Protocol Number:	ZWI-ZW25-EAP
Version:	1.0
Version Date:	02 September 2020
Protocol Title:	Expanded Access use of zanidatamab for the treatment of HER2-positive advanced solid tumors
Investigational Drug:	Zanidatamab
IND Number:	126269
Sponsor:	Zymeworks Inc. 1385 West 8th Avenue, Suite 540 Vancouver, BC, Canada V6H 3V9

PROTOCOL SYNOPSIS

Protocol Number ZWI-ZW25-EAP **Version** 1.0; 02 September 2020	**Product Name** Zanidatamab (ZW25) **Sponsor** Zymeworks Inc. 1385 West 8th Avenue, Suite 540 Vancouver, BC, Canada V6H 3V9

Title:	Expanded Access use of zanidatamab for the treatment of HER2-positive advanced solid tumors
Rationale:	Zanidatamab is an investigational drug in development for the treatment of HER2+ cancers. The purpose of this Expanded Access protocol (EAP) is treatment use of zanidatamab for patients with HER2+ cancer who do not qualify for participation in or who are unable to access an ongoing clinical study.
Target Population:	Male and female patients, age ≥ 18 years of age with HER2-positive advanced solid tumors.
Number of Patients:	Approximately 200
Objective:	Primary Objective: The objective of this protocol is to make zanidatamab available for patients with HER2-positive cancers who do not qualify for participation in, or who are otherwise unable to access an ongoing clinical study for zanidatamab.
Study Design:	This is an open-label intermediate-size EAP for use of zanidatamab in patients with HER2-positive solid tumors who are not eligible for a zanidatamab clinical study, and who in the opinion of the treating oncologist, would potentially benefit from treatment with zanidatamab while it is an investigational drug. Zanidatamab 20 mg/kg will be administered intravenously (IV) on Day 1, Day 15, and every 2 weeks thereafter, until, in the clinical judgment of the treating oncologist, the patient is no longer benefiting from continuation of the treatment, the drug receives FDA approval and becomes available by prescription, or the program is terminated by the Sponsor. Patients will undergo a medical assessment for eligibility prior to first dose. Treatment assessments are performed as per the local Standard of Care (SOC). Zanidatamab treatment will be administered every 2 weeks in a hospital or infusion center.

Primary Endpoint:	This is an intermediate-size EAP with no primary endpoint.
Exploratory Endpoints:	This is an intermediate-size EAP with no exploratory endpoints.
Measures of Interest:	• Frequency and severity of Adverse Events (AEs) • Serious Adverse Events (SAEs) • Frequency of AEs of Special Interest (AESI) • Objective response rate (ORR) by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), assessed by the treating physician • Duration of response (DOR) by RECIST 1.1 assessed by treating physician • Progression-free survival (PFS)

STUDY SCHEMATIC

Figure 1: Study Design

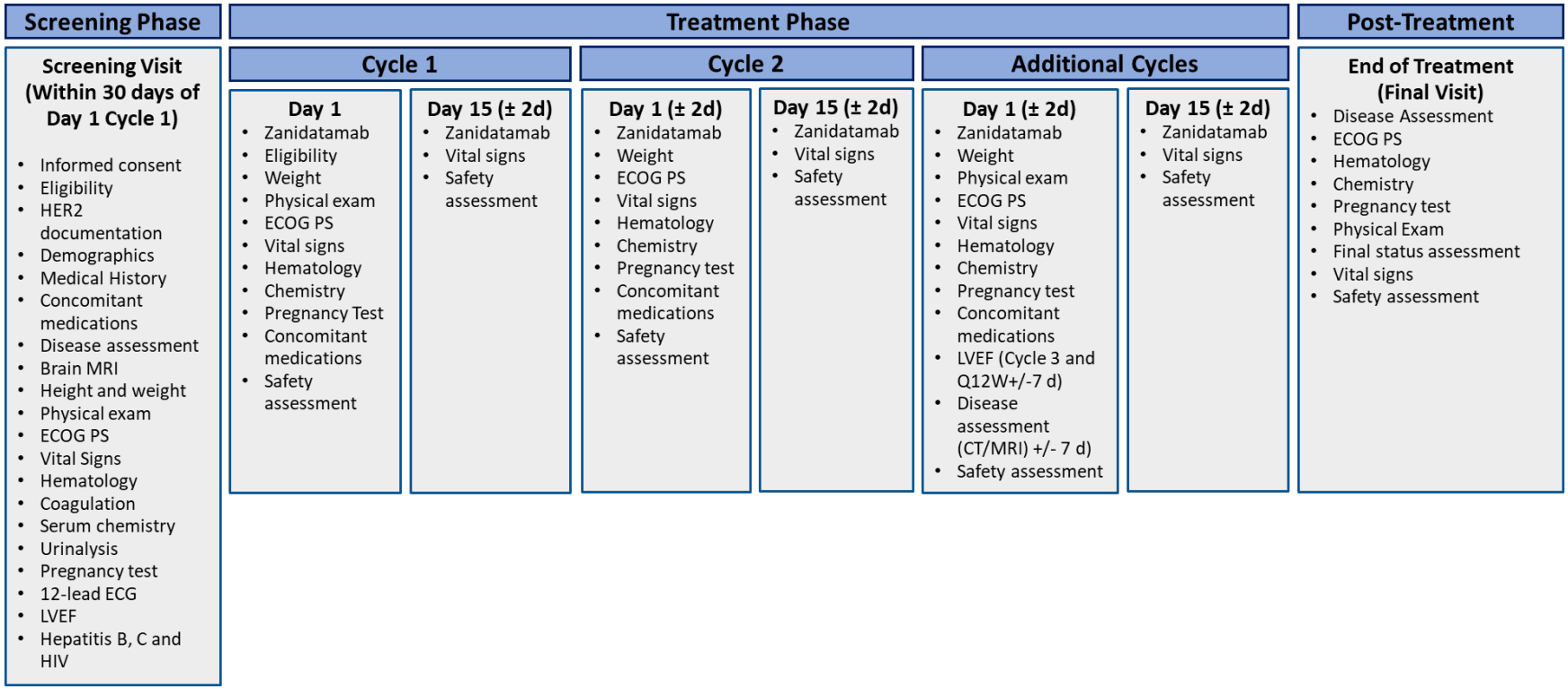


TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BC	Breast Cancer
BTC	biliary tract cancer
BUN	blood urea nitrogen
C_{ave}	average concentration
CC	cholangiocarcinoma
CD4	cluster of differentiation 4
CDx	companion diagnostics
CFR	Code of Federal Regulations
CHF	congestive heart failure
CNS	central nervous system
CR	complete response
CRF	case report form
C_{SS}	steady state concentration
CT	computed tomography
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
DCR	disease control rate
DOR	duration of response
DLT	dose-limiting toxicity
ECC	extrahepatic cholangiocarcinoma
ECD	extracellular domain
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR/ErbB	epidermal growth factor receptor
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FGFR2	fibroblast growth factor receptor 2
FISH	fluorescence in situ hybridization
GBC	gallbladder cancer

