity, or evidence of progressive disease as defined by RECIST version 1.1. Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. Subjects who, in the opinion of the clinical investigator, demonstrate ongoing clinical benefit despite radiologic progression may continue to receive treatment following discussion with and approval from the sponsor's medical monitor.

**Safety Assessments**

Subjects enrolled in Part A will be assessed for AEs. Prior to discharge, subjects should be assessed with medical history and physical examination (including vital signs). If AEs are identified, the subject should be managed according to standard medical practice.

Safety will be monitored by recording the type, frequency, and severity of AEs, including but not limited to the following:

- AESIs: infusion-related reactions, non-infectious pulmonary toxicities, and cardiac events of absolute decrease in LVEF  $\geq 10$  percentage points from pre-treatment baseline and absolute value  $< 50\%$ , and/or Grade  $\geq 2$  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, oxygen saturation [if available], and temperature)
- ECOG PS
- Concomitant medications, including opioids
- 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 and concomitant medications will be collected from the first dose through 30 days after last dose of study drug. Protocol-related SAEs and concomitant medications given for the treatment of the SAE will be collected from the time of signed informed consent. All SAEs that occur after the safety reporting period that are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

All non-serious AEs will be followed through the safety reporting period. Investigators should follow SAEs and AESIs until resolution or the event returns to baseline, stabilizes 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 will be monitored throughout the study by the sponsor and an SMC. The SMC will review DLTs and all other available safety data (defined as all AEs, including those in subjects who were not DLT-evaluable) at the end of each cohort in dose escalation to make a recommendation for the next dose level to be tested based on the mTPI methodology. At the end of dose escalation, the SMC will also review DLTs and all other available safety data to confirm the HSD and recommend whether flat dosing and/or Part B should begin to enroll. In addition to the SMC, an independent data monitoring committee (IDMC) will be available on an ad hoc basis to review any safety issue referred by the SMC or the sponsor and will act in an advisory capacity to the sponsor.

### **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) and HER2 Extracellular Domain (ECD).

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 ( $\lambda_z$ ), 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 ( $V_z$ ), 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.

All subjects will be assigned to an extensive PK schedule.

### **Efficacy Assessments**

CT and/or MRI scans will be performed at baseline and Q8W during treatment (timed from Cycle 1 Day 1). Disease response will be assessed according to RECIST 1.1. Responses are to be confirmed not less than 4 weeks following initial documentation of objective response by the investigator.

### **Statistical Analysis:**

Dose escalation and identification of the HSD in Part A Dose Escalation will be guided by the mTPI method. The proportion of subjects reporting DLTs will be reported. The DLT-evaluable (DE) analysis set includes all treated subjects in Part A who either experienced a DLT or were followed for the full DLT evaluation period (first treatment cycle) and did not receive prohibited treatment. Subjects who received < 75% of the planned zanidatamab dose during the first cycle will not be considered as part of the DE analysis set, unless they experienced a DLT. Rules for dosing decisions are shown in the following table:

***mTPI Rules for Dosing Decisions***

No. of DLTs	No. of DLT-Evaluable Subjects at Current Dose														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	
1	D	D	D	S	S	S	E	E	E	E	E	E	E	E	
2	DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	
3		DU	DU	DU	D	D	S	S	S	S	S	S	S	S	
4			DU	DU	DU	DU	DU	D	S	S	S	S	S	S	
5				DU	DU	DU	DU	DU	DU	DU	D	S	S	S	
6					DU	DU	DU	DU	DU	DU	DU	DU	DU	D	
7						DU	DU	DU	DU	DU	DU	DU	DU	DU	
8							DU	DU	DU	DU	DU	DU	DU	DU	
9								DU	DU	DU	DU	DU	DU	DU	
10									DU	DU	DU	DU	DU	DU	
11										DU	DU	DU	DU	DU	
12											DU	DU	DU	DU	
13												DU	DU	DU	
14													DU	DU	
15														DU	

D = de-escalate the dose (for the next subject enrolled); DLT = dose-limiting toxicity; DU = dose unacceptable; E = escalate the dose (for the next subject enrolled); mTPI = modified toxicity probability interval; S = same dose (for the next subject enrolled).

Summaries of subject disposition, demographics, disease characteristics, safety, disease response, 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.

***Determination of Sample Size***

With the mTPI study design, the exact number of subjects needed to complete the dose escalation portion depends on the number of subjects enrolled in each cohort. Up to approximately 48 subjects may be enrolled in this study, i.e., up to 30 in the dose escalation component of Part A and up to 18 in the safety evaluation of the 2-tiered flat dose (Figure 1). Between the dose escalation component and expansion (Part B), at least 6 PK-evaluable GEA subjects and at least 6 PK-evaluable non-GEA subjects are required at Dose Levels 1 and 2 assuming both dose levels are determined to be safe. Expansion into Part B will only proceed if Part A does not yield the required 6 PK-evaluable GEA and non-GEA subjects at Dose Levels 1 and 2.

**Table 1: Schedule of Assessments for Weight-based Dose Level 1 (20 mg/kg Q2W)**

Assessment	Screening Visit (≤28 days)	Cycles 1 and 2 (28 Days Per Cycle)							Additional 28-Day Cycles			End of Treatment <sup>a</sup>	End of Study <sup>b</sup> (+7 days)				
		Cycle 1 <sup>s</sup>						Cycle 2									
		D1	D3	D5	D8 (±2)	D15 (±2)	D22 (±2)	24 hr Post-discharge Follow-up (±4 hrs)	D1	D15 (±2)	D28 (±7)			D1	D15 (±2)	Every 8 weeks	
Administration of Zanidatamab		X				X		<b>Subjects in Part A ONLY.</b> All subjects will be followed-up via phone 24 hours (± 4hrs) following their discharge from hospital to assess their health status.	X	X		X	X				
Informed consent	X																
Medical history	X																
Inclusion/exclusion criteria	X	X <sup>g</sup>															
Demographics	X																
Disease assessment per RECIST v1.1 (CT/MRI)	X											X <sup>c</sup>			X <sup>c</sup>	X <sup>d</sup>	X <sup>d</sup>
Fresh or archived tumor tissue for HER2 and biomarkers	X <sup>e</sup>															X <sup>e</sup>	X <sup>e</sup>
Physical examination	X <sup>f</sup>	X <sup>f,g</sup>								X <sup>f,g</sup>			X <sup>f,g</sup>			X <sup>f</sup>	X <sup>f</sup>
Vital signs (BP, HR, RR, O <sub>2</sub> sat [if available], temp)	X	X <sup>h</sup>				X <sup>h</sup>				X <sup>h</sup>	X <sup>h</sup>		X <sup>h</sup>	X <sup>h</sup>		X	X
ECOG performance status	X	X <sup>g</sup>								X <sup>g</sup>			X <sup>g</sup>			X	X
Hematology	X	X <sup>g,i,j</sup>				X <sup>g,i</sup>				X <sup>g,i</sup>	X <sup>g,i</sup>		X <sup>g,i</sup>			X	X
Serum chemistry	X	X <sup>g,i,j</sup>				X <sup>g,i</sup>				X <sup>g,i</sup>	X <sup>g,i</sup>		X <sup>g,i</sup>			X	X
Coagulation	X	X <sup>g,i,j</sup>				X <sup>g,i</sup>				X <sup>g,i</sup>	X <sup>g,i</sup>		X <sup>g,i</sup>			X	X
Urinalysis	X	X <sup>g,i,j</sup>								X <sup>g,i</sup>			X <sup>g,i</sup>			X	X
Pregnancy test	X	X <sup>g,i,j</sup>								X <sup>g,i</sup>			X <sup>g,i</sup>			X	X
12-Lead ECG	X <sup>k</sup>	X <sup>k</sup>								X <sup>k</sup>			X <sup>k</sup>			X	X
Echo/MUGA <sup>l</sup>	X											X	End of Cycles 5 and 8, then every 6 months			X <sup>d</sup>	X <sup>d</sup>
Zanidatamab PK <sup>m</sup>		X	X	X		X				X	X		X <sup>m</sup>	X <sup>m</sup>		X	X
ADA, neutralizing antibodies, and ECD		X <sup>g</sup>				X <sup>g</sup>				X <sup>g</sup>	X <sup>g</sup>		X <sup>g,n</sup>			X	X
Concomitant medications <sup>s</sup>	X	X	X	X	X <sup>r</sup>	X	X <sup>r</sup>		X	X	X	X	X	X	X	X	X

AE monitoring (includes AEs, SAEs, and AESIs) <sup>y</sup>	X	X	X	X	X <sup>r</sup>	X	X <sup>r</sup>	X	X	X	X	X	X	X	X	X
Hepatitis B and C, HIV <sup>o</sup>	X	As clinically indicated														
Tryptase <sup>w</sup>		X <sup>g</sup>	As clinically indicated (optimally within 6 hours, and up to 24 hours) after IRR occurrence.													
Brain scan <sup>p</sup>	X <sup>q</sup>															
Chest CT <sup>t</sup>	X													X <sup>u</sup>	X	X
PFTs <sup>v</sup> and hemoglobin	X	As clinically indicated														
KL-6	X													X	X	X

ADA = anti-drug antibody; BP = blood pressure; CT = computed tomography; ctDNA: circulating tumor DNA; D = day; DLCO/TLCO = diffusing capacity for carbon monoxide/transfer factor for carbon monoxide; ECD = extracellular domain; ECG = electrocardiogram; Echo = echocardiogram; FVC = forced vital capacity; HBc = hepatitis B core antibody; HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HER = human epidermal growth factor receptor; HIV = human immunodeficiency virus; hr(s) = hour(s); HR = heart rate; ILD - interstitial lung disease; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; O<sub>2</sub> sat = oxygen saturation; PFTs = pulmonary function tests; PK = pharmacokinetics; Q2W = biweekly; QTcF = QT interval corrected according to Fridericia's method; RECIST v1.1 = response evaluation criteria in solid tumors version 1.1; RR = respiratory rate; temp = oral or tympanic temperature; TLC = total lung capacity.

- <sup>a</sup> The End of Treatment visit will take place at the time a subject permanently stops treatment. The End of Treatment visit and the End of Study visit may be the same visit if the subject's last zanidatamab administration was > 30 days prior to the decision to permanently stop treatment.
- <sup>b</sup> The End of Study visit will take place 30 (+7) days after the last zanidatamab administration. The End of Study visit should be performed regardless of whether or not a subject starts a new anti-cancer therapy(s).
- <sup>c</sup> Scans for RECIST assessments can be made within a ±7-day time window and based on 8-week intervals from Cycle 1 Day 1.
- <sup>d</sup> See [Sections 6.4 and 6.5](#) for details of whether a scan is required for this visit.
- <sup>e</sup> At Screening, archival tumor specimens may be used if collected < 6 months prior to enrollment and there is no intervening HER2-targeted treatment. An optional tumor biopsy may also be collected at the time of disease progression up to the End of Study visit.
- <sup>f</sup> Physical examination includes height (at screening) and body weight, as well as lung auscultation to assess early signs of ILD; physical examination can be done within 3 days before zanidatamab administration.
- <sup>g</sup> Predose.
- <sup>h</sup> Predose and postdose (within 30 minutes after the end of the infusion).
- <sup>i</sup> For safety laboratory assessments, a predose time window of 3 days before Day 1 of all cycles (and Day 15 of Cycles 1 and 2) is allowed.
- <sup>j</sup> Cycle 1 Day 1 safety laboratory tests need not be repeated if Screening laboratory tests done within 3 days before Cycle 1 Day 1.
- <sup>k</sup> On Cycle 1 Day 1, 12-lead ECG will be recorded predose and at 4 h (±15 minutes) after the start of dosing; on Day 1 of subsequent cycles, 12-lead ECG will only be recorded predose. At Screening Visit and Cycle 1 Day 1, predose ECG, for subjects with longer QTcF on the initial ECG, a follow-up ECG may be performed in triplicate and the mean of the 3 values will be used to determine eligibility.
- <sup>l</sup> Echocardiogram/MUGA is performed ±7 days for all time points after Screening.
- <sup>m</sup> The PK sampling schedule is shown in [Table 3](#).
- <sup>n</sup> ADA samples at Day 1 of Cycle 3 and then at Day 1 of every even-numbered cycle thereafter for ADA.
- <sup>o</sup> HIV testing only if indicated. If HBsAg negative, then anti-HBc antibody and anti-HBs antibody are required. If either anti-HBc or anti-HBs positive, then hepatitis B DNA levels are required. If HBsAg, anti-HBc, or anti-HBs positive, then hepatitis B DNA levels are required at screening and every 1 to 3 months during treatment. For subjects with a known history of hepatitis B infection, only hepatitis B DNA testing is required at screening and hepatitis B DNA levels are required every 1 to 3 months during treatment.
- <sup>p</sup> For subjects with brain metastases at baseline, brain MRI should be repeated at the time of all tumor assessments. Otherwise, brain MRIs can also be performed as clinically indicated. CT scanning (with contrast unless medically contraindicated) is acceptable if MRI is not feasible.

- <sup>q</sup> Brain MRI scan at Screening is only required for subjects with breast cancer, GEA, or prior history of brain metastases. CT scanning (with contrast unless medically contraindicated) is acceptable if MRI is not feasible.
- <sup>r</sup> For subjects in Part B, outpatient safety monitoring for AEs and concomitant medications may be conducted by telephone or in-person at the investigator's discretion.
- <sup>s</sup> Subjects in Part A will be hospitalized until discharge per investigator decision. Physical examination and collection of AEs and concomitant medications should be performed throughout hospitalization and on the day of discharge.
- <sup>t</sup> High-resolution chest CT without contrast. May be used for the chest imaging disease assessment requirement, if considered adequate for that purpose by the investigator.
- <sup>u</sup> Performed at Week 8, Week 16, every 16 weeks thereafter, and as clinically indicated.
- <sup>v</sup> PFTs to include FVC, TLC, DLCO/TLCO, and measurement of oxygen saturation. Hemoglobin should be measured on the same day as PFT testing.
- <sup>w</sup> Tryptase assessments not required if not available locally.
- <sup>x</sup> All concomitant medications will be recorded from the time of signed informed consent through 30 days after last dose of study drug.
- <sup>y</sup> All AEs and SAEs will be recorded from the start of study drug dosing on Cycle 1 Day 1 to 30 days after the last dose of study drug. **All protocol-related SAEs will be recorded from the time of signed informed consent.** All SAEs that occur after the safety reporting period that are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

**Note:** If Dose Level -1 (15 mg/kg Q2W) is used, then it will follow this visit/assessment schedule.

**Table 2: Schedule of Assessments for Weight-based Dose Level 2 (30 mg/kg Q3W) and Flat Dosing**

Assessment	Screening Visit (≤28 days)	Cycles 1 and 2 (21 Days Per Cycle)						Additional 21-Day cycles		End of Treatment <sup>a</sup>	End of Study <sup>b</sup> (+7 days)			
		Cycle 1 <sup>s</sup>					24 hr Post-discharge Follow-up (±4 hrs)	Cycle 2						
		D1	D3	D5	D8 (±2)	D15 (±2)		D1	D21 (±7)			D1	Every 8 weeks	
Administration of Zanidatamab		X					Subjects in Part A ONLY. All subjects will be followed-up via phone 24 hours (± 4 hours) following their discharge from hospital to assess their health status.	X		X				
Informed consent	X													
Medical history	X													
Inclusion/exclusion criteria	X	X <sup>g</sup>												
Demographics	X													
Disease assessment per RECIST v1.1 (CT/MRI)	X											X <sup>c</sup>	X <sup>d</sup>	X <sup>d</sup>
New or archived tumor tissue for HER2 and biomarkers	X												X <sup>e</sup>	X <sup>e</sup>
Physical examination	X <sup>f</sup>	X <sup>f,g</sup>							X <sup>f,g</sup>		X <sup>f,g</sup>		X <sup>f</sup>	X <sup>f</sup>
Vital signs (BP, HR, RR, O2 sat [if available], temp)	X	X <sup>h</sup>							X <sup>h</sup>		X <sup>h</sup>		X	X
ECOG performance status	X	X <sup>g</sup>							X <sup>g</sup>		X <sup>g</sup>		X	X
Hematology	X	X <sup>g,i,j</sup>							X <sup>g,i</sup>		X <sup>g,i</sup>		X	X
Serum chemistry	X	X <sup>g,i,j</sup>							X <sup>g,i</sup>		X <sup>g,i</sup>		X	X
Coagulation	X	X <sup>g,i,j</sup>							X <sup>g,i</sup>		X <sup>g,i</sup>		X	X
Urinalysis	X	X <sup>g,i,j</sup>							X <sup>g,i</sup>		X <sup>g,i</sup>		X	X
Pregnancy test	X	X <sup>g,i,j</sup>							X <sup>g,i</sup>		X <sup>g,i</sup>		X	X
12-Lead ECG	X <sup>k</sup>	X <sup>k</sup>							X <sup>k</sup>		X <sup>k</sup>		X	X
Echo/MUGA <sup>l</sup>	X									X	End of Cycles 5 and 8, then every 6 months		X <sup>d</sup>	X <sup>d</sup>
Zanidatamab PK <sup>m</sup>		X	X	X					X		X <sup>m</sup>		X	X
ADA, neutralizing antibodies, and ECD		X <sup>g</sup>							X <sup>g</sup>		X <sup>g,n</sup>		X	X
Concomitant medications <sup>x</sup>	X	X	X	X	X <sup>r</sup>	X <sup>r</sup>		X	X	X	X	X	X	X
AE monitoring (includes AEs, SAEs, and AESIs) <sup>y</sup>	X	X	X	X	X <sup>r</sup>	X <sup>r</sup>	X	X	X	X	X	X	X	
Hepatitis B and C, HIV <sup>o</sup>	X	As clinically indicated												
Tryptase <sup>w</sup>		X <sup>g</sup>	As clinically indicated (optimally within 6 hours, and up to 24 hours) after IRR occurrence.											

Brain scan <sup>p</sup>	X <sup>q</sup>											
Chest CT <sup>t</sup>	X									X <sup>u</sup>	X	X
PFTs v and hemoglobin	X	As clinically indicated										
KL-6	X									X	X	X

ADA = anti-drug antibody; BP = blood pressure; CT = computed tomography; ctDNA: circulating tumor DNA; D = day; DLCO/TLCO = diffusing capacity for carbon monoxide/transfer factor for carbon monoxide; ECD = extracellular domain; ECG = electrocardiogram; Echo = echocardiogram; FVC = forced vital capacity; HBc = hepatitis B core antibody; HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HER = human epidermal growth factor receptor; HIV = human immunodeficiency virus; hr(s) = hour(s); HR = heart rate; ILD - interstitial lung disease; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; O<sub>2</sub> sat = oxygen saturation; PFTs = pulmonary function tests; PK = pharmacokinetics; Q2W = biweekly; QTcF = QT interval corrected according to Fridericia's method; RECIST v1.1 = response evaluation criteria in solid tumors version 1.1; RR = respiratory rate; temp = oral or tympanic temperature; TLC = total lung capacity.