GCP	Good Clinical Practice
GEA	gastroesophageal adenocarcinoma
GFR	glomerular filtration rate
H2	histamine-2 receptor antagonist
HER2	human epidermal growth factor receptor 2
Hgb	hemoglobin
hIgG	human immunoglobulin
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HR	hazard ratio
ICC	intrahepatic cholangiocarcinoma
ICF	informed consent form
ICH	International Council for Harmonisation
IDH	isocitrate dehydrogenase
IEC	independent ethics committee
IgG	immunoglobulin G
IHC	immunohistochemistry
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
ISH	in situ hybridization
IV	intravenous(ly)
LMD	leptomeningeal disease
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX	modified FOLFOX (folinic acid [leucovorin], 5-FU, and oxaliplatin)
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next generation sequencing
NK-1	neurokinin-1
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival

PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PO	per oral (orally)
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	prothrombin time
QxH	every x hours
Qx mos	every x months
QxW	every x weeks
QOL	quality of life
QTcF	QTc Fridericia
RBC	red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RD	recommended dose
SAE	serious adverse event
SAP	statistical analysis plan
scFv	single-chain variable fragment
Scr	serum creatinine
SD	stable disease
SOC	system organ class
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
$t_{1/2}$	half-life
t_{max}	time to maximum concentration
ULN	upper limit of normal
Vd	volume of distribution

1 INTRODUCTION

1.1 HER2 Background

Human epidermal growth factor receptor 2 (HER2) is involved in the pathogenesis of several types of cancer. 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. Dysregulation of HER2-mediated signaling or overexpression of HER2 can result in tumorigenesis (Alajati 2015). HER-mediated tumorigenic signaling may involve homodimerization or heterodimerization. HER2 exists in a conformation that allows dimerization without ligand binding whereas HER1, HER3, and HER4 are activated by binding of epidermal growth factor ligands. Ligand binding changes the conformation of these other receptors to expose the dimerization extracellular domain (ECD) 2 and permit homo- or heterodimerization with EGFR/ErbB family members. HER2 is the preferred dimerization partner with other HER family members. Receptor dimerization leads to autophosphorylation of specific tyrosine residues and activation of intracellular signaling pathways, notably the mitogen-activated protein kinases (MAPK) and PI3K/Akt (Phosphatidylinositol 3 kinase/protein kinase B) pathways that mediate cell proliferation and cell survival, respectively (Moasser 2007). HER2 may also crosstalk synergistically with other receptor tyrosine kinase cell growth pathways and thus effective blockade of HER2 may be therapeutically beneficial in inhibiting tumor growth.

1.2 HER2 Expression in Cancers

With increasing understanding of the molecular biology of HER2, it has now been recognized that HER2 is implicated in other several forms of cancer, including breast, gastric, biliary tract, ovarian, colorectal and non-small cell lung.

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 2013), 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 ISH. HER2 overexpression or “positivity” is currently defined as IHC3+ or IHC2+ and FISH+, and is most frequently seen in breast cancers (15% to 20%) and gastric/gastroesophageal junction (GEJ) cancers (20% to 33%), where it historically has been associated with more aggressive disease and worse clinical outcomes. Variable levels of HER2 expression are also seen in numerous other cancers including biliary tract, ovarian, lung, head and neck, endometrial, bladder, and colorectal cancer.

1.3 Approved HER2-Targeted Therapies

A number of HER2-targeted agents are approved in the United States, including antibody-based therapies trastuzumab (HERCEPTIN® and biosimilars) and pertuzumab (PERJETA®), the antibody-drug conjugates (ADCs) ado-trastuzumab emastine (KADCYCLA®) and fam-trastuzumab deruxtecan-nxki (ENHERTU®), the oral small molecule dual EGFR/HER2 inhibitor

lapatinib (TYKERB®); the irreversible oral small molecule EGFR/HER2/HER4 inhibitor neratinib (NERLYNX®) and the oral small molecule kinase inhibitor of HER2 (TUKYSA®).

The majority of approved HER2-targeted therapies are approved for breast cancer, and trastuzumab is also approved for advanced HER2--overexpressing gastric/gastroesophageal junction cancer. There are no approved HER2 agents for any other HER2-high expressing cancers, or for cancers with lower levels of HER2 expression and absence of gene amplification.

1.4 Zanidatamab

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

An ongoing first-in-human study of zanidatamab, a multi-part Phase 1 study (ZWI-ZW-101; NCT02892123), is evaluating the safety, pharmacokinetics (PK), immunogenicity, and potential anti-tumor activity of zanidatamab as a single agent in combination with selected chemotherapy agents in 234 patients with locally advanced (unresectable) and/or metastatic HER2-expressing tumors. Part 1 of the study used a standard 3+3 dose-escalation design to determine the maximum-tolerated dose (MTD), optimal biological dose, or recommended dosage (RD) of zanidatamab monotherapy administered every week (QW), once every 2 weeks (Q2W), or once every 3 weeks (Q3W) to patients with any HER2-expressing cancer that had progressed after receipt of all therapies known to confer clinical benefit. The QW or Q2W dosing cohorts completed enrollment with no dose-limiting toxicities (DLTs) and the MTD was not reached. The single agent RD for further study was identified as 10 mg/kg QW or 20 mg/kg Q2W. Part 2 of Study ZWI-ZW25-101 is evaluating the safety, tolerability, and preliminary anti-tumor activity of zanidatamab monotherapy administered at a Part 1 RD in patients with selected HER2-expressing locally advanced and/or metastatic cancers in up to 5 disease-specific cohorts, including HER2-high breast cancer (IHC 3+, or IHC 2+/ fluorescence in situ hybridization [FISH+]), HER2-intermediate breast cancer (IHC 2+/FISH-negative [FISH-]), HER2-high gastroesophageal adenocarcinoma (GEA), HER2-intermediate GEA, and other HER2-high solid tumors. Patients eligible for Part 2 must have central confirmation of HER2 status based on new biopsies or archival tissues obtained ≤ 6 months without intervening HER2-directed agents. Part 3 of the study is evaluating the safety, tolerability and preliminary anti-tumor activity of zanidatamab administered in combination with selected chemotherapy agents, including paclitaxel, capecitabine, and vinorelbine, in patients with HER2-expressing breast and gastric cancers.

Zanidatamab has shown encouraging antitumor activity and tolerability both as monotherapy and in combination with chemotherapy in patients with heavily pre-treated, advanced HER2-expressing cancers. A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the most current version of the Zanidatamab Investigator's Brochure (IB).

1.5 Expanded Access Rationale

HER2 is involved in the pathogenesis and poor outcomes of several types of cancers, including breast, gastric, biliary tract, ovarian, colorectal, urogenital, non-small cell lung, and other cancers. Studies have shown that HER2 is a relevant target in many of these tumors (relevnat recent references), and targeted HER2-therapy has the potential to provide clinical benefit to patients who have disease that has progressed following approved, standard of care treatments, including HER2-targeted agents. As summarized in the current version of the zanidatamab IB has been well tolerated as a sinlge agent, and associated with durable anti-tumor activity in patients with heavily pre-treated HER2 overexpressing cancers that have progressed after standard of care treatments, including HER2-targeted agents. The purpose of this study is to provide an investigational treatment option in a controlled clinical setting to patients with refractory HER2-overexpressing cancers who are not otherwise able to participate in on ongoing zanidatamab clinical study.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

The objective of this protocol is to make zanidatamab available as a monotherapy to patients with HER2-positive cancer, who, in the opinion of the treating oncologist, would potentially benefit from treatment with zanidatamab while it is an investigational drug.