- <sup>a</sup> The End of Treatment visit will take place at the time a subject permanently stops treatment. The End of Treatment visit and the End of Study visit may be the same visit if the subject's last zanidatamab administration was > 30 days prior to the decision to permanently stop treatment.
- <sup>b</sup> The End of Study visit will take place 30 (+7) days after the last zanidatamab administration. The End of Study visit should be performed regardless of whether a subject starts a new anti-cancer therapy(s).
- <sup>c</sup> Scans for RECIST assessments can be made within a ±7-day time window and based on 8-week intervals from Cycle 1 Day 1.
- <sup>d</sup> See Sections 6.4 and 6.5 for details of whether a scan is required for this visit.
- <sup>e</sup> At Screening, archival tumor specimens may be used if collected < 6 months prior to enrollment and there is no intervening HER2-targeted treatment. An optional tumor biopsy may also be collected at the time of disease progression up to the End of Study visit.
- <sup>f</sup> Physical examination includes height (at screening) and body weight, as well as lung auscultation to assess early signs of ILD; physical examination can be done within 3 days before zanidatamab administration.
- <sup>g</sup> Predose.
- <sup>h</sup> Predose and postdose (within 30 minutes after the end of the infusion).
- <sup>i</sup> For safety laboratory assessments, a predose time window of 3 days before Day 1 of all cycles is allowed.
- <sup>j</sup> Cycle 1 Day 1 safety laboratory tests need not be repeated if Screening laboratory tests done within 3 days before Cycle 1 Day 1.
- <sup>k</sup> On Cycle 1 Day 1, 12-lead ECG will be recorded predose and at 4 h (±15 minutes) after the start of dosing; on Day 1 of subsequent cycles, 12-lead ECG will only be recorded predose. At Screening Visit and Cycle 1 Day 1, for subjects with longer QTcF on the initial ECG, a follow-up ECG may be performed in triplicate and the mean of the 3 values will be used to determine eligibility.
- <sup>l</sup> Echocardiogram/MUGA is performed ±7 days for all time points after Screening.
- <sup>m</sup> The PK sampling schedule is shown in Table 4.
- <sup>n</sup> ADA samples at Day 1 of Cycle 3 and then at Day 1 of every even-numbered cycle thereafter for ADA.
- <sup>o</sup> HIV testing only if indicated. If HBsAg negative, then anti-HBc antibody and anti-HBs antibody are required. If either anti-HBc or anti-HBs positive, then hepatitis B DNA levels are required. If HBsAg, anti-HBc, or anti-HBs positive, then hepatitis B DNA levels are required at screening and every 1 to 3 months during treatment. For subjects with a known history of hepatitis B infection, only hepatitis B DNA testing is required at screening and hepatitis B DNA levels are required every 1 to 3 months during treatment.
- <sup>p</sup> For subjects with brain metastases at baseline, brain MRI should be repeated at the time of all tumor assessments. Otherwise, brain MRIs can also be performed as clinically indicated. CT scanning (with contrast unless medically contraindicated) is acceptable if MRI is not feasible.
- <sup>q</sup> Brain MRI scan at Screening is only required for subjects with breast cancer, GEA, or prior history of brain metastases. CT scanning (with contrast unless medically contraindicated) is acceptable if MRI is not feasible.
- <sup>r</sup> For subjects in Part B, outpatient safety monitoring for AEs and concomitant medications may be conducted by telephone or in-person at the investigator's discretion.
- <sup>s</sup> Subjects in Part A will be hospitalized until discharge per investigator decision. Physical examination and collection of AEs and concomitant medications should be performed throughout hospitalization and on the day of discharge.
- <sup>t</sup> High-resolution chest CT without contrast. May be used for the chest imaging disease assessment requirement, if considered adequate for that purpose by the investigator.
- <sup>u</sup> Performed at Week 8, Week 16, every 16 weeks thereafter, and as clinically indicated.
- <sup>v</sup> PFTs to include FVC, TLC, DLCO/TLCO, and measurement of oxygen saturation. Hemoglobin should be measured on the same day as PFT testing.

- <sup>w</sup> Tryptase assessments not required if not available locally.
- <sup>x</sup> All concomitant medications will be recorded from the time of signed informed consent through 30 days after last dose of study drug.
- <sup>y</sup> All AEs and SAEs will be recorded from the start of study drug dosing on Cycle 1 Day 1 to 30 days after the last dose of study drug. **All protocol-related SAEs will be recorded from the time of signed informed consent.** All SAEs that occur after the safety reporting period that are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

**Table 3: Pharmacokinetic Sampling Schedule for Weight-based Dose Level 1 (20 mg/kg Q2W)**

Time	Cycle 1								Cycles 2, 3 and 4		Additional cycles		End of Treatment	End of Study	
	D1					D3	D5	D15		D1 and D15		D1 of even-numbered cycles			
	Pre-dose	0 h post-dose	2 h post-dose	4 h post-dose	8 h post-dose	48 h post-dose	96 h post-dose	Pre-dose	0 h post-dose	Pre-dose	0 h post-dose	Pre-dose			0 h post-dose
Allowed time window		+5 m	±15 m	±30 m	±3 h	±1 h	±1 h	-4 h	+30 m	-4 h	+30 m	-4 h	+30 m		
Pharmacokinetic serum sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D = day; h = hour; m = minutes; Q2W = biweekly.

Postdose time points indicate the time after the end of infusion.

Note: If Dose Level -1 (15 mg/kg Q2W) is used, then it will follow this PK sampling schedule.

**Table 4: Pharmacokinetic Sampling Schedule for Weight-based Dose Level 2 (30 mg/kg Q3W) and Flat Dosing**

Time	Cycle 1							Cycles 2, 3 and 4		Additional cycles		End of Treatment	End of Study
	D1					D3	D5	D1		D1 of even-numbered cycles			
	Pre-dose	0 h post-dose	2 h post-dose	4 h post-dose	8 h post-dose	48 h post-dose	96 h post-dose	Pre-dose	0 h post-dose	Pre-dose	0 h post-dose		
Allowed time window		+5 m	±15 m	±30 m	±3 h	±1 h	±1 h	-4 h	+30 m	-4 h	+30 m		
Pharmacokinetic serum sample	X	X	X	X	X	X	X	X	X	X	X	X	X

D = day; h = hour; m = minutes; Q3W = once every 3 weeks.

Postdose time points indicate the time after the end of infusion.

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## LIST OF ABBREVIATIONS

$\lambda_z$	Terminal elimination rate constant
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase (SGOT)
AUC <sub>0-∞</sub>	Area under the serum concentration-time curve from zero to infinity
AUC <sub>0-t</sub>	Area under the serum concentration-time curve from zero to the last measurable concentration
AUC <sub>tau</sub>	Area under the serum concentration-time curve from zero to the last end of dosing interval
b.i.d.	Twice daily
B <sub>max</sub>	Maximum binding capacity
BTC	Biliary tract cancer
BUN	Blood urea nitrogen
CA	Cancer antigen
CAP	College of American Pathologists
C <sub>ave</sub>	Average concentration over dosing interval
CHF	Congestive heart failure
CL	Serum clearance
C <sub>max</sub>	Maximum observed serum concentration
C <sub>max,1</sub>	Maximum observed serum concentration for dose 1
C <sub>min</sub>	Minimum observed serum concentration
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
C <sub>ss</sub>	Serum concentration at steady state
CT	Computed tomography
CTC	Circulating tumor cells
ctDNA	Circulating tumor DNA
C <sub>trough</sub>	Trough concentration
DLCO	Diffusing capacity for carbon monoxide
DLT	Dose-limiting toxicity
ECD	Extracellular domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EOT	End of Treatment
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed, paraffin-embedded

FISH	Fluorescence <i>in situ</i> hybridization
FVC	Forced vital capacity
GCP	Good Clinical Practice
GEA	Gastroesophageal adenocarcinoma
GEJ	Gastroesophageal junction
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
HER	Human epidermal growth factor receptor
hIgG	Human immunoglobulin G
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell cancer
HNSTD	Highest nonseverely toxic dose
HSD	Highest tested safe dose
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
ILD	Interstitial lung disease
INR	International normalized ratio
IRB	Institutional review board
IV	Intravenous
KRAS	Kirsten rat sarcoma
LDH	Lactate dehydrogenase
LMD	Leptomeningeal disease
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinases
MCH	Mean cell hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-generation sequencing
NK	Natural killer
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
OBD	Optimal biological dose
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PET	Positron emission tomography
PFS	Progression-free survival
PFT	Pulmonary function test
PK	Pharmacokinetic
PO	By mouth
PR	Partial response
PT	Prothrombin time
QTcF	QT interval corrected according to Fridericia's method

QW	Once weekly
Q2W	Biweekly (i.e., once every 2 weeks)
Q3W	Once every 3 weeks
RBC	Red blood cell
R <sub>Cmin</sub>	Accumulation index
RD	Recommended dosage
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	Receptor tyrosine kinase
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SMC	Safety monitoring committee
SUSAR	Suspected unexpected serious adverse reaction
t <sub>½</sub>	Apparent elimination half-life
T-DM1	Ado-trastuzumab emtansine
TG	Treatment group
TLC	Total lung capacity
TLCO	Transfer factor for carbon monoxide
t <sub>max</sub>	Time to maximum observed serum concentration
t <sub>max,1</sub>	Time to maximum observed serum concentration for dose 1
ULN	Upper limit of normal
V <sub>z</sub>	Volume of distribution in the terminal elimination phase
WBC	White blood cell
WHO	World Health Organization

# 1 INTRODUCTION

## 1.1 HER2 Background

Human epidermal growth factor receptor 2 (HER2), also known as Neu, HER2/neu, ErbB-2, CD340, and p185 is encoded by the ERBB2 gene. HER2 is a transmembrane spanning receptor-like protein and is a member of the epidermal growth factor receptor (EGFR/ErbB) family that includes 4 structurally related HER receptors: HER1 (EGFR), HER2, HER3, and HER4. Expression of HER2, which may or may not involve HER2 overexpression or gene amplification, results in proliferative pathway activation and an increase in tumor growth.

HER2 is expressed by a number of different cancers. HER2 expression is typically determined by immunohistochemistry (IHC) and/or fluorescence *in situ* hybridization (FISH), although a number of other methodologies are available. Per the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines (Wolff 2018), HER2 expression levels may be classified as 0, 1+, 2+ or 3+ by IHC depending upon the extent and pattern of staining or HER2 gene amplified as determined by FISH. HER2 overexpression is most frequently seen in gastric/GEJ cancers (21% to 32%) (Van Cutsem 2015) and breast cancers (approximately 15%) (Giordano 2014, Varga 2015). Variable levels of HER2 expression are also seen in numerous other cancers including ovarian, lung, head and neck, endometrial, bladder, and colorectal cancer.

## 1.2 HER2 Targeted Therapies

There are currently several approved HER2-targeted therapies in Japan. These include the antibody-based therapies trastuzumab (HERCEPTIN<sup>®</sup> and biosimilars) and pertuzumab (PERJETA<sup>®</sup>), the antibody-drug conjugates (ADCs) ado-trastuzumab emtansine (KADCYLA<sup>®</sup>; also referred to as T-DM1) and fam-trastuzumab deruxtecan-nxki (ENHERTU<sup>®</sup>; also referred to as DS-8201a); and the oral small molecule dual EGFR/HER2 inhibitor lapatinib (TYKERB<sup>®</sup>); All of these agents have been approved for use in HER2-overexpressing breast cancer. Trastuzumab and fam-trastuzumab deruxtecan-nxki have also been approved for use in gastric cancer.

Trastuzumab binds to the ECD4 subdomain of HER2 while pertuzumab binds to the ECD2 dimerization domain. Combined with trastuzumab for first-line treatment of breast cancer, pertuzumab blocks HER2 mediated tumorigenesis. The combination of trastuzumab and pertuzumab has also been shown to increase degradation of HER2 and thereby turn off HER2 signaling (Bertelsen 2014). Additionally, trastuzumab has been reported to inhibit the formation of p95HER2 (Arribas 2011). Trastuzumab and pertuzumab can also potentially induce killing of tumor cells by stimulating the adaptive and innate immune responses. Binding of anti-HER2 antibodies to tumor cells can mark them for recognition by antigen-presenting cells, such as dendritic cells or for phagocytosis by macrophages. Anti-HER2 antibodies activate innate immune effector mechanisms by engaging the Fc portion of Fc receptors. These mechanisms include antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-mediated cytotoxicity. T-DM1 and fam-trastuzumab deruxtecan-nxki both contain cytotoxic components

that act by inhibiting tubulin and causing DNA damage, respectively, each promoting tumor cell death.

## 1.3 HER2-expressing Malignancies

### 1.3.1 Breast Cancer

Breast cancer presents a significant health burden worldwide. In 2018, over 2 million new cases were reported with over 600,000 deaths globally (Bray 2018). In Japan, the lifetime incidence rate of female invasive breast cancer is approximately 10.6% (one in nine women) and was estimated at about 93,529 new cases of locally advanced or metastatic breast cancer diagnosed in 2018. There were approximately 14,838 breast cancer deaths in Japan in 2019; the corresponding mortality rate (per 100,000 population) is 23.4. (Vital Statistics Japan [Ministry of Health, Labour and Welfare]), In the United States (US), the lifetime incidence rate of female invasive breast cancer is approximately 12% (one in eight women), and it was estimated that over 271,270 new cases of locally advanced or metastatic breast cancer would be diagnosed in 2019 in both men and women. The 5- and 10-year relative survival rates for women with invasive breast cancer in the US are 90% and 83%, respectively. However, 5-year relative survival rates drop to 27% when metastases are present (Siegel 2019). The estimated number of breast cancer cases in both sexes and all ages in the European Union (EU) (28 countries) for 2018 was 404,920 with an estimated mortality of 98,755 cases (European Cancer Information System (ECIS) 2018).

The introduction of HER2-targeted therapy into the clinic has led to marked improvements in disease-free survival, progression-free survival (PFS), and overall survival (OS) for patients with breast cancer expressing high levels of HER2 (Schramm 2015). HER2-targeted agents indicated for the treatment of HER2-high breast cancer in Japan include trastuzumab, pertuzumab, T-DM1, fam-trastuzumab deruxtecan-nxki, and lapatinib.

Despite the benefit provided by all of these agents, none are curative in the metastatic setting, and unmet medical need persists.

### 1.3.2 Gastroesophageal Adenocarcinoma (GEA)

Gastroesophageal adenocarcinomas (GEAs) are medically defined as malignant tumors of the esophagus, stomach and/or gastroesophageal junction (GEJ), a poorly defined anatomic region where the distal esophagus joins the proximal stomach. The relatively recent term, GEA, acknowledges the evolving understanding of these cancers having similar histology and genetic profiles. Barrett's esophagus, the replacement of the typical squamous epithelium of the upper esophagus with the columnar epithelium of the stomach, is recognized as a precursor to esophageal adenocarcinoma, highlighting the relationship of GEAs arising in the esophagus to those arising in the stomach. Principal Component Analysis of messenger ribonucleic acid (mRNA) and The Cancer Genome Atlas (TCGA) subtyping has also demonstrated that adenocarcinomas of the esophagus, stomach, and GEJ have similar mRNA expression patterns and are differentiated from adenocarcinomas of the colon and from esophageal squamous cell carcinomas (Barra 2017). Based on these similarities, classifying these cancers together as GEA

is appropriate. Additionally, the natural history, response to therapies, and overall prognosis is similar between GEAs. While most GEA studies have excluded adenocarcinomas arising in the esophagus, a study of capecitabine and oxaliplatin for patients with previously untreated advanced esophagogastric cancer did not show any difference in survival based on primary site or histology (Cunningham 2008).

GEAs are a major cause of morbidity and mortality worldwide. According to GLOBOCAN 2018 data, GEA arising in the stomach (gastric cancer) is the fifth most commonly diagnosed cancer and the third leading cause of cancer death worldwide. Compared to other regions, incidence rates are markedly elevated in Eastern Asia, including Japan (Bray 2018). The incidence of GEA arising in the esophagus has been increasing over time, particularly in the US and other Western countries, following the increased incidence of Barrett's esophagus in these regions (Runge 2015). This increased incidence is also associated with an increase in cancer deaths due to GEAs from the esophagus in these regions (Hur 2013). In Japan the incidence of esophageal carcinoma has been gradually rising in men overall; however, the risk of the adenocarcinoma subtype associated with gastroesophageal reflux disease remains unclear for Japanese patients because there are few documented cases; therefore, most GEAs in Japan arise from the stomach.

Although the majority of early-stage GEAs are resectable, more than half of all patients diagnosed with early-stage GEA relapse and ultimately die of their disease (Hur 2013). Additionally, up to 80% of patients with GEAs arising in the stomach remain asymptomatic during the early stages of their disease; therefore, initial diagnosis is often delayed. Approximately 65% to 80% of patients in the US are found to have unresectable disease or distant metastases at initial diagnosis (De Vita 2014, Kanat 2015). Patients with GEA arising in the esophagus (not as common in Japan and Asia as in the US and Western Europe) are more likely to be diagnosed at an earlier stage, likely due to the presence of symptoms and screening for Barrett's esophagus (in Western countries); however, approximately half of these patients already have metastatic disease at the time of diagnosis (Hur 2013). Patients with advanced GEA generally have a poor prognosis; in metastatic GEA, including patients with gastric adenocarcinoma in Japan, the 5-year survival rate is less than 10% (Orditura 2014).

On average, HER2 is overexpressed in 20% of GEAs and has been associated with poorer prognosis than non-HER2 expressing disease (Abrahao-Machado 2016) (Creemers 2018) (Gowryshankar 2014) (Plum 2019) (Yan 2015). HER2 overexpression or "positivity" is currently defined in GEA as IHC 3+, or IHC 2+ with FISH chromosome enumeration probe (CEP) 17 ratio  $\geq 2$  (FISH-positive).

Treatment for non-metastatic GEA, regardless of HER2 status, consists of a combination of chemotherapy, surgery, and/or radiation. In the metastatic setting, treatment goals are primarily palliative, although improvements in PFS and OS have been observed. For patients with HER2-positive disease, the addition of trastuzumab, an anti-HER2 antibody, to standard first-line chemotherapy leads to improved outcomes compared with chemotherapy alone. Trastuzumab, combined with chemotherapy (capecitabine or 5-fluorouracil and cisplatin), was approved in 2010 by the US Food and Drug Administration (FDA) for previously untreated patients with HER2-overexpressing metastatic GEAs arising from the stomach and/or GEJ. Approval was based on the ToGA Study, a Phase 3, randomized trial in 594 subjects, which showed that addition of trastuzumab to standard chemotherapy significantly improved OS compared with

chemotherapy alone (median OS of 14 versus 11 months) (Bang 2010). Although this study did not include patients with GEAs arising from the esophagus, its results led to trastuzumab being incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for treatment of these patients (Ajani 2016). Trastuzumab in combination with chemotherapy (capecitabine and cisplatin) was also approved in Japan in 2011 for previously untreated patients with HER2-overexpressing metastatic GEAs arising from the stomach and/or GEJ based on the ToGA study.

While trastuzumab combined with chemotherapy has shown benefit in HER2-positive advanced or metastatic GEA, most patients eventually experience disease progression on trastuzumab (Bang 2010). For these patients, ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor 2 (VEGFR2), with or without paclitaxel has been approved in Japan, the US, and the EU as second-line therapy, though not specifically for HER2-positive GEA (CYRAMZA® 2020)(CYRAMZA®). The combination of ramucirumab plus paclitaxel was associated with a median OS of 9.6 versus 7.4 months with paclitaxel alone; median PFS was 4.4 versus 2.9 months, and the objective response rate (ORR) was 28% versus 16%, respectively (Wilke 2014). For patients for whom this combination therapy is not appropriate (due to disease status, age, comorbidities, etc.), monotherapy paclitaxel, docetaxel, irinotecan or ramucirumab may be used. Additionally, the antibody-drug conjugate, trastuzumab deruxtecan, was recently approved for use in Japan after progression on prior trastuzumab with chemotherapy for GEAs arising from the stomach and/or GEJ. Previously, SAKIGAKE designation was granted in 2018 for this agent with the indication of GEAs arising from the stomach and/or GEJ who had previously received treatment with 2 prior regimens, including a trastuzumab-based regimen. Fam-trastuzumab deruxtecan-nxki has shown improved responses and increased OS (median OS 12.5 versus 8.4 months) compared to chemotherapy in this indication (Shitara 2020).

In contrast to breast cancer, for which multiple HER2-directed therapies have shown benefit, only trastuzumab and fam-trastuzumab deruxtecan-nxki are currently recognized to show benefit for patients with HER2-positive GEA. Ado-trastuzumab (T-DM1), lapatinib, and the combination of pertuzumab and trastuzumab have all been evaluated in randomized trials with negative results (Ghosh 2016) (Hurvitz 2018) (Thuss-Patience 2017). However, newer agents with novel mechanisms of action may be more successful, as demonstrated by the recent approval of fam-trastuzumab deruxtecan-nxki.

Beyond second-line therapy, immune checkpoint inhibitors, including agents targeting the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway have shown activity in patients with GEA. Results of a randomized, double-blind, placebo-controlled, Phase 3 trial (ONO-4538-12, ATTRACTION-2) showed that the anti-PD-1 agent nivolumab improved OS in subjects with GEAs arising from the stomach or GEJ who had progressed after at least 2 prior chemotherapy regimens (Kang 2017). In the nivolumab group, the median OS was 5.26 months compared with 4.14 months in the placebo group (hazard ratio [HR] 0.63, 95% CI, 0.51–0.78;  $p < 0.0001$ ). Nivolumab was approved as third-line therapy in Japan based on these results.

Another anti-PD-1 antibody, pembrolizumab, was approved in 2017 by the FDA for patients with PD-L1-expressing GEAs arising in the stomach and/or GEJ who had progressed after 2 or more lines of chemotherapy and/or HER2-targeted therapy (KEYTRUDA® 2020). Approval was based on the results of an open-label, multicenter, Phase 2 study (KEYNOTE-059). For the

143 subjects (with PD-L1 combined positive score [CPS]  $\geq 1$  and microsatellite stable [MSS] tumor status or undetermined microsatellite instability [MSI] or mismatch repair [MMR] status), the ORR was 13.3% (95% confidence interval [CI]: 8.2, 20.0); 1.4% had a complete response (CR) and 11.9% had a partial response (PR). Among the 19 responding subjects, the DOR ranged from 2.8+ to 19.4+ months, with 11 subjects (58%) having responses of 6 months or longer and 5 subjects (26%) having responses of 12 months or longer (Fuchs 2018). However, pembrolizumab is not approved for this indication in Japan.

### 1.3.3 Other HER2-expressing Malignancies

HER2 is expressed by a number of different cancers. Although no HER2-directed therapies have been approved for indications outside of breast cancer or gastric cancer, small trials have shown activity of HER2-targeted inhibition in highly selected patients with other cancers, including colorectal (Sartore-Bianchi 2016), gallbladder (Javle 2015), and salivary gland tumors (Falchook 2014). HER2-directed therapies continue to be evaluated in a variety of other HER2-expressing malignancies, as well, including biliary tract cancer, endometrial cancer, and urothelial cancer.

## 1.4 Unmet Medical Need

The introduction of targeted HER2 agents into the clinic has been one of the great success stories in oncology. The use of these drugs in neoadjuvant/adjuvant and metastatic treatment of HER2-overexpressing breast cancer has led to marked improvements in disease-free survival, PFS, and OS (Schramm 2015). While response rates are modest with single agent HER2 inhibition, combination with chemotherapy has had dramatic effects. Dual HER2 blockade has also led to marked improvement in outcomes, particularly in the first-line metastatic setting where the combination of trastuzumab, pertuzumab, and a taxane led to a 17-month improvement in OS compared to trastuzumab and a taxane alone (Swain 2015). Further, trastuzumab is approved in combination with chemotherapy as treatment for HER2-overexpressing gastric/GEJ cancer, where it has been shown to significantly improve survival as first-line treatment for metastatic disease.

Despite the gains obtained with current HER2-directed therapy, unmet medical need remains for patients with all forms of HER2-expressing cancers. This includes HER2-overexpressing breast and gastric cancers, where all patients with metastatic disease ultimately progress even after HER2-targeted therapy, as well as those cancers for which there are currently no approved HER2-targeted treatments. In addition, patients with cancers with lower levels of HER2 expression may benefit from more potent anti-HER2 therapies that are less dependent on HER2 overexpression. Based on *in vitro* and *in vivo* studies, zanidatamab, a biparatopic HER2-specific antibody that has demonstrated promising antitumor activity in a wide variety of HER2-expressing tumors, may be able to address this need.

## 1.5 Overview of Zanidatamab

Zanidatamab (also known as ZW25) is a humanized, bispecific, immunoglobulin G isotype 1 (IgG1)-like antibody directed against the juxtamembrane extracellular domain (ECD2) and the

dimerization domain (ECD4) of HER2. Zanidatamab binds to HER2 across a range of expression levels (low to high) and induces formation of receptor clusters and receptor internalization resulting in downregulation. Zanidatamab also inhibits growth factor-dependent and independent tumor cell proliferation, as well as potentially activating antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC).

A summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the Investigator's Brochure (IB). Planned and ongoing clinical studies are also summarized in the IB.

An ongoing first-in-human study of zanidatamab, a multi-part Phase 1 trial (ZWI-ZW25-101) in the US, Canada, and the Republic of Korea, is evaluating the safety, pharmacokinetics (PK), immunogenicity, and potential antitumor 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. The RDs for further study were identified as 10 mg/kg QW, 20 mg/kg Q2W, and 30 mg/kg Q3W.

## 1.6 Rationale for the Current Trial

Based on encouraging Phase 1 data, multiple other studies are ongoing or planned, including Phase 2 multinational studies in breast cancer and GEA, a global registrational Phase 2 study for the treatment of HER2-expressing biliary tract cancers, and a global Phase 3 registrational study in subjects with HER2-positive GEA. However, zanidatamab has not yet been evaluated in Japan. This study of zanidatamab is designed to assess the safety and tolerability of zanidatamab and to establish the PK profile of zanidatamab in Japanese subjects. In this study, 2 weight-based doses, 20 mg/kg Q2W and 30 mg/kg Q3W, and a 2-tiered flat dose (1,800 mg for subjects < 70 kg and 2,400 mg for subjects  $\geq$  70 kg) Q3W are being studied.

Both of the weight-based doses and schedules have already demonstrated safety in the first-in-human study (ZWI-ZW25-101) conducted outside of Japan, including in subjects from the Republic of Korea.

Dose Level 1 of zanidatamab for this study is 20 mg/kg Q2W, which is the dose at which the largest number of subjects (n=150), including 43 Korean subjects, have been evaluated to date. Among the DLT-evaluable subjects treated at this dose and schedule, there have been no DLTs and zanidatamab was well tolerated with very few  $\geq$  Grade 3 or serious zanidatamab-related events.

Dose Level 2, the highest dose level being evaluated in this study, is 30 mg/kg Q3W and it has also previously been evaluated in the Phase 1 study conducted outside Japan and shown to be safe as monotherapy and in combination with chemotherapy. There have been no DLTs at this dose level and few  $\geq$  Grade 3 or serious zanidatamab-related events. However, fewer subjects (n=21 including 5 Korean) have been treated at this dose level to date.

A preliminary population PK analysis of zanidatamab utilized the Phase 1 study data set (ZWI-ZW25-101; PK data cutoff date of 30 Dec 2019) and included 137 subjects, 43 of which

had GEA. In the analysis, exposure of zanidatamab was observed to be similar between Asian and non-Asian subjects (not significantly different by the likelihood ratio test for  $V_c$  [ $p=0.309$ ] or  $CL$  [ $p=0.733$ ]). Asian subjects had lower median body weight, higher incidence of GEA cancer, and higher likelihood to be male; these non-race-based factors showed significant impact on zanidatamab exposure while the Asian/non-Asian categorical covariate was not significant.

Preliminary results from Study ZWI-ZW25-101 also showed that subjects with GEA had 20% faster clearance of zanidatamab than subjects with other malignancies. This is consistent with data for other therapeutic antibodies (trastuzumab, pertuzumab, bevacizumab, and nivolumab) (Han 2014, Kang 2014, Osawa 2019, Quartino 2019). Treatment of GEA subjects with high-dose trastuzumab (vs standard-dose) plus chemotherapy resulted in increased  $C_{trough}$  without increased OS (HELOISE study) (Shah 2017). This difference is large enough to require examining the PK of zanidatamab in GEA subjects separately from non-GEA subjects. Therefore, the PK for GEA and non-GEA subjects will be considered separately. There have been no meaningful safety differences noted for GEA subjects ( $n=64$ ) vs. non-GEA subjects ( $n=130$ ) in the Phase 1 study conducted outside Japan.

The 2-tiered flat dose has not previously been evaluated; however, its exposure is expected to be similar to the 30 mg/kg dose level based on simulation of weight-based and flat dosing using the zanidatamab population PK Model. Both flat (CV: 43.5%) and weight-based dosing (CV: 43.4%) resulted in similar variation in steady state trough concentration. Based on this simulation, higher body weights tended to have higher exposure with the body weight-scaled dosing, while lower body weights have higher exposure with flat dosing. A hybrid approach between weight-based and flat dosing utilizing a two-tiered flat dose with weight cut point at 70 kilograms ( $< 70$  kg,  $\geq 70$  kg) is anticipated to reduce variability in exposure across body weight quartiles compared to single-tier flat and/or weight-based dosing. The proposed flat dose is 1,800 mg (subject weight  $< 70$  kg) or 2,400 mg (subject weight  $\geq 70$  kg) IV every 3 weeks. This dose is based on the clinical data from the Phase 1 study and the population PK analyses presented in this section. Switching from weight-based dosing to a 2-tiered flat dose addresses exposure variability across the body weight quartiles.

## 2 OBJECTIVES AND ENDPOINTS

Study Objectives and Endpoints	
Objectives	Endpoints
<b>Primary:</b>	
<ul style="list-style-type: none"> <li>To characterize the safety and tolerability of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Frequency of dose-limiting toxicities (DLTs)</li> <li>Frequency and severity of adverse events (AEs)</li> <li>Frequency of serious adverse events (SAEs) and deaths</li> <li>Frequency and severity of adverse events of special interest (AESIs)</li> <li>Frequency and severity of clinical laboratory abnormalities</li> <li>Frequency of electrocardiogram (ECG) abnormalities</li> <li>Frequency of left ventricular ejection fraction (LVEF) abnormalities</li> <li>ECOG PS</li> <li>Frequency of dose reductions of zanidatamab</li> </ul>
<b>Secondary:</b>	
<ul style="list-style-type: none"> <li>To evaluate the PK profile of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Serum concentrations of zanidatamab as a function of time post-dosing</li> <li>PK parameters for single (first) dose and multiple doses</li> </ul>
<ul style="list-style-type: none"> <li>To explore the potential antitumor effects of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Objective response rate (ORR) assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria</li> <li>Duration of response (DOR)</li> <li>Disease control rate (DCR)</li> <li>Clinical benefit rate (CBR)</li> <li>Progression-free survival (PFS)</li> </ul>
<ul style="list-style-type: none"> <li>To characterize the immunogenicity of zanidatamab monotherapy</li> </ul>	<ul style="list-style-type: none"> <li>Frequency, duration, and time of onset of anti-drug antibodies (ADA), neutralizing antibodies, and HER2 extracellular domain (ECD)</li> </ul>

### 3 INVESTIGATIONAL PLAN

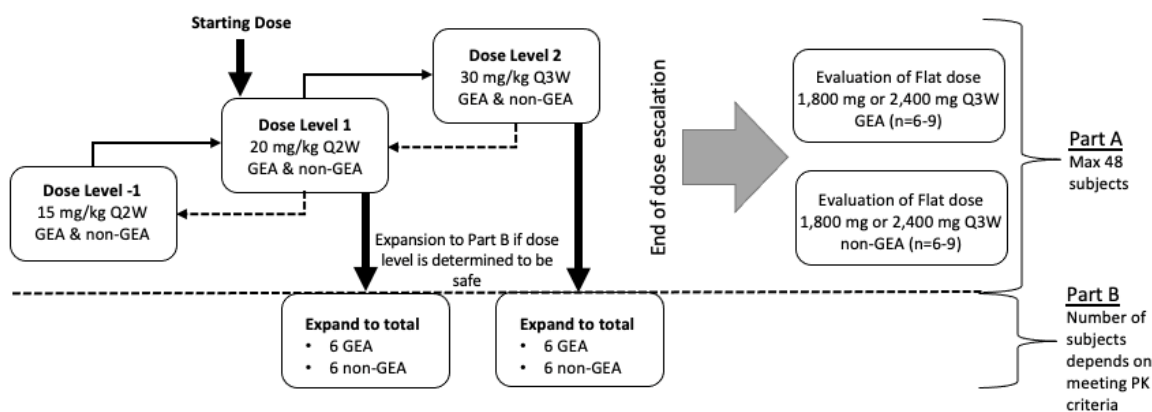
#### 3.1 Summary of Study Design

##### 3.1.1 Overview

This is a Phase 1, multicenter, open-label, dose escalation and dose expansion study to evaluate the safety and tolerability of zanidatamab in Japanese subjects and to establish the PK profile of zanidatamab in Japanese subjects. Eligible subjects include those with locally advanced (unresectable) or metastatic HER2-expressing cancers. Subjects will have either HER2-expressing GEA or another HER2-expressing solid tumor (i.e., non-GEA). For GEA, gastric cancer-specific guidelines (Bartley 2017) will be used to assess HER2-expression levels. For non-GEA cancers, ASCO/CAP guidelines for assessing HER2 expression in breast cancer (Wolff 2018) will be used.

The study will consist of a dose escalation with 2 planned weight-based dose levels and evaluation of 2-tiered flat dosing to establish the safety profile of zanidatamab (Part A). Following dose escalation, dose expansion will be opened at each weight-based dose level to establish the PK profiles of subjects with GEA or non-GEA cancers (Part B). A schematic of the study design is shown in Figure 1.

**Figure 1: Study Overview**



GEA = gastroesophageal adenocarcinoma; PK = pharmacokinetic; Q2W = every 2 weeks; Q3W = every 3 weeks.

In Part A: Up to 30 subjects may be enrolled in the dose escalation component and up to 18 may be enrolled in the flat dosing component.

In Part B (Expansion), enrollment will proceed such that, across the dose-escalation component and Part B there are at least 6 PK-evaluable GEA and at least 6 PK-evaluable non-GEA subjects at each dose level (DL1 and DL2) for a total of at least 24 PK-evaluable subjects.

In Part A (Dose escalation and evaluation of 2-tiered flat dosing), first, at least 8 subjects will be treated following the modified toxicity probability interval (mTPI) method (Ji 2010) to evaluate the safety, tolerability, and PK of zanidatamab and to identify the highest tested safe dose (HSD). Up to 50% of subjects enrolled to Part A may have GEA and 50% or greater must have non-GEA cancers.

All subjects enrolled in Part A will be dosed at least 24 hours apart on Cycle 1 Day 1 and be assessed for DLTs. Study drug administration, DLT evaluation, and safety observation during the DLT period will be carried out in the hospital setting and subjects will be under hospitalization management in principle. Subjects will be monitored per institutional standards during hospitalization, and AEs and concomitant medications will be recorded throughout this period. Discharge will be permitted for subjects with no safety concerns following study drug administration and observation for at least 24 hours. Subjects who are determined by the investigator to be manageable in the outpatient setting can be discharged. The investigator's decision to discharge a subject will be based on clinical evaluation of the subject and any laboratory and/or radiological tests deemed necessary by the investigator. All subjects will be followed up via phone 24 hours after their discharge to evaluate their health status.

The mTPI method uses a Bayesian statistical framework and a beta-binomial hierarchical model to compute the posterior probabilities of 3 intervals that reflect the relative distance between the toxicity rate of each dose level to the target DLT rate. Dosing decision rules are determined for a target DLT rate of 23% with an equivalence interval ranging from 20% to 25%. The 3 intervals will be (0, 20%), (20%, 25%), and (25%, 100%), and the corresponding dosing decision rules would be:

- Escalate if the current DLT rate is most likely  $< 20\%$ .
- Continue at the same dose if the current DLT rate is most likely equal to or greater than 20% and less than 25%.
- De-escalate if the current DLT rate is likely  $\geq 25\%$ .