3 STUDY ENDPOINTS

3.1 Primary

This is an intermediate-size EAP with no primary endpoint.

3.2 Measures of Interest

- Frequency and severity of Adverse Events (AEs)
- Serious Adverse Events (SAEs)
- Frequency of AEs of Special Interest (AESI)
- Objective response rate (ORR) by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), assessed by the treating physician
- Duration of response (DOR) by RECIST 1.1 assessed by treating physician
- Progression-free survival (PFS)

4 STUDY PLAN

4.1 Study Design and Duration

This is an open-label intermediate-size EAP for use of zanidatamab in patients with HER2-positive solid tumors who are not eligible for a zanidatamab clinical study, and who in the opinion of the treating oncologist, would potentially benefit from treatment with zanidatamab while it is an investigational drug.

This EAP entails visits every two weeks until market availability or until the Sponsor has decided to terminate this EAP. Eligible patients will receive zanidatamab 20 mg/kg by intravenous (IV) infusion every two weeks. Patients should be observed during and for at least 1 hour after the end of the infusion for symptoms of infusion related reactions.

Zanidatamab treatment will continue until, in the clinical judgement of the treating oncologist, the patient is no longer benefiting from continuation of the treatment, the drug becomes approved and available by prescription, or the study is terminated. Patients will be assessed during study visits as outlined in Table 1: Schedule of Events. Patients who discontinue treatment with zanidatamab for any reason should have an End of Treatment (EoT) assessment.

Standard of care (SOC) computed tomography (CT) and/or magnetic resonance imaging (MRI) scans will be performed prior to Cycle 1, Day 1 and every 8 weeks (Q8W) during treatment timed from Cycle 1 Day 1. Disease response will be assessed according to RECIST 1.1 by the treating oncologist.

Cancers frequently associated with central nervous system (CNS) involvement (e.g., brain metastases, leptomeningeal disease [LMD]) are to follow standard of care as appropriate. Where clinically indicated, the treating oncologist should ascertain CNS involvement with a brain MRI according to standard of care, and any CNS involvement should be recorded.

Safety assessments will include monitoring for AEs, SAEs, deaths, physical examinations, vital signs, body weight, and ECOG PS.

The schedule of assessments is presented in Table 1.

4.2 Study Schematic

Figure 1: Study Design

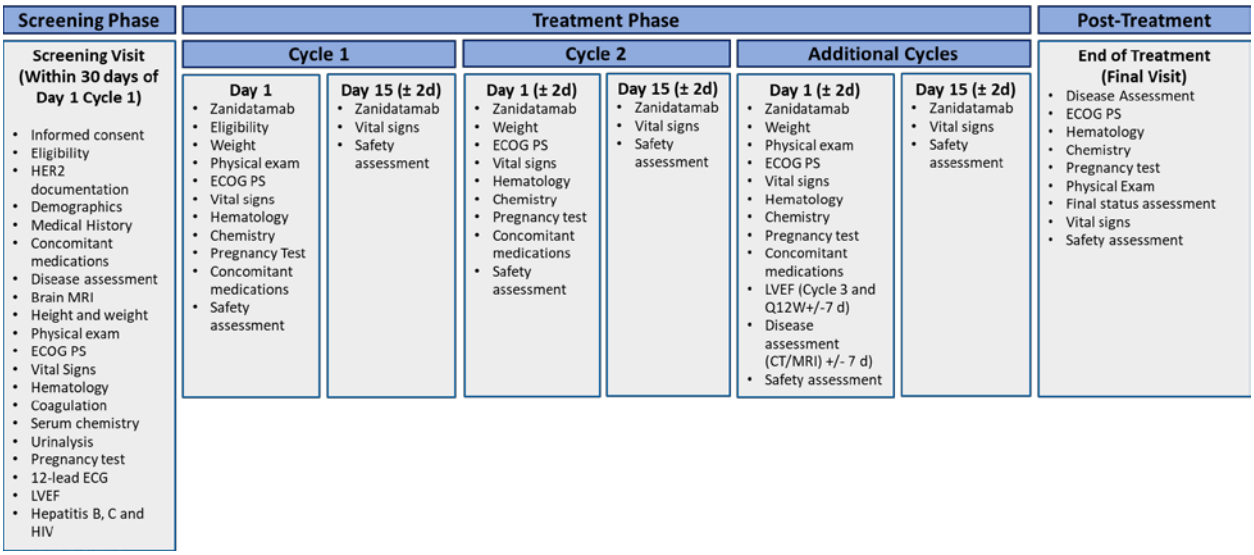


Table 1: Schedule of Events

		Cycle 1		Cycle 2		Additional Cycles		
	Screening (Within 30 days of Cycle 1, Day 1)	**D1**	**D15** (±2d)	**D1** (±2d)	**D15** (±2d)	**D1** (±2d)	**D15** (±2d)	**End of Treatment** (Final Visit)[11]
Zanidatamab[1]		X	X	X	X	X	X	
Informed consent	X							
Medical history	X							
Eligibility	X	X						
HER2 documentation	X							
Demographics	X							
Disease assessment (CT/MRI)[2]	X[2]					X[2]		X[2]
Brain MRI[3]	X							
Height	X							
Weight[4]	X	X		X		X		
Physical exam	X	X[5]		X		X[5]		X
ECOG PS	X	X		X		X		X
Vital signs[6]	X	X	X	X	X	X	X	X
Hematology	X	X		X		X		X
Coagulation[7]	X							
Serum chemistry	X	X		X		X		X
Urinalysis	X							
Pregnancy test[8]	X	X		X		X		X
12-lead ECG	X							
LVEF[9]	X						X[9]	
Hepatitis B, C and HIV[10]	X							
Concomitant Medications	X	X		X		X		X
Safety assessment		X	X	X	X	X	X	X

[1] Zanidatamab dosing and administration – Doses must be adjusted for patients who experience a ≥ 10% change in weight from baseline.
[2] Disease assessment – according to local standard of care (SOC) approximately every 8 weeks after first dose of cycle 1 and at End of Treatment visit.
[3] Brain MRI - Cancers frequently associated with brain metastases and LMD are to follow standard of care as appropriate. MRI within 60 days of screening are acceptable.
[4] Weight prior to each dos and on Day 1 of each cycle, prior to dose. Adjust dose for patients who experience a ≥ 10% change in weight from baseline.
[5] Physical examination (PE) Cycle 1 Day 1 is performed prior to the first dose; PE does not need to be repeated if assessment completed for screening within the previous 7 days. PE is performed according to SOC and/or every 3 months and End of Treatment.
[6] Vital Signs – at Screening and on dosing days; the assessment should be performed pre-dose and post-dose.
[7] Coagulation -The coagulation panel must be repeated at subsequent cycles at the discretion of the treating oncologist.
[8] Urine/Serum Pregnancy Test is for Women of Childbearing Potential (WOCBP) only. Pregnancy test should be performed prior to zanidatamab treatment on Day 1 of each cycle and at the end of zanidatamab therapy. Urine dipstick will be used where permitted; otherwise a serum pregnancy test conducted at a local laboratory. A serum test will be done locally to confirm any positive or equivocal urine pregnancy tests.
[9] LVEF by cardiac echo or MUGA; assessment within 30 days of first dose of zanidatamab; assess at Cycle 3 and approximately every 3 months.
[10] Hepatitis B, C and HIV if clinically indicated.
[11] Within 30 days after the last dose of zanidatamab, or upon termination or withdrawal from treatment all patients will have a follow-up visit.