Rules for dosing decisions are shown in [Table 5](#) in which E represents escalating the dose, S represents staying at the same dose, and D represents de-escalating the dose. Decision DU (dose unacceptable) means that the current dose level is unacceptable because of high toxicity and should be excluded from future dosing in the study.

**Table 5: The mTPI Rules for Dosing Decisions in This Study**

No. of DLTs	No. of DLT-Evaluable Subjects at Current Dose														
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	
1	D	D	D	S	S	S	E	E	E	E	E	E	E	E	
2	DU	DU	D	S	S	S	S	S	S	S	S	S	S	E	
3		DU	DU	DU	D	D	S	S	S	S	S	S	S	S	
4			DU	DU	DU	DU	DU	D	S	S	S	S	S	S	
5				DU	DU	DU	DU	DU	DU	DU	D	S	S	S	
6					DU	DU	DU	DU	DU	DU	DU	DU	DU	D	
7						DU	DU	DU	DU	DU	DU	DU	DU	DU	
8							DU	DU	DU	DU	DU	DU	DU	DU	
9								DU	DU	DU	DU	DU	DU	DU	
10									DU	DU	DU	DU	DU	DU	
11										DU	DU	DU	DU	DU	
12											DU	DU	DU	DU	
13												DU	DU	DU	
14													DU	DU	
15														DU	

D = de-escalate the dose (for the next subject enrolled); DLT = dose-limiting toxicity; DU = dose unacceptable; E = escalate the dose (for the next subject enrolled); mTPI = modified toxicity probability interval; S = same dose (for the next subject enrolled).

Decisions on dose escalation and subsequent cohort size will be made by the sponsor in consultation with the safety monitoring committee (SMC) after completion of each cohort. The SMC will review DLTs and all other available safety data (defined as all AEs, including those in subjects who were not DLT-evaluable) at the end of each cohort in dose escalation to make a recommendation for the next dose level to be tested based on the mTPI methodology. Subjects in the current cohort must be observed for the full duration of the DLT period (1 treatment cycle) before the next cohort of subjects is enrolled. In addition, Cycle 1 Day 1 dosing must be at least 24 hours apart for sequential subjects enrolled to Part A. At least 2 DLT-evaluable (DE) subjects (defined in [Section 3.1.2](#)) will be treated per dose level prior to dose escalation, and subjects will enroll in cohorts of 2 until the first DLT is observed. After the first DLT is observed at a given dose level, a minimum of 3 DE subjects per cohort will be required at that dose level before additional enrollment or escalation to a higher dose. In dose escalation, subjects who are considered not evaluable for DLT during Cycle 1 may be replaced. A minimum of 6 DE subjects will be observed at the HSD before the HSD (20 mg/kg Q2W or 30 mg/kg Q3W) is determined. At least 50% of subjects per cohort must have a non-GEA diagnosis (i.e., 1 subject per 2-subject cohort, or 2 subjects per 3-subject cohort).

Zanidatamab dosing will be evaluated for the following weight-based dose levels:

- Dose Level 1: 20 mg/kg Q2W on Days 1 and 15 of a 28-day cycle
- Dose Level 2: 30 mg/kg Q3W on Day 1 of a 21-day cycle

All subjects enrolled in dose escalation will be assessed for DLTs. The HSD is defined as the highest dose level that has enrolled at least 6 subjects and has a DLT rate of < 25%. If the

evaluation is completed by reaching the maximum number of subjects (30) and the dose level being evaluated has a DLT rate  $\geq 25\%$  and/or fewer than 6 subjects have been evaluated, the dose level will be considered as “not-tolerable”. If the mTPI method indicates that evaluating a dose lower than 20 mg/kg Q2W is warranted, the SMC may recommend evaluation of a lower dose level (Dose Level -1 [i.e., 15 mg/kg Q2W]). If Dose Level -1 is determined not to be safe, then the study stops.

During dose escalation, each dose level will be evaluated sequentially; however, subjects may be enrolled concurrently within an individual cohort. If approved by the SMC, up to 1 additional subject may be enrolled in a cohort to account for any potential non-DLT-evaluable subjects. Additionally, dose-escalation subjects who are determined by the SMC not to be DLT-evaluable may be replaced.

At the end of dose escalation, the SMC will review DLTs and all other available safety data to confirm the HSD and recommend whether flat dosing and/or Part B should begin to enroll. If the HSD established per the mTPI method is 30 mg/kg Q3W, an additional 6 to 9 subjects with GEA and 6 to 9 subjects with non-GEA cancers will be enrolled to receive zanidatamab at the following flat dose level, which approximates the exposure of subjects treated at 30 mg/kg Q3W:

- 1,800 mg (for subjects < 70 kg) or 2,400 mg (for subjects  $\geq 70$  kg) Q3W on Day 1 of a 21-day cycle.

DLT evaluation of flat dosing in GEA and non-GEA subjects will occur in parallel. Enrollment into each of the GEA and non-GEA flat dosing groups will proceed as follows and require the same safety measures included for dose escalation (e.g., dosing of subsequent subjects at least 24-hours apart on Cycle 1 Day 1 and hospitalization until discharge per investigator decision):

1. Three subjects will be enrolled into the first cohort of subjects.
2. If there is no more than 1 DLT within the first cohort of subjects, an additional cohort of 3 subjects will enroll; however, if there is more than 1 DLT observed within the first cohort of subjects, evaluation of flat dosing will stop, and all further subjects will be enrolled to available slots in Part B.
3. If there is no more than 1 DLT in the first 2 cohorts of subjects (6 subjects total enrolled), Part A Flat Dosing will be complete, and all further subjects will be enrolled to available slots in Part B.
4. If there are 2 DLTs within the first 2 cohorts of subjects, an additional cohort of 3 subjects will enroll; however, if there are more than 2 DLTs observed within the first 2 cohorts of subjects, evaluation of flat dosing will stop, and all further subjects will be enrolled to available slots in Part B.

No more than 9 subjects total are planned to be enrolled into each flat dosing group of GEA and non-GEA cancers; however, subjects may be replaced if they are deemed not evaluable for DLTs and/or PK. The 2-tiered flat dosing will be determined to be safe if there is no more than one DLT among the first 6 subjects enrolled or no more than 2 DLTs among 9 total subjects in each group (GEA and non-GEA).

At the completion of dose escalation, dose expansion (Part B) may be activated by the sponsor to reach approximately 12 subjects per dose level, inclusive of subjects in Part A. Dose expansion will enroll subjects with GEA and non-GEA cancers such that, across the entire study (Parts A and B combined), there will be at least 6 PK-evaluable GEA subjects and at least 6 PK-evaluable non-GEA subjects at each of the 2 weight-based dose levels. The subjects will be enrolled into Part A Flat Dose slots prior to Part B slots, unless otherwise approved by the Jazz Pharmaceuticals Medical Monitor. If Part A Flat Dosing is still enrolling, but a slot is not available during a DLT-evaluation period, subjects may enroll into Part B.

During Part B, enrollment into the higher dose level will be prioritized first, unless otherwise approved by the Jazz Pharmaceuticals Medical Monitor. Part B will enroll GEA and non-GEA subjects distributed as necessary so that a total of 6 GEA and 6 non-GEA subjects are enrolled into each of the two highest dose levels considered safe. If no DLTs occur in Part A and all subjects are PK-evaluable, final enrollment into the weight-based dose levels will be as shown in [Table 6](#). There will be no dose expansion of the flat dosing groups (GEA and non-GEA) in Part B.

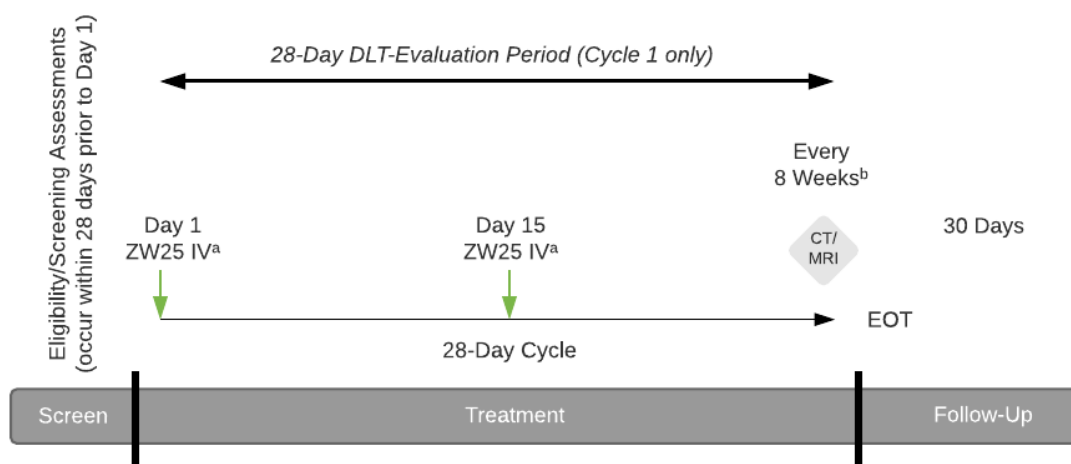
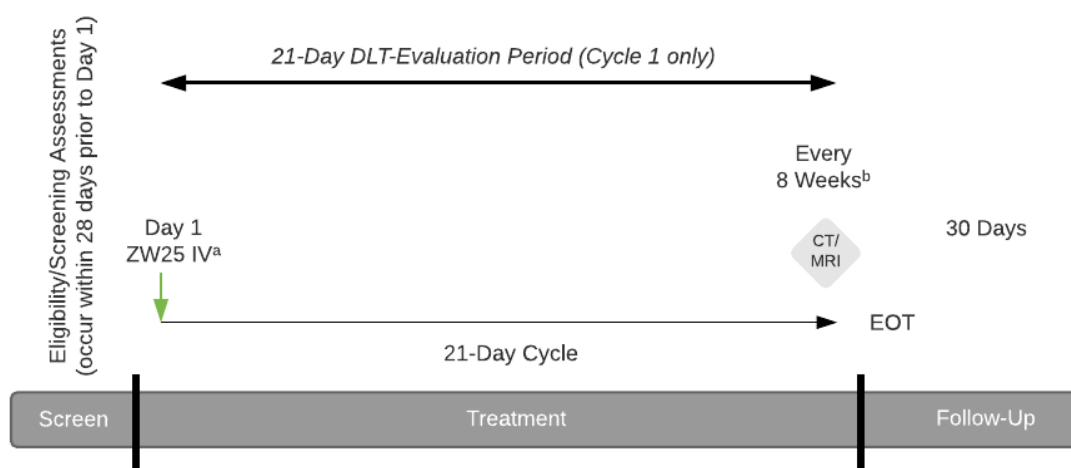
**Table 6: Part B Enrollment Schema**

Dose Level	Study Part		
	Part A	Part B	Total
Dose Level 1	2 subjects	10 subjects	12 subjects
Dose Level 2	6 subjects	6 subjects	12 subjects

The final enrollment number for the entire study will depend on DLT and PK evaluability. Subjects who are not PK-evaluable will be replaced to ensure there are at least 6 PK-evaluable GEA and 6 PK-evaluable non-GEA subjects per dose level at each weight-based dose level, and at least 6 PK-evaluable GEA and 6 PK-evaluable non-GEA subjects enrolled to flat dosing.

Zanidatamab will be administered intravenously (IV) on Days 1 and 15 of a 28-day cycle (i.e., Q2W) or on Day 1 of a 21-day cycle (both represented in [Figure 2](#)). CT and/or MRI scans will be performed at baseline and Q8W during treatment (timed from Cycle 1 Day 1). Disease response will be assessed according to RECIST 1.1. Responses will be confirmed not less than 4 weeks following initial documentation of objective response by the investigator. Safety will be monitored throughout the study. Subjects will be followed until death or approximately 30 days after discontinuation of study treatment, whichever occurs first.

Treatment may be continued for additional cycles as long as there is no evidence of clinical progression, unacceptable toxicity, or evidence of progressive disease as defined by RECIST 1.1. Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. Subjects who, in the opinion of the clinical investigator, demonstrate ongoing clinical benefit despite radiologic progression may continue to receive treatment following discussion with and approval from the sponsor's medical monitor.

**Figure 2: Study Diagram****Study Design for Weight-Based Dose Level 1****Study Design for Weight-Based Dose Level 2 and Flat Dosing**

CT = computed tomography; DLT = dose-limiting toxicity; EOT = end of treatment; IV = intravenously; MRI = magnetic resonance imaging; ZW25 = zanidatamab.

a: Planned dose levels are Dose Level 1 = 20 mg/kg every 2 weeks (Q2W) and Dose Level 2 = 30 mg/kg every 3 weeks (Q3W).

If Dose Level -1 (15 mg/kg Q2W) is used, then it will follow the same study design as Dose Level 1 (also Q2W dosing).

Planned flat dosing is 1,800 mg Q3W (for subjects < 70 kg) or 2,400 mg Q3W (for subjects ≥ 70 kg).

b: Timed from Cycle 1 Day 1.

Note: Despite the depiction of only 1 cycle in this diagram, the computed tomography / magnetic resonance imaging (CT/MRI) disease assessments are performed every 8 weeks during treatment (timed from Cycle 1 Day 1).

Computed tomography (CT) and/or magnetic resonance imaging (MRI) scans will be performed at baseline and Q8W during treatment timed from Cycle 1 Day 1. Disease response will be assessed according to RECIST 1.1 with objective responses to be confirmed not less than 4 weeks following initial documentation.

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 4.03 (14 July 2010) to match the version used in Study ZWI-ZW25-101. Safety

assessments will include monitoring for SAEs, AESIs, and deaths, clinical laboratory values (including hematology, coagulation, serum chemistry, and urinalysis), physical examination, vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature), body weight, ECOG performance status, 12-lead ECG, and echocardiogram or multiple gated acquisition scan (MUGA). Safety and study conduct will be monitored by a SMC, which will be tasked with monitoring the safety of participants through regular and/or ad hoc meetings (see [Section 3.1.3](#)).

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

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 and protein expression. Archival tumor tissue may also be used. Gastric cancer-specific guidelines ([Bartley 2017](#)) will be used to assess HER2 expression in GEA. ASCO/CAP guidelines for assessing HER2 expression in breast cancer ([Wolff 2018](#)) will be used to assess HER2-expression levels for all non-GEA cancers. If possible, an additional optional tumor biopsy may be obtained, at the time of disease progression, from an accessible site to allow for assessment of changes in HER2 amplification and expression.

### 3.1.2 Dose-limiting Toxicities

All subjects in Part A (dose escalation and flat dosing) will be assessed for DLTs. Defined using the NCI-CTCAE version 4.03, 14 July 2010, DLTs are events that occur during the first cycle (28 days for Q2W dosing or 21 days for Q3W dosing) of zanidatamab treatment, are considered possibly related, probably related or related to zanidatamab, and meet the criteria described below. Events for which there is an alternative clinical explanation (e.g., clearly related to an intercurrent illness, disease progression, or concomitant chemotherapy) will not be considered DLTs. The relationship of AEs to study drug treatment will be determined by the investigator. To be considered DE, a subject must receive  $\geq 75\%$  of the planned dosing for zanidatamab during the first cycle of treatment or experienced a DLT. During dose escalation, subjects considered not DE will be replaced.

#### DLT Criteria Non-Hematologic

Any non-hematologic AE  $\geq$  Grade 3 in severity that is related to zanidatamab is considered a DLT, with the following exceptions:

- Grade 3 fatigue lasting  $\leq 3$  days
- Grade 3 diarrhea, nausea, or vomiting that resolves to  $\leq$  Grade 1 or baseline within 3 days with adequate supportive care
- Grade 3 rash without maximal use of corticosteroids or anti-infectives
- Infusion reaction  $\leq$  Grade 3 (for management of infusion reactions, see [Section 5.2.2.2](#))

Laboratory abnormalities  $\geq$  Grade 4 will be considered a DLT.

Any toxicities that are related, probably related, or possibly related to zanidatamab that do not resolve to  $\leq$  Grade 1 or baseline within 2 weeks may be considered a DLT based upon review by the study SMC.

Greater than a 2-week delay in the start of Cycle 2 due to unresolved toxicity clearly related to zanidatamab alone will be considered a DLT.

#### Hematologic DLT Criteria

The following hematologic AEs that are related to zanidatamab are considered DLTs:

- Neutropenia of Grade 3 or 4 with fever (fever must be present for the Grade 3 or 4 neutropenia to be considered a DLT, and is defined as a temperature of  $\geq 38.5^{\circ}\text{C}$ )
- Absolute neutrophil count (ANC) of  $< 500/\mu\text{L}$  for  $> 7$  days
- Grade 3 thrombocytopenia associated with significant bleeding or requiring platelet transfusion
- Grade 4 thrombocytopenia
- Grade 4 anemia or any grade of anemia requiring blood transfusion

#### Hepatic DLT Criteria

In addition to the non-hematologic DLT criteria detailed above, the following hepatic AEs that are related to zanidatamab are considered DLTs:

- Grade  $\geq 3$  elevation of transaminases (ALT/SGPT or AST/SGOT) that is NOT thought to be due to disease progression or other medical illness
- Grade 3 or 4 elevation of bilirubin irrespective of transaminases that is NOT thought to be due to disease progression or other medical illness
- Any single instance of  $\text{AST/ALT} > 3 \times \text{ULN}$  AND total bilirubin  $> 2 \times \text{ULN}$  that is NOT thought to be due to disease progression or other medical illness

#### Cardiac DLT Criteria

In addition to the non-hematologic DLT criteria detailed above, the following cardiac AEs that are related to zanidatamab are considered DLTs:

- LVEF below institutional limits and  $\geq 10$  percentage points below pre-treatment baseline
- Grade 2 symptomatic heart failure

The first cardiac DLT due to LVEF decline will result in withholding of the drug until recovery of the ejection fraction to prior levels. If subjects remain off zanidatamab for more than 4 weeks beyond the next scheduled dose they will be removed from the study. For further management of cardiac DLT(s) and/or left ventricular dysfunction, see [Section 5.2.2.1](#).

### 3.1.3 Safety Monitoring

#### 3.1.3.1 Safety Monitoring Committee (SMC)

Safety and study conduct will be monitored throughout the study by the study SMC, consisting of the study investigators and sponsor representatives. The SMC will meet a minimum of once every two weeks during enrollment and on an ad hoc basis.

For the purpose of the SMC DLT review, a subject must receive  $\geq 75\%$  of the planned dosing for zanidatamab during the first cycle of treatment or experienced a DLT. During dose escalation, subjects considered not DLT-evaluable will be replaced.