4.3 Rationale for Dose Selection

An ongoing first-in-human study of zanidatamab, a multi-part Phase 1 study (ZWI-ZW-101; NCT02892123), is evaluating the safety, pharmacokinetics (PK), immunogenicity, and potential anti-tumor activity of zanidatamab as a single agent and in combination with selected chemotherapy agents in 234 patients with locally advanced (unresectable) and/or metastatic HER2-expressing tumors. Part 1 of the study used a standard 3+3 dose-escalation design to determine the maximum-tolerated dose (MTD), optimal biological dose, or recommended dosage (RD) of zanidatamab monotherapy administered every week (QW), once every 2 weeks (Q2W), or once every 3 weeks (Q3W) to patients with any HER2-expressing cancer that had progressed after receipt of all therapies known to confer clinical benefit. PK data from Part 1 were examined and modeled. Analyses of 10 mg/kg QW and 20 mg/kg Q2W dosing showed dose-proportional and non-linear PK, with steady state reached by the end of Cycle 2. The half-life ($t_{1/2}$) of 10 mg/kg QW was approximately 123 hours, and the $t_{1/2}$ of 20 mg/kg Q2W was approximately 150 hours. The overall exposure was similar for 10 mg/kg QW and 20 mg/kg Q2W. The trough values were maintained above the minimum predicted efficacious level.

Data from the ZWI-ZW25-101 study support a recommended dose of zanidatamab 20 mg/kg IV every two (2) weeks. The dose regimen of 20 mg/kg IV every 2 weeks is being administered in the Phase 2 study ZWI-Z25-203 and for this expanded access program.

5 STUDY POPULATION

Patients must meet all of the inclusion criteria to be eligible for this study.

5.1 Inclusion Criteria

1. Signed informed consent must be obtained prior to the initiation of any study-required procedures.
2. Male or female, ≥ 18 years of age
3. Histologically confirmed HER2-positive locally advanced or metastatic cancer that has progressed after receipt of available therapies known to confer clinical benefit.
    a. Patients must have IHC 3+ HER2 overexpression, HER2 (ERBB2) gene amplification based on either in situ hybridization (ISH)/FISH, or be positive by next-generation sequencing (NGS) using an FDA approved assay.
    b. Additional criteria for cancer subtypes:
        i. Patients with colorectal cancer must be KRAS wild-type
        ii. Patients with NSCLC must have ALK wild-type, EGFR wild-type, and ROS1 fusion negative as determined by standard methods
        iii. Patients with ovarian cancers must be KRAS wild type
4. Left ventricular ejection fraction (LVEF) ≥ 50%
5. Ineligible to participate or has no access to an ongoing zanidatamab or other Zymeworks clinical study (e.g., ZW49 clinical study). Refer to www.clinicaltrials.gov.
6. In the opinion and clinical judgement of the treating oncologist, potential benefit outweighs potential risk of receiving an investigational therapy, based on the individual patient's medical history and program eligibility criteria and judged by the treating oncologist to be medically suitable for treatment with zanidatamab
7. Adequate hematologic function, defined as
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelet count ≥ 75 x 10^9/L (not requiring transfusion support), and
    b. Hemoglobin (Hgb) ≥ 9 g/dL (patients with chronic anemia that is supported by intermittent red blood cell [RBC] transfusions are eligible).
    c. Prothrombin time (PT) and partial thromboplastin time (PTT) < 1.5 x ULN
8. Adequate non-hematologic function, defined as
    a. Total serum bilirubin ≤ 1.5 x the upper limit of normal (ULN), or ≤ 3 x ULN in documented Gilbert syndrome.
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN.

c. If organ function abnormalities are considered due to tumor, total serum bilirubin must be ≤ 2 x ULN and AST/ALT ≤ 5X ULN

d. Serum creatinine 1.5 X ULN

9. Females of childbearing potential and non-sterile male must agree to practice highly effective methods of birth control (as described in Section 5.3.2) for the duration of the study and for 12 months after the last dose of study drug. In addition, non-sterile males must avoid sperm donation for the duration of the study and for 12 months after the last dose of study drug.

5.2 Exclusion Criteria

Patients are not eligible for treatment with zanidatamab if one or more of the following criteria are applicable:

1. History of allergic reactions to zanidatamab or agent biologically similar to zanidatamab, except for Grade 1 or 2 infusion related reactions that were successfully managed or known allergy to one of the excipients.
2. Participating in other studies involving investigational drug(s) ≤ 3 weeks before the first dose of zanidatamab.
3. Systemic anti-cancer therapy ≤ 3 weeks before the first dose of zanidatamab.
4. Radiotherapy ≤ 2 weeks of the first dose of zanidatamab
5. Major surgery (defined as requiring general anesthesia) within 3 weeks of the first dose of zanidatamab
6. Unstable severe uncontrolled medical condition (e.g., unstable cardiac function, clinically significant interstitial lung disease, pneumonitis or unstable pulmonary condition)
7. The following central nervous system (CNS) brain lesions are excluded from the study:

    a. Untreated or unstable brain lesions requiring immediate local therapy or symptomatic CNS metastases.

    b. Radiation treatment for CNS metastases within 4 weeks before the first dose of zanidatamab.

    c. Known history of or ongoing LMD. If LMD has been reported radiographically, but is not suspected clinically by the investigator, the subject must be free of neurological symptoms of LMD.

    The following CNS brain lesions are permitted:

    d. Stable brain lesions are permitted if stable, as defined by patients who are off steroids and anticonvulsants and are neurologically stable with no evidence of radiographic progression for at least 4 weeks at the time of screening.

8. Concurrent uncontrolled or active hepatobiliary disorders or untreated or ongoing complications after laparoscopic procedures or stent placement, including but not limited to active cholangitis, unresolved biliary obstruction, biloma or abscess. Any complications should be resolved within 2 weeks prior to the first dose of zanidatamab.

9. Significant acute infection or chronic infections that have not stabilized with treatment.
10. Active hepatitis, including the following criteria:
    a. Acute or chronic hepatitis B (Exception: patients who are hepatitis B surface antigen positive are eligible if they have HBV DNA less than 500 IU/mL)
    b. Infection with hepatitis C (Exception: patients who have no history of curative viral treatment and are documented to be viral load negative are eligible; patients who have completed curative viral therapy ≥ 12 weeks prior to enrollment, and viral load is negative are eligible)
11. Infection with human immunodeficiency virus HIV with uncontrolled disease.
12. Females who are breastfeeding or pregnant, and females and males planning a pregnancy.
13. Any toxicity related to prior cancer therapies that has not resolved to ≤ Grade 1, with the following exceptions:
    a. Alopecia and peripheral neuropathy, which must have resolved to ≤ Grade 2 NCI-CTCAE version 5
    b. CHF, which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely
    c. Anemia, which must have resolved to ≤ Grade 2
14. Use of corticosteroids administered at doses equivalent to >15 mg per day of prednisone within 2 weeks of first zanidatamab dosing unless otherwise approved by the medical monitor. Topical, ocular, intra-articular, intranasal, and/or inhalational corticosteroids are permitted.
15. QTc Fridericia (QTcF) > 470 ms assessed within 30 days of screening
16. History of myocardial infarction or unstable angina within 6 months prior to enrollment, CHF (NYHA Class 3 or 4), or clinically significant cardiac disease, such as ventricular arrhythmia requiring therapy, or uncontrolled hypertension.
17. Acute or chronic uncontrolled pancreatitis or Child-Pugh Class C liver disease.
18. History of noncompliance to medical regimens
19. Any other medical, social, or psychosocial factors that, in the opinion of the treating oncologist would pose a safety risk.

5.3 Childbearing Potential and Contraception

5.3.1 Definitions

A person of childbearing potential is anyone born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in

women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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

According to the inclusion and exclusion criteria, pregnant or breastfeeding patients cannot be included in the study, and adequate contraceptive measures should be taken to prevent female patients of childbearing potential or female partners of male patients (either of whom are of childbearing potential) from getting pregnant during study participation and for at least 12 months after the last dose of study drug (see Section 5.3.2).

Patients will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. If a female patient is pregnant, the investigator will immediately discontinue the patient from further treatment with zanidatamab and only those procedures that would not expose the patient to undue risk will be performed, such as final safety laboratory studies.

The investigator should also be notified of pregnancy occurring during the EAP but confirmed after completion of the study.

In the event that a female patient or female partner of a male patient is found to be pregnant after inclusion in the study, the pregnancy will be followed to term with patient/partner consent.

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.

5.3.2 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 2.

Table 2: Acceptable Methods of Highly-Effective Birth Control

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

a Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method. A patient should not take more than one agent listed in the first two 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 study 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 study and the preferred and usual lifestyle of the patient.

Unacceptable methods of contraception (either because they have a failure rate of > 1% per year or because they are considered unacceptable methods in clinical studies per the CTFG guidance document) are listed in Table 3.

Table 3: 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

5.4 Removal From Therapy or Assessment

Zymeworks or their designee must be notified if a patient is withdrawn from zanidatamab treatment or from the EAP. The reason(s) for withdrawal must be documented in the patient's medical records and CRF.

5.4.1 Treatment Discontinuation

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

- Any AE, laboratory abnormality or intercurrent illness which, in the opinion of the treating physician, indicates that continued participation in the EAP is not in the best interest of the patient
- Lost to follow-up
- Withdrawal of informed consent (patient's decision to withdraw for any reason)
- Physician decision - non-AE, non-progressive disease
- Clinically progressive disease, as determined by the treating oncologist. Patients with non-symptomatic radiologic progression may continue zanidatamab.
- Pregnancy, or planned pregnancy
- Poor compliance with recommended treatment schedule
- Other, non-AE
- Termination of the EAP by Zymeworks, Inc. for any reason, including approval of zanidatamab and availability via prescription

If a patient has not received zanidatamab for more than 4 weeks due to an AE, the treating physician should contact the Early Access Care (phone: 1-203-441-7938; or by email Zymeworks.EAP@earlyaccesscare.com) to discuss whether the patient should continue to receive study treatment.

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

All patients who discontinue should comply if possible, with protocol-specified assessment procedures as outlined in Table 1 Schedule of Events, including survival follow-up.

5.4.2 Patient Withdrawal from EAP

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

- Withdrawal of consent
- Lost to follow-up
- Pregnancy or planned pregnancy
- Death

6 TREATMENTS

6.1 Treatments Administered

Patients will be treated with zanidatamab administered as monotherapy.

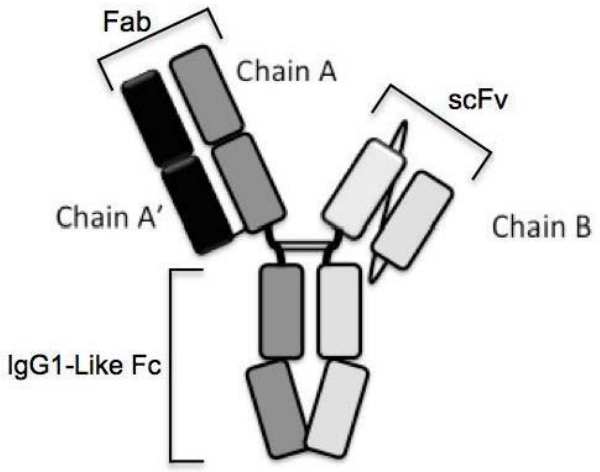
6.2 Investigational Study Drug (Zanidatamab)

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

6.2.1 Description

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

Figure 2: Structure of Zanidatamab



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

6.2.2 Dose and Administration

Dosing for zanidatamab will be given as follows:

- 20 mg/kg IV zanidatamab; dosing Q2W on Days 1 and 15 of each 28-day cycle

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

Dosing is based on the patient's actual body weight at Cycle 1, Day 1. Doses must be adjusted for patients who experience a ≥ 10% change in weight from baseline. Other dose adjustments for changes in body weight are permitted per institutional standard. Detailed instructions for dose preparation are provided in the Pharmacy Manual.

Infusion-related reactions (IRR) have been reported with zanidatamab. Pre-medication prior to infusion of zanidatamab is required and should follow local standard of care. Premedications are outlined in Section 6.2.7.

Recommendations for management of and potential dose modifications for zanidatamab-associated toxicity are provided in Table 4.

In the event of symptomatic development of symptoms of heart failure, LVEF should be assessed. Guidelines for management of zanidatamab-associated left ventricular dysfunction are provided in Table 5.

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

Table 4: Recommended Management and Potential Dose Modifications for ZW25-Associated Toxicity

Adverse Event Related to Zanidatamab	Action for Zanidatamab
Grade 1 or Grade 2 nausea and vomiting	• Suggest a 5-hydroxytryptamine (5-HT3) receptor antagonist until resolution of symptoms, or a prochlorperazine. • No dose modification of zanidatamab is required. • For breakthrough nausea or vomiting, consider olanzapine 5 or 10 mg daily for 3 days. For patients already receiving olanzapine, prochlorperazine may be used.
Grade 3 or Grade 4 nausea and vomiting	• Suggest a 5-HT3 receptor antagonist plus a glucocorticoid especially dexamethasone); consider adding a neurokinin-1 (NK-1) receptor antagonist to a 5-HT3 receptor antagonist and glucocorticoids if the latter combination is not sufficient for symptom relief. • Do not administer zanidatamab until severity ≤ Grade 1 or pretreatment level. • Optional dose reduction to 15 mg/kg Q2W after symptoms resolved to ≤ Grade 1 or pretreatment 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.
Grade 1 or Grade 2 diarrhea	• Suggest starting loperamide 4 mg PO after first loose stool and continuing 2 mg every 8 hours (Q8H) until no stool output for > 24 hours. • If symptoms progress to Grade 1 or 2 diarrhea, increase loperamide to 2 mg every 4 hours (Q4H) until no diarrhea. • Oral hydration with fluid that contains water, salt and glucose, such as broth or Gatorade. • No dose modification of zanidatamab is needed.