The SMC will review DLTs and all other available safety data (defined as all AEs, including those in subjects who were not DLT-evaluable) at the end of each cohort in dose escalation to make a recommendation for the next dose level to be tested based on the mTPI methodology (Table 5). At the end of dose escalation, the SMC will also review DLTs and all other available safety data to confirm the HSD and recommend whether flat dosing and/or Part B should begin to enroll.

#### 3.1.3.2 Independent Data Monitoring Committee (IDMC)

In addition to the SMC, an independent data monitoring committee (IDMC) will be available on an ad hoc basis to review any safety issue referred by the SMC or the sponsor and will act in an advisory capacity to the sponsor. The IDMC responsibilities include:

- Consider relevant information that may have an impact on the safety of the participants of the study
- Protect the safety of the study participants as defined below:
  - o Adverse events that are  $\geq$  Grade 4 will be reviewed by the IDMC unless determined to be clearly unrelated to zanidatamab by the SMC. Further enrollment to the study will be paused until the IDMC has reviewed all AEs potentially related to zanidatamab that are  $\geq$  Grade 4.
  - o The SMC may refer other safety issues including interstitial lung disease (ILD) to the IDMC as needed, during which time enrollment may be paused until IDMC review.
  - o Make recommendations to Jazz Pharmaceuticals concerning continuation, termination or other modifications of the study based on referred safety issues. The IDMC may also recommend additional meetings, as they consider appropriate, to protect the safety of study participants.
- The first planned IDMC review of the cumulative safety data will occur once dose escalation is completed for the weight-based doses in Part A. After enrollment of either GEA or non-GEA subjects is complete and a sufficient number are considered PK-evaluable, the IDMC will review the cumulative safety and PK data from all subjects enrolled to make a recommendation on the interpretation of safety and PK data in GEA

or non-GEA subjects, as applicable. A cumulative review of the study data will also be performed after enrollment of all PK-evaluable GEA and non-GEA subjects is complete.

## 3.2 Discussion and Rationale for Study Design

The following weight-based zanidatamab dose levels will be evaluated: 20 mg/kg IV Q2W and 30 mg/kg IV Q3W. If dose de-escalation from 20 mg/kg Q2W per the mTPI methodology is required, a lower dose level (Dose Level -1) (i.e., 15 mg/kg Q2W) is available for evaluation.

Part A of the study will consist of dose escalation in order to determine the HSD between the tested weight-based dose levels. Once dose escalation is complete and initial safety of the drug is demonstrated, an additional 6 to 9 GEA subjects and 6 to 9 non-GEA subjects will be enrolled to evaluate a 2-tiered flat dosing strategy.

The mTPI dose-escalation method was chosen for this study because of potential advantages it has over the traditional “3+3” approach for dose finding. These advantages include treatment of fewer subjects at unsafe doses (thereby improving safety) and allowing for flexible cohort sizes. Flat dosing is not included in the mTPI design, as the flat dosing is intended to approximate the 30 mg/kg weight-based dosing and, therefore, is not considered a higher dose level than 30 mg/kg.

Subjects who experience a DLT may continue in the study at the discretion of the investigator with dose modifications as needed ([Section 5.2.2](#)).

At the completion of dose escalation, dose expansion (Part B) may be activated by the sponsor to further evaluate the safety and antitumor activity of zanidatamab. Across dose escalation and dose expansion combined, there will be at least 6 PK-evaluable GEA subjects and at least 6 PK-evaluable non-GEA subjects at each weight-based dose level for a total of at least 24 PK-evaluable subjects. This will allow for the collection of additional information about the safety, tolerability, PK, and antitumor activity of zanidatamab. Across Part A and Part B combined, there will be at least 6 PK-evaluable GEA subjects and at least 6 PK-evaluable non-GEA subjects at each dose level. A sufficient number of GEA subjects at each dose level is required to characterize the PK of zanidatamab. Preliminary results from Study ZWI-ZW25-101 showed that subjects with GEA had 20% faster clearance of zanidatamab than subjects with other malignancies. This difference is large enough to require examining the PK of zanidatamab in GEA subjects separately from non-GEA subjects.

### 3.2.1 Method of Assigning Subjects to Treatment Groups

During dose escalation (Part A), subject allocation to a cohort within each dose level will be determined by mTPI decision rules as illustrated in [Table 5](#), and will occur upon approval of subject enrollment by the sponsor. During dose expansion (Part B), subjects will be enrolled based upon available subject slots and on tumor type (GEA vs non-GEA) and which dose level(s) are open for enrollment. Subjects will be enrolled into Part A Flat Dose slots (GEA or non-GEA) prior to Part B slots, unless otherwise approved by the Jazz Pharmaceuticals Medical Monitor. If Part A Flat Dosing is still enrolling, but a slot is not available during a DLT-evaluation period, subjects may enroll into Part B.

### 3.2.2 Rationale for Selection of Doses

It is anticipated that all subjects receiving weight-based dosing in the study will receive 20 mg/kg zanidatamab IV Q2W or 30 mg/kg zanidatamab IV Q3W, depending on dose level. Both doses were tested in the monotherapy part of the Phase 1, dose-escalation study of zanidatamab (ZWI-ZW25-101) conducted outside Japan.

If required to de-escalate from Dose Level 1 (20 mg/kg zanidatamab Q2W), then there is the possibility that some subjects will be treated with Dose Level -1 (15 mg/kg Q2W), which is a 25% dose reduction from Dose Level 1.

All subjects enrolled to flat dosing will receive 1,800 mg (for subjects < 70 kg) or 2,400 mg (for subjects  $\geq$  70 kg) Q3W. This 2-tiered flat dosing schedule is intended to approximate the 30 mg/kg weight-based dosing schedule.

Refer to [Section 1.6](#) for a detailed description of dose selection for this study.

### 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. Disease Diagnosis: Any locally advanced (unresectable) and/or metastatic HER2-expressing (HER2 1+, 2+, or 3+ by IHC) cancer (including but not limited to gastroesophageal adenocarcinoma [GEA], biliary tract, breast, ovarian, colorectal, and non-small cell lung) that has progressed after receipt of all therapies known to confer clinical benefit (unless ineligible to receive a specific therapy).
2. Male or female Japanese subjects,  $\geq 20$  years of age at the time of signing informed consent.
3. ECOG performance status 0 or 1
4. Adequate hepatic function, as follows:
  - a. Aspartate aminotransferase (AST)  $\leq 2.5 \times$  the upper limit of normal (ULN) per institutional values (if liver or bone metastases are present,  $\leq 5 \times$  ULN)
  - b. Alanine aminotransferase (ALT)  $\leq 2.5 \times$  ULN per institutional values (if liver or bone metastases are present,  $\leq 5 \times$  ULN)
  - c. Total bilirubin  $\leq 1.5 \times$  ULN per institutional values
5. Adequate renal function (serum creatinine  $\leq 1.5 \times$  ULN or calculated glomerular filtration rate  $>50$  mL/min)
6. Hematological function, as follows:
  - a. Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$
  - b. Platelet count  $\geq 75 \times 10^9/L$
  - c. Hemoglobin  $\geq 9$  g/dL
  - d. Prothrombin time (PT) and activated partial thromboplastin time (aPTT)  $< 1.5 \times$  ULN
7. LVEF  $\geq 50\%$  as determined by either echocardiogram or multiple gated acquisition scan (MUGA)
8. Evaluable disease (target or non-target lesions per RECIST version 1.1)
9. Able to provide a fresh formalin-fixed, paraffin-embedded (FFPE) tumor sample for retrospective central evaluation of HER2 status; archival tumor specimens may be used if it is collected  $\leq 6$  months prior to enrollment and there is no intervening HER2 targeted

treatment, unless otherwise approved by the medical monitor. Study eligibility may be based on local or central read (using ASCO/CAP guidelines) of fresh or archived tumor biopsy; if local read is used for eligibility, archived or fresh FFPE biopsy must be provided for retrospective centralized review unless otherwise approved by the sponsor.

10. Female subjects of childbearing potential and male subjects with a partner of childbearing potential must be willing to use 2 methods of birth control with a failure rate of less than 1% per year during the study and for 7 months after the last dose of study drug. These include, but are not limited to, established use of oral contraceptives, or placement of intra-uterine device or intra-uterine system (as described in [Section 4.3.2](#)).

In addition, female subjects must agree not to donate oocytes, and male subjects must avoid sperm donation for the duration of the study and for 7 months after the last dose of study drug.

11. Signed informed consent prior to any study procedures, except pre-screening for HER2 status.

## 4.2 Exclusion Criteria

1. Treatment with experimental therapies within 4 weeks before first zanidatamab dosing
2. Treatment with other cancer therapy not otherwise specified within 4 weeks before zanidatamab dosing
3. Treatment with anthracyclines within 90 days before first zanidatamab dosing or total lifetime dose exceeding 300 mg/m<sup>2</sup> adriamycin or equivalent
4. Treatment with trastuzumab, pertuzumab, lapatinib, or T-DM1 within 3 weeks before the first zanidatamab dose
5. Untreated brain metastases, unless approved by the medical monitor (subjects with treated brain metastases who are off steroids and anticonvulsants and are stable for at least 1 month at the time of Screening are eligible). All breast cancer and GEA subjects should undergo screening for brain metastases prior to starting treatment. Those subjects found to have untreated brain metastases may be rescreened following appropriate therapy.
6. History of or ongoing leptomeningeal disease (LMD). If LMD has been reported radiographically on baseline MRI but is not suspected clinically by the investigator, the subject is eligible if he or she is free of neurological symptoms of LMD as documented by the investigator
7. Major surgery or radiotherapy within 3 weeks before the first zanidatamab dose
8. Pregnant or breastfeeding women. Women who are breastfeeding may be enrolled in the study if they cease breastfeeding for the duration of the study and for 7 months after completion of study treatment.

9. History of life-threatening hypersensitivity to monoclonal antibodies or to recombinant proteins or excipients in drug formulation
10. Any other cancer within 3 years before the first zanidatamab dose with the exception of contralateral breast cancer, adequately treated cervical carcinoma in situ, or adequately treated basal or squamous cell carcinoma of the skin, or any other cancer that has undergone curative treatment, with approval from the sponsor medical monitor.
11. Acute or chronic uncontrolled renal disease, pancreatitis, or liver disease (with exception of subjects with Gilbert's Syndrome, asymptomatic gall stones, liver metastases, or stable chronic liver disease per investigator assessment)
12. Peripheral neuropathy: > Grade 2 NCI-CTCAE version 4.03
13. Prior history of interstitial lung disease
14. History of noncompliance to medical regimens
15. Known active hepatitis B or C or known infection with human immunodeficiency virus (HIV). Subjects who are hepatitis B surface antigen [HBsAg] positive are eligible if they have hepatitis B virus (HBV) DNA less than 500 IU/mL or 2,500 copies/mL with monitoring and/or antiviral prophylaxis as appropriate.
16. Known SARS-CoV-2 infection; subjects with prior infection that has resolved per local institutions' requirements and screening guidance are eligible
17. 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 study medical monitor.
18. QTc Fridericia (QTcF) > 470 ms. Note: For subjects with longer QTcF on initial ECG, follow-up ECG may be performed in triplicate and the mean of the 3 values will be used to determine eligibility.
19. Any toxicity related to prior cancer therapies that has not resolved to  $\leq$  Grade 1, with the following exceptions: alopecia; neuropathy (which must have resolved to  $\leq$  Grade 2); congestive heart failure (CHF), which must have been  $\leq$  Grade 1 in severity at the time of occurrence and must have resolved completely; and Grade 2 hypothyroidism or panhypopituitarism related to treatment with immunotherapy (subject must be on a stable dose of hormone replacement therapy).
20. Clinically significant cardiac disease such as ventricular arrhythmia requiring therapy, uncontrolled hypertension, or any history of symptomatic CHF.
21. Known myocardial infarction or unstable angina within 6 months before the first zanidatamab dose.

## 4.3 Childbearing Potential

### 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 12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes.

A person who can father children is anyone born male who has testes and who has not undergone surgical sterilization (e.g., vasectomy followed by a clinical test proving that the procedure was effective). 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 during study participation and for at least 7 months after the last dose of study drug (see [Section 4.3.2](#)).

Female subjects must agree not to donate oocytes and male subjects must agree not to donate sperm for the duration of the study and for 7 months after the last dose of zanidatamab.

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. 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.

The investigator should also be notified of pregnancy occurring during the study or within 7 months following the last study treatment administration but confirmed after completion of the study.

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 7](#).

**Table 7: Acceptable Methods of Highly-Effective Birth Control**

<ul style="list-style-type: none"> <li>• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation<sup>a</sup>: <ul style="list-style-type: none"> <li>○ oral<sup>c</sup></li> <li>○ intravaginal</li> <li>○ transdermal</li> </ul> </li> <li>• Progestogen-only hormonal contraception associated with inhibition of ovulation<sup>a</sup>: <ul style="list-style-type: none"> <li>○ Oral</li> <li>○ Injectable</li> <li>○ Implantable<sup>b</sup></li> </ul> </li> <li>• intrauterine device (IUD)<sup>b,c</sup></li> <li>• intrauterine hormone-releasing system (IUS)<sup>b,c</sup></li> <li>• bilateral tubal occlusion<sup>b</sup></li> <li>• vasectomised partner<sup>b,c</sup></li> <li>• sexual abstinence<sup>d</sup></li> </ul>
--

a A subject should not use more than one method listed in the first 2 bullet categories (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.

e Approved contraceptive methods in Japan

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 8](#).

**Table 8: 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 Assessments

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 of consent
- Physician decision (non-AE, non-progressive disease [PD])
- Pregnancy
- PD (either radiographic or unequivocal clinical progression; see [Section 7.2](#))
- Protocol violation
- Study termination by sponsor
- Other, non-AE

Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes.

If a subject has not received zanidatamab for more than 4 weeks beyond the next scheduled dose, he/she will be withdrawn from study treatment unless approval is obtained from the medical monitor to continue on study treatment.

If a subject starts subsequent non-study anti-cancer therapy, then 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 6.6](#)) and the End of Study visit ([Section 6.7](#)). The End of Study visit should be performed regardless of whether a subject starts a new anti-cancer therapy(s).

#### **4.4.2 Subject Withdrawal from Study**

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

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

## 5 TREATMENTS

### 5.1 Treatments Administered

Subjects will be treated with zanidatamab administered as monotherapy.

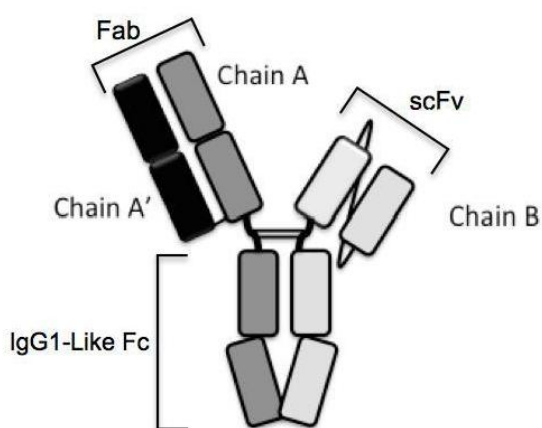
### 5.2 Investigational Study Drug (Zanidatamab)

Detailed information describing the preparation, administration, and storage of zanidatamab is located in the Pharmacy Manual. Study drug must be diluted as instructed in the Pharmacy Manual prior to administration.

#### 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 in [Figure 3](#). The IgG1-like fragment crystallizable (Fc) region of zanidatamab contains complementary mutations in each CH3 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 arm of antibody (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, 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 produced using a Chinese hamster ovary (CHO) clonal cell line. Zanidatamab is being developed as a treatment for locally advanced (unresectable) and/or metastatic HER2-expressing cancers.

**Figure 3: 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 5.2.6.1](#).

Dosing for zanidatamab (see [Section 5.2.2.1](#) for information regarding dose modifications) will be given as follows:

### Weight-based dosing:

- Dose Level 1: 20 mg/kg IV zanidatamab; dosing Q2W on Days 1 and 15 of each 28-day cycle
- Dose Level 2: 30 mg/kg IV zanidatamab; dosing Q3W on Day 1 of each 21-day cycle
- Dose Level -1 (to be used only if dose de-escalation from Dose Level 1 is needed): 15 mg/kg IV zanidatamab; dosing Q2W on Days 1 and 15 of each 28-day cycle.

### Flat dosing:

- 1,800 mg (for subjects < 70 kg) or 2,400 mg (for subjects  $\geq$  70 kg) Q3W on Day 1 of a 21-day cycle

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 60 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. [Section 5.2.2.2](#) provides guidelines for the management of infusion reactions.

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

All subjects enrolled in Part A will be dosed at least 24 hours apart on Cycle 1 Day 1 and be assessed for DLTs. Study drug administration, DLT evaluation, and safety observation will be carried out in the hospital setting and subjects will be under hospitalization management in principle. Subjects will be monitored per institutional standards during hospitalization, and AEs and concomitant medication will be recorded throughout this period. Discharge will be permitted for subjects with no safety concerns following study drug administration and observation for at least 24 hours. Subjects who are determined by the investigator to be manageable in the outpatient setting can be discharged. The investigator's decision to discharge will be based on clinical evaluation of the subject and any laboratory and/or radiological tests deemed necessary by the investigator. All subjects will be followed up via phone 24 hours after their discharge to evaluate their health status.

### 5.2.2.1 Dose Modifications

Recommendations for management of and potential dose modifications for zanidatamab-associated toxicity are provided in [Table 9](#). Guidelines for management of zanidatamab-associated left ventricular dysfunction are provided in [Table 10](#). Individual subjects who experience DLTs ([Section 3.1.2](#)) can continue on study drug (subject to dose modifications in this section based on the toxicities experienced) if the investigator, sponsor's medical monitor, and the SMC have discussed it and agree. Subjects with symptoms or findings consistent with  $\geq$  Grade 2 ILD should hold treatment with zanidatamab pending evaluation per institutional standards. Zanidatamab will be permanently discontinued for zanidatamab-associated  $\geq$  Grade 2 ILD that is confirmed.

For Dose Level 1 and Dose Level -1 Q2W dosing regimens, there must be a minimum of 12-days between zanidatamab doses. For cycle counting purposes, 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 28-day cycle is delayed by  $\geq$  12 days, then that dose will be considered skipped. The next dose delivered will be Day 1 of the subsequent cycle. For Dose Level 2 and Flat Dosing Q3W dosing regimens, since only one dose is administered per cycle, if a cycle is delayed for any reason, the next dose delivered will be considered Day 1 of the cycle that was delayed.