Adverse Event Related to Zanidatamab	Action for Zanidatamab
Grade 3 or Grade 4 diarrhea	• Aggressive fluid hydration and clear liquid diet. • Suggest loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider octreotide 100 or 150 mcg subcutaneously Q8H for patients with persistent diarrhea despite 48 hours of loperamide. If patients are refractory to both loperamide and octreotide, gastroenterologist should be consulted. • For Grade 3 diarrhea, optional dose reduction of zanidatamab to 15 mg/kg Q2W after symptoms resolved to ≤ Grade 1 or pretreatment level. For Grade 4 symptoms or recurrent Grade 3 symptoms despite maximum use of loperamide and octreotide, dose reduction is mandatory.
Grade 1 or Grade 2 rash	• Suggest topical steroid as needed. • No dose modification of zanidatamab is needed.
Grade 3 or Grade 4 rash	• 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. • Do not administer zanidatamab until severity ≤ Grade 1 or pretreatment level. • For Grade 3 rash, optional dose reduction of zanidatamab to 15 mg/kg Q2W after symptoms resolved to ≤ Grade 1 or pretreatment level. For Grade 4 symptoms or recurrent Grade 3 symptoms despite maximum use of topical and oral corticosteroid, dose reduction is mandatory.

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.

Table 5: Management of Left Ventricular Dysfunction

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

LVEF = left ventricular ejection fraction

6.2.2.1 Infusion Reactions

All patients should receive pre-treatment prophylaxis for IR. Management of infusion reactions are at the discretion of the treating oncologist / investigator and stancard of care. Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions thoughout treatment administration and up to 30 minutes post treatment.

Table 6: Zanidatamab Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE grade	Treatment modification for zanidatamab
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for worsening symptoms. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate, unless otherwise approved by the medical monitor.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for $\leq$ 24 hours.	Stop infusion. Once symptoms have resolved or decreased to Grade 1 in severity the infusion may be resumed at 50% of the previous rate. Closely monitor for worsening symptoms. Proper medical management should be instituted as described in the text accompanying this table. Subsequent infusions should be given after premedication and at the reduced infusion rate, unless otherwise approved by the medical monitor.
Grade 3 Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described in the text accompanying this table. Infusion should not be restarted even if signs and symptoms completely resolve. With medical monitor approval the patient may be dosed at the next scheduled treatment.

NCI-CTCAE grade	Treatment modification for zanidatamab
Grade 4 Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug treatment. Hospitalization is recommended.
Grade 5 Death	N/A

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

Once the zanidatamab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it may only be increased for subsequent infusions with medical monitor approval and premedication must be administered.

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

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

6.2.3 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.

6.2.4 Drug Accountability

In accordance with local regulatory requirements, the Physician or designated site personnel must document the amount of zanidatamab dispensed for designated patients. At the end of the study, drug accountability will be completed and maintained according to local hospital procedure and a drug accountability log will be provided to Early Access Care. Drug accountability logs will be completed and maintained according to local hospital procedure. An electronic record for drug accountability may be used for drug accountability.

Remaining drug will be approved for destruction after consulting with Early Access Care. Local institutional policy for drug destruction will be followed.

6.2.5 Packaging and Labeling

Zanidatamab is supplied as a sterile, lyophilized, single use, preservative free for intravenous (IV) infusion vial containing a nominal fill volume of 6 mL (300 mg). The drug product is formulated at 50 mg/mL.

Refer to the Pharmacy Manual for packaging and labeling.

6.2.6 Dose Preparation Instructions

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

6.2.7 Infusion Related Reactions

Infusion related reactions (IRRs) have been observed with zanidatamab treatment. Premedication (e.g., corticosteroids, antihistamines, and acetaminophen) is required approximately 30 to 60 minutes prior to the initiation of infusion of zanidatamab. The physician will pre-medicate according to standard of care. Acknowledgement of pre-medication administration is recorded on the Dosing Record Form.

Recommended pre-medication includes:

- Hydrocortisone 100 mg IV or dexamethasone 10 mg IV or equivalent
- Antihistamine: diphenhydramine 50 mg PO or IV or equivalent
- Acetamiophen or paracetamol 650 mg to 1000 mg PO

For patients 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 above recommended pretreatment.

6.2.7.1 Allowed Concomitant Therapy

Clinically indicated therapy, including transfusions and bisphosphonates (e.g., Zometa®), growth factors and colony-stimulating factors are at the discretion of the treating physician and following standard of care.

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)

The treating oncologist / investigator should contact the Sponsor representative, Early Access Care, to discuss concomitant therapies if uncertain.

6.2.7.2 Prohibited Concomitant Therapy

Patients may not receive cancer-related investigational, or systemic anti-neoplastic therapy during the study. Chinese or other herbal medicines for the treatment of cancer are also prohibited. Use of alternative supplemental therapies is discouraged and use of any such product must be recorded.

6.3 Duration of Study Treatment

Patients receiving zanidatamab should be managed by the treating oncologist according to standard of care. Treatment is continued provided the patient is deriving clinical benefit as assessed by the oncologist. Patients may continue treatment with zanidatamab until, in the clinical judgement of the Physician, the patient is no longer benefitting from continuation of the treatment, the drug receives approval, or the Sponsor decides to terminate the program. At the conclusion of the program, Physicians will be notified and provide information about the Final Visit.

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

7 STUDY ACTIVITIES

A schedule of events is provided in Table 1.

Study activities are listed by visit in this section and descriptions of study assessments are presented in Section 8.

7.1 Screening Visit (Day –30 to 1)

The screening procedures listed below will be completed within 30 days before first administration of treatment with zanidatamab. In case a patient cannot receive their first treatment within the required time windows for the screening assessments, Early Access Care should be contacted to discuss the assessment. Procedures done as part of standard of care within the 30-day window and meeting study requirements may be used for EAP purposes.

- Informed consent
- Eligibility (per the inclusion and exclusion criteria)
- Medical history
- Documentation of HER2-positive disease (refer to Section 5.1)
- Demographic data
- Concomitant medications
- Disease assessment per RECIST 1.1 (CT/MRI scans) according to standard of care
- Height and body weight
- Physical examination
- ECOG PS
- Vital signs
- Hematology, serum chemistry and urinalysis by local laboratory, for ascertainment of eligibility.
- Coagulation panel - The coagulation panel must be repeated at subsequent cycles at the discretion of the treating oncologist.
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.
- 12-lead ECG for assessment of QTcF and eligibility
- LVEF assessed by echocardiogram or multigated acquisition scan (MUGA)
- Hepatitis B surface antigen, hepatitis C antibody, and HIV tests (HIV 1/2 Ag/Ab combination immunoassay) should be obtainted if clinically indicated

7.2 Treatment Period

7.2.1 Cycle 1

7.2.1.1 Cycle 1 Day 1

Prior to dosing:

- Confirm patient eligibility per inclusion/exclusion criteria
- Body weight
- Physical exam (does not need to be repeated if completed for screening within the previous 7 days)
- ECOG PS (does not need to be repeated if completed for screening within the previous 7 days)
- Vital signs
- Hematology
- Serum chemistry
- Concomitant medications
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead. Test does not need to be repeated if completed for screening within the previous 3 days.

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

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

7.2.1.2 Cycle 1 Day 15 (±2 days)

Prior to dosing:

- Vital signs

Administer study treatment:

- Zanidatamab administration

Post-dose activities

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

7.2.2 Cycle 2

7.2.2.1 Cycle 2 Day 1 (±2 days)

Prior to dosing:

- Body weight
- ECOG PS
- Vital signs
- Hematology
- Serum chemistry
- Concomitant medications
- Pregnancy test: urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

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

7.2.2.2 Cycle 2 Day 15 (±2 days)

Prior to dosing:

- Vital signs

Administer study treatment:

- Zanidatamab administration

Post-dose activities

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

7.2.3 Each Additional 4-Week Cycles

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

Prior to dosing:

- Body weight
- Physical exam
- ECOG PS

- Vital signs
- Hematology
- Serum chemistry
- Pregnancy test: urine pregnancy test performed for women of childbearing potential.
- Concomitant medications

Administer study treatment:

- Zanidatamab administration

Post-dose activities:

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

LVEF: Assessment of LVEF is performed on Cycle 3, Day 1 (+/- 7 days) and approximately every 12 weeks.

- Disease assessment (CT/MRI scan results ascertained as SOC; date and results of one or more CT/MRI will be recorded) on Cycle 3 Day 1 (+/- 7 days) and approximately every 8 weeks.

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

Prior to dosing:

- Vital signs

Administer study treatment:

- Zanidatamab administration

Post-dose activities

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

7.3 End of Treatment (Final Visit)

Within 30 days after the last dose of zanidatamab, or upon termination or withdrawal from treatment, all patients will have a follow-up visit, which will include the following assessments:

- Disease assessment (CT/MRI scan results ascertained as SOC; date and results of one or more CT/MRI will be recorded)
- ECOG PS
- Hematology
- Serum chemistry
- Physical examination

- Final status assessment
- Vital signs
- Safety assessment
- Urine pregnancy test performed for women of childbearing potential. A serum test must be performed if the urine pregnancy test is positive or equivocal. In the event that a urine pregnancy test is not available, a serum pregnancy test can be used instead.

8 STUDY ASSESSMENTS

8.1 Screening Assessments

Only patients who meet all inclusion and exclusion criteria specified in Section 5 will be approved for participation in the EAP.

The eligibility case report form will be used to document relevant medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any current medications.

Documentation of HER2-positive status is required for baseline documentation, including method(s) (IHC, FISH, ISH, NGS).

Hepatitis B, hepatitis C and HIV status testing will be documented at screening, according to medical history and standard of care. Where clinically indicated, testing for hepatitis B surface antigen, hepatitis C antibody, and HIV will be performed at the local lab during screening. This will be documented on the eligibility CRF and individual data will not be collected.

For female patients of childbearing potential, pregnancy testing 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. This is considered standard practice and the data will not be collected.

LVEF ascertained by cardiac echocardiogram, or MUGA will be assessed within 30 days of the first zanidatamab dose.

8.2 Response Assessments

Tumor response will be evaluated at the visits outlined in Table 1.

All CT and MRI imaging will be performed locally, according to SOC, and assessed by the treating oncologist/ investigator. Additional imaging, such as nuclear bone scans, may be done as appropriate at the discretion of the investigator.

Treating oncologist / investigator assessment of response will be used for all treatment-related decisions. Disease response will be assessed according to RECIST 1.1 (Eisenhauer 2009) by treating oncologist / investigator.

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

In instances where patients appear to have unequivocal clinical progression and it is not possible or feasible for the patient to undergo radiologic assessment should the treating oncologist / investigator ascertain continue treatment with zanidatamab the patient’s clinical data must be available for CRF source verification through remote monitoring.

8.3 Safety Assessments

Assessment of safety during the course of this study will consist of the surveillance and recording of AEs, SAEs, clinical laboratory tests, LVEF results, and physical examination findings. Other safety assessments include evaluation of ECOG PS, and vital signs.

8.3.1 Adverse Events

8.3.1.1 Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 Code of Federal Regulations (CFR) 312.32, IND safety reporting, an AE is any untoward medical occurrence in a patient or clinical investigational patient 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 AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All AEs (regardless of relationship to study drug) should be recorded from Cycle 1 Day 1 (during and post-dose) through the end of the safety reporting period (see Section 8.3.1.3). 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 patient 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 of ≥24 hours 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 patient's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the molecule or study treatment regimen before conception or during pregnancy.
Important Medical Event:	An adverse event that may not be immediately life- threatening or result in death or hospitalisation but may jeopardise the subject or require medical or surgical intervention to prevent one of the outcomes listed above.

Adverse Event Severity

AE severity should be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

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

Relationship of the Adverse Event to Study Treatment

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

Related: There is evidence to suggest a causal relationship between the drug and the AE, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

There is a reasonable possibility of a relationship based on facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible.

8.3.1.2 Procedures for Recording Adverse Events

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

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

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms “Disease Progression”, “Progression of Disease” or “Malignant Disease Progression” and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression should be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition,

complications from progression of the underlying malignancy should be reported as unrelated AEs or SAEs.

Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 12 months after the last dose of study drug including any pregnancies that occur in the partner of a male study patient. Only report pregnancies that occur in a male patient's partner if the estimated date of conception is after the male patient's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 24 hours of becoming aware of a pregnancy using the following contact information: drugsafety@zymeworks.com (refer to the fax numbers specified on the Pregancy Report Form).

All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported to the sponsor.

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, should also be reported as SAEs.

8.3.1.3 Reporting Periods for 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 or prior to beginning the next course of anticancer therapy, whichever occurs first. However, all study protocol-related AEs are to be recorded from the time of signing the main informed consent for the study. 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.

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 patient dies, is lost to follow-up, or withdraws consent, or study closure.

All non-serious AEs will be followed through the safety reporting period. All AESIs will be followed until resolution, return to baseline, or study closure.

8.3.1.4 Serious Adverse Events Require Immediate Reporting

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

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

- Patient number – a unique alpha numeric number assigned to the individual
- Date of event onset
- Description of the event
- Study treatment

The completed SAE form is to be emailed (drugsafety@zymeworks.com) or faxed to the sponsor's Drug Safety Department within 24 hours (refer to the fax numbers specified on the SAE report form).

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

8.3.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, to the sponsor (see Section 8.3.1.4).

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

8.3.2 Adverse Events of Special Interest

AESIs are infusion reactions, LVEF absolute decreases of ≥ 10 percentage points below baseline LVEF, and symptomatic heart failure. AESIs should be recorded as AEs and reported as SAEs when appropriate. AESIs should continue to be followed until resolution or return to baseline or study closure.

8.3.3 Clinical Laboratory Tests

Samples for clinical laboratory tests will be obtained at selected timepoints specified in Table 1.