**Table 9: Recommended Management and Potential Dose Modifications for Zanidatamab -Associated Toxicity**

Adverse Event Related to Zanidatamab	Action for Zanidatamab
Grade 1 or Grade 2 nausea and vomiting	<ul style="list-style-type: none"> <li>Suggest a 5-HT3 receptor antagonist until resolution of symptoms, or a prochlorperazine.</li> <li>No dose modification of zanidatamab is required.</li> <li>For breakthrough nausea or vomiting, consider olanzapine 5 or 10 mg daily for 3 days. For subjects already receiving olanzapine, prochlorperazine may be used.</li> </ul>
Grade 3 or Grade 4 nausea and vomiting	<ul style="list-style-type: none"> <li>Suggest a 5-HT3 receptor antagonist plus a glucocorticoid especially dexamethasone); consider adding a NK-1 receptor antagonist to a 5-HT3 receptor antagonist and glucocorticoids if the latter combination is not sufficient for symptom relief. Treat until resolution of symptoms to <math>\leq</math> Grade 1.</li> <li>Do not administer zanidatamab until severity <math>\leq</math> Grade 1 or pre-treatment level.</li> <li>Optional dose reduction after symptoms resolved to <math>\leq</math> Grade 1 or pre-treatment level for Grade 3 nausea and vomiting. For Grade 4 symptoms or recurrent Grade 3 symptoms despite maximum use of 5-HT3 antagonists, glucocorticoids and NK-1 antagonist, dose reduction to the next lowest dose level is mandatory.<sup>a</sup></li> </ul>
Grade 1 or Grade 2 diarrhea	<ul style="list-style-type: none"> <li>Oral hydration with fluid that contains water, salt, and glucose, such as broth or Gatorade.</li> <li>Suggest loperamide 4 mg PO followed by 2 mg Q4H until no diarrhea.</li> <li>No dose modification of zanidatamab is needed.</li> </ul>

Adverse Event Related to Zanidatamab	Action for Zanidatamab
Grade 3 or Grade 4 diarrhea	<ul style="list-style-type: none"> <li>Aggressive fluid hydration and clear liquid diet.</li> <li>Suggest loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider octreotide 100 or 150 mcg subcutaneously Q8H for subjects with persistent diarrhea despite 48 hours of loperamide. If subjects are refractory to both loperamide and octreotide, gastroenterologist should be consulted.</li> <li>For Grade 3 diarrhea, optional dose reduction of zanidatamab after symptoms resolved to <math>\leq</math> Grade 1 or pre-treatment level. For Grade 4 symptoms or recurrent Grade 3 symptoms despite maximum use of loperamide and octreotide, dose reduction is mandatory.<sup>a</sup></li> </ul>
Grade 1 or Grade 2 rash	<ul style="list-style-type: none"> <li>Suggest topical steroid as needed.</li> <li>No dose modification of zanidatamab is needed.</li> </ul>
Grade 3 or Grade 4 rash	<ul style="list-style-type: none"> <li>Suggest initiation with topical steroid; if insufficient, consider oral corticosteroid. Wound care for possible erosion and ulceration to prevent infection, and analgesics for pain control if necessary.</li> <li>Do not administer zanidatamab until severity <math>\leq</math> Grade 1 or pre-treatment level.</li> <li>For Grade 3 rash, optional dose reduction of zanidatamab after symptoms resolved to <math>\leq</math> Grade 1 or pre-treatment level. For Grade 4 symptoms or recurrent Grade 3 symptoms despite maximum use of topical and oral corticosteroid, dose reduction is mandatory.<sup>a</sup></li> </ul>

5-HT3 = 5-hydroxytryptamine; AE = adverse event; NK-1 = neurokinin-1; PO = per oral (orally); Q2H = every 2 hours; Q4H = every 4 hours; Q8H = every 8 hours; Q2W = every 2 weeks; Q3W = every 3 weeks.

<sup>a</sup> For subjects receiving zanidatamab at 20 mg/kg Q2W, the recommended reduced dose is 15 mg/kg Q2W; For subjects receiving zanidatamab at 30 mg/kg Q3W, the recommended reduced dose is 20 mg/kg Q3W; For subjects receiving zanidatamab at 1800 mg Q3W, the recommended reduced dose is 1400 mg Q3W; For subjects receiving zanidatamab at 2400 mg Q3W, the recommended reduced dose is 1800 mg Q3W.

**Table 10: Management of Left Ventricular Dysfunction**

Left Ventricular Dysfunction (Regardless of Causality)	Action for Zanidatamab
<ul style="list-style-type: none"> <li>Absolute decrease in LVEF <math>\geq</math> 16 percentage points from pre-treatment baseline, or</li> <li>LVEF <math>&lt;</math> 50% and absolute decrease of <math>\geq</math> 10 percentage point below pre-treatment baseline</li> </ul>	<ul style="list-style-type: none"> <li>Suspend dosing for at least 4 weeks</li> <li>Repeat LVEF assessment within 4 weeks</li> <li>Dosing maybe resumed within 4 to 8 weeks if LVEF returns to <math>\geq</math> 50% and the absolute decrease is <math>\leq</math> 15 percentage points from baseline; otherwise permanently discontinue zanidatamab</li> </ul>
<ul style="list-style-type: none"> <li>Grade <math>\geq</math> 2 heart failure</li> </ul>	<ul style="list-style-type: none"> <li>Hold zanidatamab. Referral to a cardiologist is recommended. If Grade <math>\geq</math> 2 heart failure is confirmed, permanently discontinue.</li> </ul>

DLT = dose-limiting toxicity; LVEF = left ventricular ejection fraction

Note: The first cardiac DLT due to LVEF decline will result in withholding of the drug until recovery of the ejection fraction to prior levels.

### 5.2.2.2 Infusion Reactions

In the event of an infusion reaction, zanidatamab infusion should be interrupted and medical therapy administered according to institutional standard of care (which, depending upon severity

of the event, may include but not be limited to use of H<sub>1</sub> and H<sub>2</sub> inhibitors, corticosteroids, oxygen, IV fluids, epinephrine, and bronchodilators). Subjects should be evaluated and carefully monitored until complete resolution of signs and symptoms. Zanidatamab should be permanently discontinued in subjects who experience a life-threatening (Grade 4) infusion reaction. In the event of a Grade 3 infusion reaction the infusion should be stopped immediately, and the subject managed per institutional standards. The infusion should not be restarted even if signs and symptoms completely resolve. However, with approval of the sponsor's medical monitor, the subject may be dosed at the next scheduled treatment. Such subjects should receive additional prophylactic medication in addition to the mandatory corticosteroid, diphenhydramine, and acetaminophen. Also, the duration of infusion should be increased.

If feasible, blood samples for evaluation of PK, tryptase and/or ADA may be drawn during or as soon as possible (optimally within 6 hours, and up to 24 hours) after an infusion reaction.

### **5.2.3 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.

### **5.2.4 Packaging and Labeling**

Refer to the Pharmacy Manual for packaging and labeling.

### **5.2.5 Preparation**

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

### **5.2.6 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.

#### **5.2.6.1 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. Pre-treatment 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

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.

### **5.2.6.2 Allowed Concomitant Therapy**

Supportive therapy, including transfusions, bisphosphonates (e.g., Zometa<sup>®</sup>), and granulocyte colony-stimulating factor (G-CSF), are allowed on study except as noted in [Section 5.2.6.3](#). 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.

### **5.2.6.3 Prohibited Concomitant Therapy**

Subjects may not receive cancer-related surgery, radiotherapy, other investigational, or systemic anti-neoplastic therapy during the study. Traditional 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. The use of growth factors and/or transfusions is prohibited during the DLT evaluation period for subjects in Part A.

## **5.3 Duration of Study Treatment**

Subjects may continue on study treatment until radiographically confirmed disease progression per RECIST 1.1, unequivocal clinical progression, unacceptable toxicity, consent withdrawal, physician decision, pregnancy, protocol violation, start of a subsequent anti-cancer therapy, or study termination by the sponsor. Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. 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, in the opinion of the clinical investigator, demonstrate ongoing clinical benefit despite radiologic progression may continue to receive treatment following discussion with and approval from the sponsor's medical monitor.

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

## **5.4 Treatment Compliance**

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

## 6 TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are performed. For Dose Level 1 (20 mg/kg zanidatamab IV Q2W) and Dose Level -1 (if used, 15 mg/kg zanidatamab IV Q2W), the planned study assessments are detailed in [Table 1](#) and the PK sampling schedule is in [Table 3](#). For Dose Level 2 (30 mg/kg zanidatamab IV Q3W), the planned study assessments are detailed in [Table 2](#) and the PK sampling schedule is in [Table 4](#).

### 6.1 Screening Visit

Screening procedures will be completed within 28 days before first administration of zanidatamab. Pre-screening for HER2 status is allowed before subject's consent. In case a subject cannot receive their first treatment within the required time windows for the screening assessments, rescreening should be performed before first zanidatamab administration. 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
- Full medical history, including concomitant illnesses/diseases and concomitant medications and diagnostic information
- Eligibility (against the inclusion and exclusion criteria)
- Demographic data, including ethnic origin, date of birth, and sex
- Disease assessment per RECIST version 1.1 (CT/MRI)
- Physical examination, including height and body weight
- ECOG performance status
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards])
- Samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests
- 12-lead ECG Note: For subjects with longer QTcF on initial ECG, follow-up ECG may be performed in triplicate and the mean of the 3 values will be used to determine eligibility.
- Samples for hepatitis B surface antigen [HBsAg] and hepatitis C antibody.
  - If HBsAg positive, then hepatitis B DNA levels are required to determine eligibility
  - If HBsAg negative, then anti-HBc antibody and anti-HBs antibody are required
  - If either anti-HBc or anti-HBs positive, then hepatitis B DNA levels are required

- o For subjects with a known history of hepatitis B infection, only hepatitis B DNA testing is required at screening.
- HIV tests if indicated
- Adverse events
- Concomitant medications
- New biopsy or archived tumor tissue (see [Section 4.1](#))
- Echocardiogram/MUGA
- Brain MRI scan or CT scan if MRI not feasible [CT with contrast unless medically contraindicated]; only required for subjects with breast cancer, GEA, or a history of brain metastases)
- Bone scan (if clinically indicated [e.g., bone pain and/or known history of bone metastases])
- High-resolution chest CT
- PFTs and hemoglobin
- KL-6

## 6.2 Zanidatamab Q2W Dosing Treatment Period

For subjects on zanidatamab Q2W, the treatment cycle is 28 days with zanidatamab given on Days 1 and 15.

For subjects enrolled in Part A, dosing of subsequent subjects on Cycle 1 Day 1 will be at least 24 hours apart. Study drug administration, DLT evaluation, and safety observation during the DLT period will be carried out in the hospital setting and subjects will be under hospitalization management in principle. Subjects will be monitored per institutional standards during hospitalization, and AEs and concomitant medications will be recorded throughout this period. Discharge will be permitted for subjects with no safety concerns following study drug administration and observation for at least 24 hours. Subjects who are determined by the investigator to be manageable in the outpatient setting can be discharged. The investigator's decision to discharge a subject will be based on clinical evaluation of the subject and any laboratory and/or radiological tests deemed necessary by the investigator. All subjects will be followed up via phone 24 hours after their discharge to evaluate their health status.

### 6.2.1 Cycle 1 Day 1

Day 1 is the first dosing day of the cycle.

- Review inclusion/exclusion criteria, predose. Subjects must still meet inclusion/exclusion criteria prior to receiving treatment.

- Physical examination, including body weight, predose
- Adverse events, predose and postdose
- Concomitant medications
- ECOG performance status, predose
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards]), predose and postdose (within 30 minutes after the end of the infusion)
- 12-lead ECG, predose and 4 h after the start of dosing. Note: For predose ECG only, for subjects with longer QTcF on initial ECG, follow-up ECG may be performed in triplicate and the mean of the 3 values will be used to determine eligibility.
- Samples for hematology, coagulation, serum chemistry, urinalysis, tryptase level (not required if not available locally), and pregnancy (if applicable) tests, predose with an allowed time window of 3 days
- Samples for antibodies (ADA) and HER2 ECD, predose
- Zanidatamab administration
- PK sampling, predose and postdose (Table 3)

### **6.2.2 Cycle 1 Days 3 and 5**

- PK sampling
- Adverse events
- Concomitant medications

### **6.2.3 Cycle 1 Day 8 ( $\pm$ 2 Days; Part B only)**

- Outpatient safety monitoring for AEs and concomitant medications (may be conducted by telephone or in-person at the investigator's discretion)

### **6.2.4 Cycle 1 Day 15 ( $\pm$ 2 Days)**

- Adverse events, predose and postdose
- Concomitant medications
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards]), predose and postdose (within 30 minutes after the end of the infusion)

- Samples for hematology, coagulation, and serum chemistry, predose with an allowed time window of 3 days
- Samples for ADA and HER2 ECD, predose
- Zanidatamab administration
- PK sampling, predose and at the end of infusion

### **6.2.5 Cycle 1 Day 22 ( $\pm$ 2 Days; Part B only)**

- Outpatient safety monitoring for AEs and concomitant medications (may be conducted by telephone or in-person at the investigator's discretion)

### **6.2.6 Cycle 2 Day 1**

Day 1 is the first dosing day of the cycle.

- Physical examination, including body weight, predose
- Adverse events, predose and postdose
- Concomitant medications
- ECOG performance status, predose
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards]), predose and postdose (within 30 minutes after the end of the infusion)
- 12-lead ECG, predose
- Samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests, predose with an allowed time window of 3 days
- Samples for ADA and HER2 ECD, predose
- Zanidatamab administration
- PK sampling, predose and at the end of infusion

### **6.2.7 Cycle 2 Day 15 ( $\pm$ 2 Days)**

- Adverse events, predose and postdose
- Concomitant medications
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards]), predose and postdose (within 30 minutes after the end of the infusion)

- Samples for hematology, serum chemistry, and coagulation, predose with an allowed time window of 3 days
- Samples for ADA and HER2 ECD, predose
- Zanidatamab administration
- PK sampling, predose and at the end of infusion

### **6.2.8 Cycle 2 Day 28 ( $\pm$ 7 Days)**

- MRI/CT scan (based on an 8-week interval from Cycle 1 Day 1)
- Echocardiogram/MUGA
- Adverse events
- Concomitant medications

### **6.2.9 Additional Cycles**

#### **6.2.9.1 Day 1**

Day 1 is the first dosing day of the cycle.

- Physical examination, including body weight, predose
- Adverse events, predose and postdose
- Concomitant medications
- ECOG performance status, predose
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards]), predose and postdose (within 30 minutes after the end of the infusion)
- 12-lead ECG, predose
- Samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests, predose with an allowed time window of 3 days
- Zanidatamab administration
- PK sampling, predose and at the end of infusion (Day 1 of even-numbered cycles only)
- ADA and HER2 ECD sampling predose at Cycles 3 and 4 and even-numbered cycles thereafter

### 6.2.9.2 Day 15 ( $\pm$ 2 Days)

- Adverse events, predose and postdose
- Concomitant medications
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards]), predose and postdose (within 30 minutes after the end of the infusion)
- Zanidatamab administration
- PK sampling, predose and at the end of infusion at Cycles 3 and 4

## 6.3 Zanidatamab Q3W Dosing Treatment Period

For subjects on zanidatamab Q3W, the treatment cycle is 21 days with zanidatamab given on Day 1.

For subjects enrolled in Part A, dosing of subsequent subjects on Cycle 1 Day 1 will be at least 24 hours apart. Study drug administration, DLT evaluation, and safety observation during the DLT period will be carried out in a hospital setting, and subjects will be under hospitalization management in principle. Subjects will be monitored per institutional standards during hospitalization, and AEs and concomitant medications will be recorded throughout this period. Discharge will be permitted for subjects with no safety concerns following study drug administration and observation for at least 24 hours. Subjects who are determined by the investigator to be manageable in the outpatient setting can be discharged. The investigator's decision to discharge a subject will be based on clinical evaluation of the subject and any laboratory and/or radiological tests deemed necessary by the investigator. All subjects will be followed up via phone 24 hours after their discharge to evaluate their health status.

### 6.3.1 Cycle 1 Day 1

Day 1 is the first dosing day of the cycle. Procedures are identical to those for Cycle 1 Day 1 for Q2W dosing except that the PK sampling schedule is in [Table 4](#).

### 6.3.2 Cycle 1 Days 3 and 5

- PK sampling
- Adverse events
- Concomitant medications

### **6.3.3 Cycle 1 Day 8 ( $\pm$ 2 Days; Part B only)**

- Outpatient safety monitoring for AEs and concomitant medications (may be conducted by telephone or in-person at the investigator's discretion)

### **6.3.4 Cycle 1 Day 15 ( $\pm$ 2 Days; Part B only)**

- Outpatient safety monitoring for AEs and concomitant medications (may be conducted by telephone or in-person at the investigator's discretion)

### **6.3.5 Cycle 2 Day 1**

Day 1 is the first dosing day of the cycle. Procedures are identical to those for Cycle 1 Day 1 for Q2W dosing.

### **6.3.6 Cycle 2 Day 21 ( $\pm$ 7 Days)**

- Echocardiogram/MUGA
- Adverse events
- Concomitant medications

### **6.3.7 Additional Cycles**

There is a scheduled visit only on Day 1 of additional cycles.

Day 1 is the first dosing day of the cycle. Procedures are identical to those for Additional Cycles Day 1 for Q2W dosing except that PK sampling will also occur on Day 1 of Cycle 3.

## **6.4 Every 8 Weeks ( $\pm$ 7 Days)**

- MRI/CT scan (based on 8-week intervals from Cycle 1 Day 1)
- Adverse events
- Concomitant medications
- High-resolution chest CT (may be the same scan used for disease assessment, if appropriate; required every 16 weeks after the Week 16 scan if not being used for disease assessments)
- KL-6

## 6.5 End of Cycle 5, End of Cycle 8, and Every 6 Months Thereafter ( $\pm$ 7 Days)

- Echocardiogram/MUGA (timing is based on theoretical cycles [i.e., not considering dose delays] and months, all timed from Cycle 1 Day 1)

## 6.6 End of Treatment Visit

The End of Treatment visit will take place at the time a subject permanently stops treatment. The End of Treatment visit and the End of Study visit may be the same visit, if the subject's last zanidatamab administration was  $> 30$  days prior to the decision to permanently stop treatment.

- Adverse events
- Concomitant medications
- Physical examination, including body weight
- ECOG performance status
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards])
- 12-lead ECG
- Samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests
- Echocardiogram/MUGA (not required if  $\leq 3$  months since last scan)
- PK sampling (only required if subject has completed less than 6 months of treatment)
- Samples for ADA and HER2 ECD
- MRI/CT scan (not required if  $\leq 4$  weeks since previous scan)
- High-resolution chest CT (may be the same scan used for disease assessment, if appropriate)
- KL-6
- Optional tumor biopsy in case of disease progression

## 6.7 End of Study Visit

The End of Study visit will take place 30 days (+ 7-day window) after the last administration of zanidatamab. The End of Study visit should be performed regardless of whether a subject starts a new anti-cancer therapy(s).

- Adverse events
- Concomitant medications
- Physical examination, including body weight
- ECOG performance status
- Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation [if available], temperature [oral or tympanic per institutional standards])
- 12-lead ECG
- Samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests
- Echocardiogram/MUGA (not required if  $\leq 3$  months since last scan)
- PK sampling (only required if subject has completed less than 6 months of treatment)
- Sample for ADA
- MRI/CT scan (only required if feasible, and last scan showed unconfirmed PR/CR and performed  $\geq 4$  weeks prior)
- High-resolution chest CT (may be the same scan used for disease assessment, if appropriate)
- KL-6
- Optional tumor biopsy in case of disease progression

## 7 STUDY ASSESSMENTS

For Dose Level 1 (20 mg/kg zanidatamab IV Q2W) and Dose Level -1 (if needed, 15 mg/kg zanidatamab IV Q2W), the planned study assessments are detailed in [Table 1](#) and the PK sampling schedule is in [Table 3](#). For Dose Level 2 (30 mg/kg zanidatamab IV Q3W), the planned study assessments are detailed in [Table 2](#) and the PK sampling schedule is in [Table 4](#).

### 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, any treatment for prior malignancies and response to prior treatment, and any current medications.

Tumor biopsies will be collected from all subjects at either pre-screening or screening and processed as FFPE tissues to assess HER2 amplification and protein expression by IHC. 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. Enrollment decisions will be based on local or central assessments of HER2 expression.

All samples will be run in a central laboratory under Clinical Laboratory Improvement Amendments (CLIA) guidelines.

Tests for hepatitis B surface antigen and hepatitis C antibody will be performed at screening. If HBsAg positive, then hepatitis B virus DNA is required at screening and every 1 to 3 months during treatment. If HBsAg negative, then anti-HBc antibody and anti-HBs antibody are required at screening. If either anti-HBc antibody or anti-HBs antibody positive, then hepatitis B DNA levels are required at screening and every 1 to 3 months during treatment. For subjects with a known history of hepatitis B infection, only hepatitis B DNA testing is required at screening, then every 1 to 3 months during treatment. Subjects with hepatitis B DNA levels  $\geq 20$  IU/mL ( $\geq 2.1$  log copies/mL) should be administered appropriate antiviral therapy (e.g., nucleoside analogs) according to local and institutional standards. HIV testing will be performed at screening if indicated. A blood test to establish baseline tryptase level for the purpose of characterizing potential IRRs will be performed (not required if not available locally). 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

#### 7.2.1 CT and MRI Scans for Tumor Response

Measures of anti-tumor activity will be evaluated based on response assessments made according to RECIST version 1.1 ([Section 12.1](#)). Clinical response of CR, PR, SD, or PD will be

determined at each assessment by the investigator. PD includes progressive disease per RECIST version 1.1 and clinical disease progression per investigator. Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes.

Tumor response will be evaluated based on CT and/or MRI scans (using the same methodology for each scan of the same subject) of the chest, abdomen, and pelvis plus additional areas of known or suspected tumor involvement (e.g., brain, extremities). The radiological assessment will be performed at the visits according to the description provided in the assessment schedule (Table 1 or Table 2, depending on the dosing regimen). If appropriate for tumor assessment, high-resolution chest CT scans should be used in order to assess ILD, as well as disease response; otherwise, separate high-resolution chest CT scans should be used in conjunction with PFTs and KL-6 to assess for ILD at protocol specific time points (see Table 1, Table 2, and Section 7.5.9).

Objective responses and tumor progression will be evaluated locally.

### 7.2.2 Biopsy for Biomarkers

Local or central results for HER2 expression can be used for study eligibility determination but all subjects should have tumor samples submitted to the central laboratory.

If possible, an FFPE tumor sample taken  $\leq 6$  months prior to enrollment with no intervening HER2 targeted treatment will be submitted at screening for evaluation of HER2 status. HER2 eligibility may be based on local or central read of new or archived tumor biopsy collected  $\leq 6$  months prior to enrollment. If a subject is unable to provide a biopsy taken  $\leq 6$  months prior to enrollment, archived tissue collected  $> 6$  months prior to enrollment may be used if approved by the sponsor's medical monitor.

Gastric cancer-specific guidelines (Bartley 2017) will be used to assess HER2 expression in GEA. ASCO/CAP guidelines for assessing HER2 expression in breast cancer (Wolff 2018) will be used to assess HER2-expression levels for all non-GEA cancers.

An optional tumor biopsy may also be collected from the time of disease progression up to the end of study visit.

## 7.3 Pharmacokinetic Assessments

Venous blood samples for measurement of serum concentrations of zanidatamab will be drawn at time points specified in the assessment schedule (Table 1 or Table 2, depending on the dosing regimen). The actual date and time (24-h clock time) of each sampling will be recorded in the subject's source document at the site. The sampling window for each time point is identified in the PK sampling schedule (Table 3 or Table 4, depending on the dosing regimen). Deviations from planned sampling windows will be assessed before database lock for the impact on PK and may be excluded from time point 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 ( $\lambda_z$ ), 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 ( $V_z$ ), 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 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 h have elapsed since the last dose of study drug, if possible. The sample will be recorded as an unscheduled time point 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 Immunogenicity Assessments

Blood samples to test for antibodies to zanidatamab and HER2 ECD will be obtained at the time points outlined in the schedule of assessments (Table 1 or Table 2, depending on the dosing regimen). If a subject terminates early from the clinical trial, all efforts will be made to collect blood samples to test for antibodies to zanidatamab and HER2 ECD unless consent has been withdrawn. Additional samples may be drawn in the event of an infusion reaction.

The immunogenicity testing will be performed in 3 steps: 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 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 the anti-zanidatamab antibody potential for neutralizing activity on zanidatamab.

HER2 ECD testing will be performed using a clinically-validated assay (ADVIA Centaur HER-2/neu Immunoassay). Serum concentration of HER2 ECD at each timepoint will be determined.

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

## 7.5 Safety Assessments

Safety assessments will consist of AEs, hematology, coagulation, serum chemistry, urinalysis, ADAs and neutralizing antibodies, vital signs, physical examination (including body weight and lung auscultation), ECG, ECOG performance status, and echocardiogram/MUGA.

Pregnancy tests per local standards will also be performed at the specified time points, as applicable.

Safety will be monitored throughout the study by the Sponsor and an SMC. The SMC will be tasked with monitoring the safety of subjects and assessing DLTs through regular and/or ad hoc meetings. In addition, an IDMC will be available on an ad hoc basis to review any safety issue referred by the SMC or the sponsor and will act in an advisory capacity to the sponsor. See [Section 3.1.3](#) for additional details.

### 7.5.1 Adverse Events

#### 7.5.1.1 Adverse Event Definition

##### 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 main informed consent for the study through Cycle 1 Day 1 pre-dose, only study protocol-related SAEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on Cycle 1 Day 1 should be recorded on the medical history page.
- 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 7.5.1.3](#)). 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	An important medical event which, based upon appropriate medical judgment, may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other SAE criteria.

AE = adverse event; SAE = serious adverse event.

### Adverse Event Severity

AE severity should be graded using the NCI-CTCAE, version 4.03. These criteria are provided in the study manual. Adverse Events which do not have a corresponding CTCAE term will be assessed according to the NCI-CTCAE, version 4.03 general guidelines for grading.

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).

**Table 11: Adverse Event Grade Assessment Guidelines (Per NCI-CTCAE v4.03)**

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) <sup>a</sup>
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL <sup>b</sup>
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

ADL = activities of daily living; AE = adverse event; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

### 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.

#### 7.5.1.2 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

### **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 event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- 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**

Do not use the term “disease progression” alone when reporting AEs, including 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”). Otherwise, it is acceptable to report the specific disease (e.g., non-small cell lung cancer) as an SAE.

## Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 7 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.

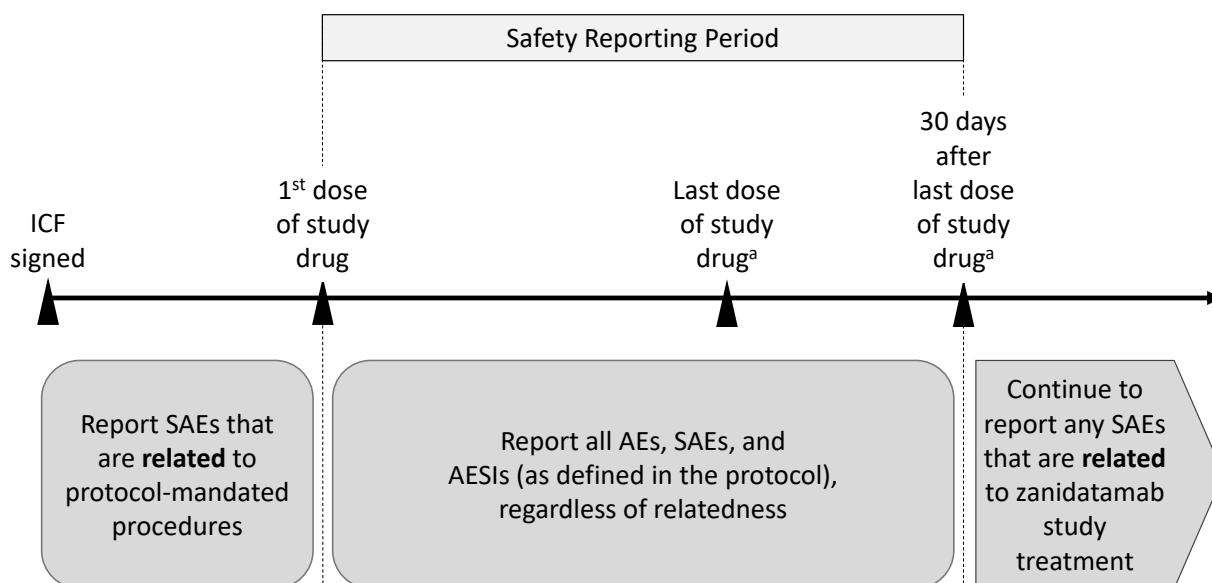
Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug will also be recorded on the Adverse Events CRF.

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 7.5.1.1](#)) should be reported as SAEs.

### 7.5.1.3 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 main informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

**Figure 4: Adverse Event Reporting Periods**



AE = adverse event; AESI = adverse event of special interest; ICF = informed consent form; SAE = serious adverse event.

a All pregnancies are reported through 7 months after the last dose of zanidatamab.

SAEs 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. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest (AESIs) may be followed until resolution, return to baseline, or study closure.

#### **7.5.1.4 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 (or its representatives), 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
- Study treatment
- Investigator assessment of relationship

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 (or its representatives) as soon as it becomes available.

Investigators are to report the event to the representative's medical monitoring support center (MMS) via phone on holidays (including Saturday and Sunday, Japan time), if they consider the events are critical and/or may affect the continuation of the trial.

TEL: +49 621 878 2850 or Japan toll free 03 4477 5856

FAX: +49 621 8782 828

Email: ZW25-102@prahs.com

#### **7.5.1.5 Sponsor Safety Reporting to Regulatory Authorities**

Investigators are required to report all SAEs to the sponsor (or its representatives) (see [Section 7.5.1.4](#)).

The sponsor (or its representatives) will report all SAEs to regulatory authorities as required per local regulatory reporting requirements.

### 7.5.2 Adverse Events of Special Interest

AESIs are infusion-related reactions, non-infectious pulmonary toxicities, and cardiac events of absolute decrease in LVEF of  $\geq 10$  percentage points below pre-treatment baseline and absolute value  $< 50\%$ , and/or Grade  $\geq 2$  heart failure. AESIs should be recorded as adverse events and reported as SAEs when appropriate. AESIs should continue to be followed until resolution or return to baseline or study closure. AESIs should be recorded on the relevant eCRF and reported as SAEs when appropriate. Additional data related to AESIs may be collected in the eCRF.

### 7.5.3 Clinical Laboratory Evaluation

Samples for clinical laboratory tests will be obtained at selected timepoints specified in the assessment schedule (Table 1 or Table 2, depending on the dosing regimen).

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 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
- Phosphorus

The estimated GFR should be calculated using a standard equation (the calculation ‘eGFR creat’ recommended by the Japanese Society of Nephrology is preferred).

KL-6, a sialylated carbohydrate antigen, will be measured at screening/baseline and other specific timepoints to assess changes that may be associated with ILD.

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.

If local testing is available, tryptase blood tests will be performed to characterize IRRs. A blood sample for baseline tryptase will be drawn pre-dose on Cycle 1 Day 1. In the event of an IRR (of any grade severity), if feasible, a blood sample should be drawn during or as soon as possible (optimally within 6 hours, and up to 24 hours) after the IRR.

#### **7.5.4 Vital Signs**

Vital signs measurements include heart rate, blood pressure, respiratory rate, oxygen saturation (if available), and temperature. Vital signs will be recorded at selected timepoints specified in the assessment schedule ([Table 1](#) or [Table 2](#), depending on the dosing regimen) 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.

#### **7.5.5 Physical Examination**

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. During lung examination, auscultation should be performed to assess early signs of ILD (e.g., crackles at the lung bases in the posterior axillary line). Height will only be measured at screening. Weight will be measured as part of all physical examinations.

#### **7.5.6 ECOG Performance Status**

ECOG PS will be assessed at selected timepoints specified in the assessment schedule ([Table 1](#) or [Table 2](#), depending on the dosing regimen). ECOG PS scores are described below:

Grade	Criteria and Description According to ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	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	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

### 7.5.7 Electrocardiogram

The 12-lead ECGs will be recorded at selected timepoints specified in the assessment schedule (Table 1 or Table 2, depending on the dosing regimen) 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 Adverse Event CRF. At least the following parameters should be assessed: heart rate, PR interval, QRS complex, and QTcF. For the Cycle 1 Day 1 predose ECG only, for subjects with longer QTcF on initial ECG, follow-up ECG may be performed in triplicate and the mean of the 3 values will be used to determine eligibility.

### 7.5.8 Echocardiogram/MUGA

Echocardiograms or MUGAs are recorded at selected timepoints specified in the assessment schedule (Table 1 or Table 2, depending on the dosing regimen). 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 5.2.2.1.

### 7.5.9 Pulmonary Function Testing

Pulmonary function tests (PFTs) will be obtained at screening/baseline as specified in the assessment schedule (Table 1 or Table 2, depending on the dosing regimen) and as clinically indicated. PFTs should include measurement of FVC, TLC, DLCO/TLCO, and percutaneous arterial oxygen saturation (SpO<sub>2</sub>). Hemoglobin should be measured on the same day as PFT testing and the DLCO/TLCO result corrected for hemoglobin level. If feasible, SpO<sub>2</sub> should be measured on room air. PFT findings must be recorded on the ILD CRF, and findings that are abnormal and clinically significant must be recorded on Prior Medical History CRF (at baseline/screening) or on the Adverse Event CRF (after Cycle 1 Day 1). If SpO<sub>2</sub> is not measured on room air, the amount of oxygen delivery at the time of measurement must be recorded on the ILD CRF.

PFTs should be used in conjunction with high-resolution chest CT scans and KL-6 to evaluate ILD, as clinically indicated.

## 7.6 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. AEs will be assessed per CTCAE v.4.03 for consistency with prior safety data generated in the Phase 1 study outside Japan.

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) at their discretion.

The investigator must permit the IRB, 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 as described in the Monitoring Plan but may be modified by the rate of subject recruitment.

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

- 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. Data to be recorded directly on the eCRF will be identified. Any changes to the data 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 Hypothesis

This is an open-label Phase 1 PK study. No statistical hypotheses will be tested.

### 9.2 Determination of Sample Size

With the mTPI study design, the exact number of subjects needed to complete the dose escalation portion is unknown because it depends on the number of subjects enrolled in each cohort. Up to approximately 48 subjects may be enrolled in this study, i.e., up to 30 in the dose-escalation component of Part A and up to 18 in the safety evaluation of the 2-tier flat dose (Figure 1). Between the dose-escalation component and expansion (Part B), at least 6 PK-evaluable GEA subjects and at least 6 PK-evaluable non-GEA subjects are required at Dose Level 1 and 2 assuming both dose levels are determined to be safe. Expansion into Part B will only proceed if Part A does not yield the required 6 PK-evaluable GEA and non-GEA subjects at Dose Levels 1 and 2.

### 9.3 Analysis Sets

For the purposes of analysis, the subject analysis sets are defined in Table 12.

**Table 12: Subject Analysis Sets**

Analysis Set	Description
Safety	A subject is considered safety evaluable if he/she received any amount of zanidatamab. The safety analysis set will be used for all summaries of safety data and immunogenicity data.
Measurable disease	A subject is considered as part of the measurable disease analysis set if he/she is in the safety analysis set and has unidimensional measurable disease at baseline according to RECIST version 1.1 criteria. This analysis set will be used to summarize efficacy endpoints.
Response Evaluable	A subject is considered as part of the response evaluable analysis set if he/she is in the measurable disease analysis set and has at least one evaluable, post-baseline disease assessment (per RECIST 1.1) or discontinued study treatment due to death or clinical progression. This analysis set will be used to summarize efficacy endpoints.
Pharmacokinetic	A subject is considered PK-evaluable if he/she received zanidatamab and has at least 4 measurable concentrations from postdose Cycle 1 Day 1 through pre-dose Cycle 2 Day 1. Subjects for which the PK profile cannot be adequately characterized, or who have protocol deviations (or other characteristics defined in the SAP) that could affect the PK evaluation, will be flagged and excluded from either PK parameters derivation or PK concentration summary statistics based on the type of the deviation. The PK analysis set will be used for the summaries of all PK data.

## **9.4 Statistical and Analytical Plans**

The statistical analysis plan (SAP) will be developed and finalized before database lock and will provide additional details regarding the statistical methods, endpoints, and analyses to be performed as well as the procedures for accounting for missing, unused, and spurious data, 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 all subjects have either completed all study visits per protocol or discontinued the study.

#### **9.4.1.1 Randomization and Blinding**

This is an 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**

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**

Data may be analyzed in subgroups based on cancer type (e.g., GEA vs non-GEA) and/or zanidatamab dose level. Details, including any additional subgroups of interest, will be provided in the SAP.

### 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

Efficacy endpoints are secondary for this study and include the following:

- ORR
- DOR
- DCR
- CBR
- PFS

#### Endpoint Definitions

##### *Objective Response Rate (ORR)*

Objective response rate is defined as the proportion of subjects who achieve a best overall response of either CR or PR as determined by the RECIST 1.1 criteria. The ORR and the corresponding exact 2-sided binomial 95% CI, calculated using the method of Clopper-Pearson (Clopper 1934) will be provided.

***Duration of Response (DOR)***

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. If the overall number of subjects with confirmed objective response is too small for meaningful analyses, a descriptive analysis will be performed instead. This analysis will present summary statistics for the DOR and number of subjects with disease progression and number censored.

In addition, the proportion of subjects with a DOR  $\geq$  16 weeks and the corresponding 95% CI will be calculated.

Results may be presented by zanidatamab dose and cancer type.

***Disease Control Rate (DCR)***

A subject is said to have achieved disease control if they have a best overall response of CR, PR, or SD according to RECIST version 1.1 criteria. The proportion of subjects who achieve a disease control response and the corresponding exact 2-sided 95% CIs calculated using the method of Clopper-Pearson ([Clopper 1934](#)) will be provided.

***Clinical Benefit Rate (CBR)***

Clinical benefit is defined as achieving SD for  $\geq$  24 weeks or a confirmed, best overall response of CR or PR per RECIST 1.1. The proportion of subjects with clinical benefit and corresponding exact 2-sided 95% CIs calculated using the method of Clopper-Pearson ([Clopper 1934](#)) will be provided.

***Progression-Free Survival (PFS)***

PFS time is defined as the time from the first dose of zanidatamab to the date of documented disease progression per RECIST version 1.1 ([Section 12.1](#)), clinical progression (defined in [Section 7.2.1](#)), or death from any cause. 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% CIs will be computed ([Kaplan 1958](#)). The mean PFS times will also be reported.

**9.4.7 Pharmacokinetic Analyses**

PK endpoints are secondary for this study.

Pharmacokinetic analyses will be performed based on PK analysis set as defined in [Section 9.3](#).

Pharmacokinetic concentrations will be summarized by zanidatamab dose and cancer type and presented graphically as individual and mean plots.

The following PK parameters will be derived for single dose using PK sampling data after Dose 1:

- $C_{\max,1}$ : maximum observed serum concentration for dose 1
- $t_{\max,1}$ : time to maximum observed serum concentration for dose 1
- $AUC_{0-t}$ : area under the serum concentration-time curve from zero to the last measurable concentration for dose 1
- $\lambda_z$ : terminal elimination rate constant
- $t_{1/2}$ : apparent elimination half-life
- $AUC_{0-\infty}$ : area under the serum concentration-time curve from zero to infinity for Dose 1
- CL: serum clearance
- $V_z$ : volume of distribution in the terminal elimination phase

Elimination parameters will be calculated if data allow to meet standard PK acceptance criteria.

The following PK parameters will be derived for multiple doses using PK sampling data after all doses:

- $AUC_{\tau}$ : area under the serum concentration-time curve from zero to the last end of dosing interval for Dose 1
- $C_{ave}$ : average concentration over dosing interval, calculated as  $AUC_{\tau}/\tau$  where  $\tau$  is the dosing interval, for Dose 1
- $C_{\max,i}$  and  $C_{\min,i}$  ( $C_{\text{trough}}$ ) for all doses (*if* – dose number, 1-22 or more)
- $R_{C_{\min}}$ : accumulation index, calculated as  $C_{\min}(\text{last dose})/C_{\min}(\text{first dose})$
- $C_{ss}$ : trough concentration at steady state

The attainment of steady state will be determined by repeated measures analysis of variance (ANOVA) using aggregate assessment of trough concentrations.

Dose proportionality and effect of cancer type will be assessed by appropriate statistical methods based on available data. Single dose PK parameters ( $C_{\max}$ ,  $AUC_{0-\infty}$ , CL, etc.) as well as multiple dose parameters such as  $C_{\max,i}$ ,  $C_{\min,i}$ ,  $C_{ss}$  will be used in these analyses.

The details of PK analysis will be described in the SAP.

### 9.4.8 Immunogenicity Analyses

Immunogenicity endpoints are secondary for this study.

All immunogenicity listings and analyses will be based on the Safety Analysis Set as described in [Section 9.3](#).

Subjects developing an antibody response to zanidatamab will be listed. The listing will be done for Tier 1 – screening assay for each subject and time point in positive/negative format. For the samples positive in screening assay the confirmation positive/negative results (Tier 2) and titer (Tier 3) will be added. If available, domain specificity data and anti-zanidatamab neutralizing antibodies will be listed and summarized as well.

The time-course of immunogenicity will be summarized: first cycle at which ADAs are observed, number of cycles in which measurable ADA's are present, whether or not ADA's return to baseline values during the course of treatment, and the number of cycles elapsed until ADA's return to baseline values.

Serum concentrations of HER2 ECD will be listed for each subject. The serum HER2 ECD concentration at each timepoint will be summarized with summary statistics (mean, standard deviation, coefficient of variation, geometric mean, etc.)

Effect of immunogenicity on PK and specifically clearance of zanidatamab will be explored.

The details of immunogenicity analyses will be described in the SAP.

### 9.4.9 Safety Variables

No inferential testing will be performed on safety data. Safety data will be summarized using descriptive statistics. At the end of the study, appropriate summaries of all safety data will be provided as defined below.

Adverse events will be listed individually by subject. The zanidatamab dose level and cancer type will be included in the listing.

The number of subjects experiencing an AE will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of subjects with AEs in different categories (e.g., causally related, CTCAE grade  $\geq 3$ ) will be summarized by dose level or cancer type, and overall. Serious AEs will be summarized separately.

Any study protocol-related SAE occurring before the first dose of zanidatamab will be included in the data listings but will not be summarized in the summary table of AEs. Summary tables will exclude AEs observed more than 30 days after the administration of the last dose of zanidatamab, with the exception of SAEs assessed as related by the investigator.

Hematology, serum chemistry, coagulation, vital signs, body weight, estimation of ejection fraction, and ECG data will be listed individually by subject and suitably summarized. For all laboratory variables that are included in the CTCAE version 4.03, the CTCAE grade will be

provided. Summary statistics of the number of non-missing observations, mean, median, standard deviation, minimum, and maximum will be reported.

Details of any deaths will be listed for all subjects.

For urinalysis parameters, any qualitative assessments will be summarized for all subjects with results of negative, trace, or positive.

All physical examination and ECOG performance status data will be listed individually by subject.

#### **9.4.10 Interim Analyses**

There is currently no official interim analysis planned for this study. However, formal IDMC review of the cumulative safety and PK data will be performed during the trial. Details of the IDMC review are provided in the IDMC charter. Based on enrollment and data, interim (sub-) analyses may be conducted during the course of the study and interim analyses may be presented at medical conferences (e.g., ESMO-Asia).

## **10 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS**

### **10.1 Institutional Review Board**

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. 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 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 together with the approved ICF must be filed in the study files.

The head of the study site will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study provided by investigators or sponsor. The investigator will submit written summaries of the study status to the IRB via the head of study site as required. On completion of the study, the IRB 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.

#### **10.3.1 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-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 his/her 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. The study subjects will be informed about this new information and re-consent will be obtained.

### **10.3.2 Subject Confidentiality**

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRB approving this research, and the Japan PMDA, 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 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.

## **10.4 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 along with the head of study site's instruction. 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:

- Three years after the final marketing approval

- At least 3 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.

## **10.5 Clinical Trial Agreement**

Payments by the sponsor to 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.

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## **12 APPENDICES**

## 12.1 Appendix A: Response Evaluation Criteria in Solid Tumors

### MEASUREMENT OF EFFECT

#### Antitumor Effect – Solid Tumors

For the purposes of this study, subjects should be re-evaluated for response every 8 weeks timed from Cycle 1 Day 1. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST version 1.1 criteria.

#### Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with zanidatamab.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

#### Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 20$  mm by chest x-ray, as  $\geq 10$  mm with CT scan, or  $\geq 10$  mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial

effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

“Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### **Methods for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Magnetic resonance imaging is also acceptable in certain situations (e.g., for body scans).

## Response Criteria

### *Evaluation of Target Lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

### *Evaluation of Non-Target Lesions*

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or principal investigator).

### ***Evaluation of Best Overall Response***

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

#### **For Subjects with Measurable Disease (i.e., Target Disease)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 4 wks. From baseline**
PD	Any	Yes or No	PD	no prior SD, PR, or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response; PD = progressive disease; SD = stable disease; wks = weeks.

\* See RECIST version 1.1 manuscript for further details on what is evidence of a new lesion.

\*\* Only for non-randomized trials with response as primary endpoint.

\*\*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “*symptomatic deterioration*.” Every effort should be made to document the objective progression even after discontinuation of treatment.

#### **For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; SD = stable disease.

\* Non-CR/non-PD” is preferred over “stable disease” for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

### **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

### **Progression-Free Survival**

Progression-free survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

## 12.2 Appendix B: Document History

Version	Date
Original	26-Feb-2021
Amendment 1	05-Apr-2021
Amendment 2	29-Nov-2021
Amendment 3	22-Feb-2022
Amendment 4	03-Oct-2023

**Summary of Changes in Amendment 4**

<b>Section(s)</b>	<b>Change</b>	<b>Rationale</b>
Global	<ul style="list-style-type: none"> <li>Changed sponsor name and address to Jazz Pharmaceuticals.</li> <li>Added “JZP598” as a synonym for zanidatamab.</li> </ul>	Administrative changes. Incorporated the most current Sponsor and Medical Monitor information, which has changed since the last amendment as a result of Jazz Pharmaceutical’s, acquisition of zanidatamab from Zymeworks, Inc. (Note, this change nullifies the sponsor address change in Administrative Letter #3, dated 20 April 2023).
Cover Page	Updated company affiliation and title for [REDACTED].	Changed to align with Jazz Pharmaceutical’s acquisition of zanidatamab. (Note, this change nullifies the change in Medical Monitor information in Administrative Letter #3, dated 20 April 2023).
Synopsis Table 1 Table 2 Section 4.2 (Exclusion Criteria #18) Section 6.1 Section 6.2.1 Section 7.5.7	Added language to allow for repeat ECG in triplicate to be performed and the mean used to determine eligibility.	Added to provide guidance on how study sites should proceed if the ECGs being used to assess eligibility during screening and Cycle 1 Day 1 show QTcF prolongation
Section 5.2.2.1, Table 9	Added recommended dose reductions due to AE in footnotes.	Provides information to clarify recommended dose reductions due to AE requiring dose reduction as per Administrative Letter # 3, dated 20 April 2023
Section 12.4	Added protocol approval signature page.	Administrative change to align with Jazz Pharmaceutical’s processes.

**Summary of Changes in Amendment 3**

<b>Section(s)</b>	<b>Change</b>	<b>Rationale</b>
Title page, Synopsis, and page headers	Updated date and amendment number	To update the information for Amendment 3
Throughout protocol	Minor formatting and editorial changes	To improve clarity and achieve consistency
Synopsis Table 1 Table 2 3.1.1 5.2.2 6.2 6.3	Updated the requirement for hospitalization during the DLT period to allow for discharge of subjects who do not demonstrate safety concerns.	Given that the incidence of toxicities requiring hospitalization is low, allowing outpatient management of these subjects at the investigator's discretion will mitigate subject discomfort due to the required extended hospitalization (28 days in Dose Level 1 and 21 days in Dose Level 2 and Flat Dosing cohorts) while ensuring subject safety.
Synopsis 4.1 4.3.1	Updated text and inclusion criterion #10 to clarify acceptable methods of contraception, required female subjects to avoid donating oocytes, and changed the length of time for contraception and avoidance of sperm and oocyte donation from 12 months to 7 months.	Align with contraception requirements with other HER2-targeting therapies, i.e., trastuzumab and pertuzumab
Synopsis 4.2	Added anticonvulsants to Exclusion Criterion #5	Align with exclusion criteria across the zanidatamab program.
Synopsis 4.2	Updated Exclusion Criterion #8 timeframe for avoiding breastfeeding from 12 months to 7 months	Align with contraception requirements with other HER2-targeting therapies, i.e., trastuzumab and pertuzumab
Synopsis 7.5.2	Updated AESI criteria	Align AESI collection across the zanidatamab program
Synopsis Table 1 Table 2	Added text around the assessment and reporting of AEs and concomitant medications	Clarification and consistency across the zanidatamab program
1.2	Updated text about trastuzumab	Clarification of indication
1.5	Updated text about zanidatamab	Align across the zanidatamab program
3.1.1 7.1	Removed reference to exploratory biomarkers	Clarification

<b>Section(s)</b>	<b>Change</b>	<b>Rationale</b>
3.1.3.2	Added text about IDMC	Clarification of timing and scope of IDMC assessment
4.3.1 7.5.1.2	Updated timeframe for reporting pregnancy and follow-up requirements	Align across zanidatamab program
Table 10	Updated management of left ventricular dysfunction	Simplification and consistency across zanidatamab program
6.2.9.2	Added PK sampling	To align with Table 3
7.5.1.1	Updated SAE criteria and AE severity assessment	Align SAE criteria and AE severity assessment across the zanidatamab program
7.5.1.3	Added AE reporting period figure and updated text	Clarification and consistency across the zanidatamab program
9.4.10	Updated text about interim analyses	Simplification and clarification

**Summary of Changes in Amendment 2**

<b>Section(s)</b>	<b>Change</b>	<b>Rationale</b>
Table 2	For the Q3W dosing regimen (weight-based Dose Level 2 and Flat Dosing) schedule of assessments, removed the $\pm 2$ day visit window for the Cycle 2 Day 1 visit.	Correction to align with Section 6.3.5.
Section 3.1.1, Figure 1, Section 3.1.3.2, Section 3.2, Section 3.2.1, Section 9.4.10, Synopsis	Added evaluation of flat dosing in 6 to 9 subjects with non-GEA cancers to Part A of the study design.	Evaluate the safety and characterize the PK of zanidatamab administered in subjects with non-GEA cancers.
Section 3.1.2, Section 3.1.3.1	Clarified the definition of DLT-evaluable subjects.	Remove redundancy
Section 4.1	Aligned language for Inclusion Criterion 10 with synopsis.	Correction to align with synopsis.
Section 4.4.1, Section 6.7, Table 1, Table 2	The End of Study visit should be performed regardless of whether a subject starts a new anti-cancer therapy(s).	Clarification
Section 5.2.2.1	The minimum for 12 days between zanidatamab doses applies to the Q2W dosing regimen.	Clarification.
Section 5.2.2.2, Section 6.2.1, Section 7.1, Section 7.5.3, Table 1, Table 2	Added baseline tryptase level testing pre-dose on Cycle 1 Day 1 and in the event of an IRR.	Allow characterization of potential IRRs.
Section 6.1, Section 6.2, Section 6.6, Section 6.7, Section 7.5.4, Synopsis, Table 1, Table 2	Added that oxygen saturation measurement (if available) should be collected as part of vital signs.	If oxygen saturation is measured as a standard vital sign at the investigational site, it should be reported.

<b>Section(s)</b>	<b>Change</b>	<b>Rationale</b>
Section 6.6, Table 1, Table 2	The End of Treatment visit and the End of Study visit may be the same visit, if the subject's last zanidatamab administration was > 30 days prior to the decision to permanently stop treatment.	Clarification
Section 7.5.1.1, Synopsis	During the time period after signing the main informed consent for the study through Cycle 1 Day 1 pre-dose, only study protocol-related SAEs should be recorded.	Align with program safety reporting requirements.
Section 7.5.1.1	Deleted "accidental" abortion.	Correction. Abortion is not accidental.
Section 7.5.2	Added that additional data related to AESIs may be collected in the eCRF.	Clarification
Section 1.5, Section 3.1.1, Section 3.1.3.2, Section 4.1, Section 5.1, Section 5.2.2.1, Synopsis	Made administrative changes to align between synopsis and protocol sections, and incorporated changes communicated in previous protocol administrative letters released after Amendment 1.	Administrative changes.

**Summary of Changes in Amendment 1**

<b>Section(s)</b>	<b>Change</b>	<b>Rationale</b>
Section 3.1.2	Revised hematologic DLT criterion from $\geq$ Grade 3 ANC to $\geq$ Grade 3 neutropenia	Clarification
Section 3.1.2 Section 4.4.1	Clarified time frame for reinitiation of zanidatamab following a dose delay	Clarification
Section 5.2	Added description of the zanidatamab manufacturing process	To provide additional information to investigators regarding the study drug
Section 5.2.6.2	Specified that growth factor support is limited to G-CSF	To clarify that only supportive growth factors approved in Japan are permitted on study
Section 7.1	Added statement that subjects with prior hepatitis B infection should be monitored and treated for hepatitis B reactivation according to local and institutional standards	To provide additional guidance to investigators regarding hepatitis B reactivation
Section 7.5.1.4	Added contact information for the representative's medical monitoring support center	To clarify resources available to study personnel
Synopsis Table 1 Section 4.2 Section 6.1 Section 7.1	Clarified testing for hepatitis B and hepatitis C infection at screening, with ongoing monitoring for hepatitis B reactivation during treatment as indicated	To align with region-specific guidelines

## 12.3 Appendix C: Investigator Signature Page

**Protocol Title:** Phase 1 Zanidatamab Monotherapy Trial in Japanese Subjects with Locally Advanced (Unresectable) and/or Metastatic HER2-expressing Cancers

**Protocol Number:** ZWI-ZW25-102

### Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining prior approval of Jazz Pharmaceuticals and of the IRB. I will submit the protocol amendments and/or any ICF modifications to Jazz Pharmaceuticals and IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Jazz Pharmaceuticals, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

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Investigator Signature

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Date

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Printed Name

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Institution

## 12.4 Appendix D: Protocol Approval Signature

**Protocol Title:** Phase 1 Zanidatamab Monotherapy Trial in Japanese Subjects with Locally Advanced (Unresectable) and/or Metastatic HER2-expressing Cancers

**Protocol Number:** ZWI-ZW25-102

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

██████████ MD, MBA  
Medical Director  
Jazz Pharmaceuticals, Inc.

**See Document Approval page  
for eSignature and date of approval**