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

Table 7: Clinical Laboratory Tests

Hematology	Serum Chemistry
• Hemoglobin • Hematocrit • White blood cell (WBC) count (total and differential) • RBC count • Platelet count • Mean corpuscular volume • Mean cell hemoglobin (MCH) • MCH concentration	• Creatinine • Blood urea nitrogen (BUN) • AST • ALT • Alkaline phosphatase • Lactate dehydrogenase • Total bilirubin • Albumin • Total protein • Sodium • Potassium • Chloride • Glucose • Uric Acid • Calcium • Magnesium

Urinalysis • pH • glucose • ketones • blood protein • microscopy (if indicated)	Coagulation • prothrombin time (PT) • international normalized ratio (INR) • activated partial thromboplastin time (aPTT)

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

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

For female patients of childbearing potential, pregnancy tests will be performed at screening and on Day 1 of each cycle, as specified in the assessment schedule Table. The tests may be done using the blood samples taken for clinical chemistry. A urine pregnancy test is also acceptable.

8.3.4 Vital Signs

Vital sign measurements include heart rate, blood pressure, respiratory rate, and temperature. Vital signs will be recorded at selected timepoints specified in Table 1.

Vitals will be performed as standard of care both pre- and post-dose. Post-dose assessments should be done within approximately 30 minutes after the end of the zanidatamab infusion.

8.3.5 Physical Examination

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

Physical examination at other timepoints will be according to standard of care and/or every 3 months and end of treatment.

8.3.6 ECOG Performance Status

ECOG PS will be assessed at on Day 1 of each cycle. ECOG PS scores are described in Appendix A.

8.3.7 Electrocardiogram

12-lead ECGs will be recorded during screening for ascertainment of the following parameters: heart rate, PR interval, QRS complex, and QTc Fridericia (QTcF). QTcF > 470 ms (based on average of 3 consecutive ECGs) assessed within 30 days of screening is not permissible for treatment and is an exclusion.

8.3.8 Echocardiogram/MUGA

Echocardiograms or MUGAs are recorded at selected time points specified in Table 1. Echocardiograms or MUGAs will be recorded locally and will be assessed for an estimate of the ejection fraction. The same method must be used throughout the study. Management of left ventricular dysfunction is described in Section 6.2.1 Table 5.

9 DATA QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Audit and Inspection

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

9.2 Monitoring

Minimal data for each patient will be recorded on a paper CRF and date fields will be recorded. Data collection must be completed for each patient signing an ICF and undergoes screening assessment.

This is an Intermediate Expanded Access Protocol and the nature of such treatment protocols deems them exempt from requirements of site monitoring. Remote monitoring for compliance with safety reporting and other protocol requirements will be conducted.

9.3 Drug Accountability

It is the responsibility of the investigator to ensure the current disposition record of investigational product (those supplied by the sponsor) is maintained at each study site where the study drug is inventoried. Records or logs must comply with applicable regulations and guidelines and should include:

- amount of study drug received
- label ID number or batch number as shipped and received at site
- amount dispensed for each patient
- amount destroyed at the site if applicable, according to hospital procedure

Hospital electronic drug accountability log may be used in place of the paper drug accountability log. The drug accountability log will be maintained at the study center. All discrepancies must be accounted for and documented.

10 DATA ANALYSIS METHODS

10.1 General Procedures

This Expanded Access Protocol does not have a formal statistical analysis, since no hypothesis will be tested. Data pertaining to treated patients may be summarized in a descriptive manner.

Categorical variables will be tabulated with counts and percentages. Continuous variables will be summarized with descriptive statistics only (e.g., n, mean, standard error, median, minimum and maximum).

For tabulations of adverse events, multiple occurrences of the same event are counted only once per patient.

10.2 Determination of Sample Size

This Intermediate-Size Expanded Access Protocol will treat up to 200 patients. No formal sample size calculations were performed.

10.2.1 Patient Characteristics

Tabulations of demographic and baseline characteristics may be made for all treated patient Demographic and baseline data (sex, age [years], race, ethnicity, height [cm], and weight [kg]) will be summarized for all patients receiving a dose. Age (years) will be calculated as the number of years between the date of birth and the date of informed consent.

10.2.2 Efficacy Analyses

The endpoints listed below will be based on the treating oncologist / investigator assessment of disease response per RECIST 1.1.

10.2.2.1 Objective Response Rate

Objective response is defined as achieving a best overall response of CR or PR per RECIST 1.1. For patients with measurable disease, the number and percentage with an objective response will be calculated.

Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. This will be irrespective of whether or not patients discontinued treatment or received subsequent therapy prior to progression.

10.2.2.2 Progression-free Survival

PFS is defined as the time from the first dose of zanidatamab treatment to the date of documented disease progression (per RECIST 1.1), clinical progression, or death from any cause. Unequivocal clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers (e.g., increase in disease-related pain), or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. A marked deterioration in ECOG performance status may also indicate unequivocal clinical progression. Median PFS will be computed using the Kaplan-Meier method.

10.2.2.3 Disease Control Rate

Disease control is defined as a best overall response of CR, PR or SD per RECIST 1.1. For patients with measurable disease, the number and percentage of patients achieving DCR will be calculated.

10.2.2.4 Duration of Response

DOR is defined as the time from the first objective response (CR or PR) to documented PD per RECIST 1.1, clinical progression, or death from any cause. For patients with an objective response, the median DOR will be computed using the Kaplan-Meier method.

10.2.3 Safety Analyses

The variables listed below will be summarized for safety.

10.2.3.1 Adverse Events

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

TEAEs are defined as events with an onset during or after receipt of the first dose of zanidatamab and up to and including 30 days after the last dose but prior to the start of a new anti-cancer therapy.

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

In addition, treatment-related AEs and AEs which lead to premature discontinuation of study treatment will summarized.

10.2.3.2 Deaths and Serious Adverse Events

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

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

10.2.3.3 ECOG Performance Status

ECOG PS over time will be listed by patient. The baseline status, worst status post-baseline, and status at the End of Treatment visit will be summarized using counts and percentages.

11 INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

11.1 Institutional Review Board/Independent Ethics Committee

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

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

11.2 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 EAP. On completion of the EAP, the regulatory authorities will be notified that the EAP has ended, as required.

11.3 Ethical Conduct of the Study

The treating oncologist / investigator(s) and all parties involved in this EAP 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.

11.3.1 Informed Consent

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

The treating oncologist / investigator is responsible for ensuring that no patient undergoes any EAP-related examination or activity before that patient has been presented with the risks and benefits and given written informed consent to participate in the EAP, unless the procedure was done as part of standard of care.

The treating oncologist / investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits and potential risks and inconveniences of the EAP in simple terms, using the IRB/IEC-approved ICF. The patient 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 patient will be given ample time to consider the study. Patients 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 patient ICF will be provided to the patient or their legally authorized representative.

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

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

11.3.2 Patient Confidentiality

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

All personal data collected and processed for the purposes of this EAP should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA 1996) and applicable national and/or local laws and regulations on personal data protection and consistent with the ICFs or authorizations from the study patients. 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 patient identities.

11.4 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 patient), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives.

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

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

It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all patient medical records and other source

documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

11.5 Clinical Trial Agreement

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

12 REFERENCES

1. Alajati A, et al. (2015) "Interaction of CDCP1 with HER2 enhances HER2-driven tumorigenesis and promotes trastuzumab resistance in breast cancer." Cell Rep. 11(4):564-576.
2. Eisenhauer, E. A., et al. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer 45(2): 228-247.
3. Meric-Bernstam, F., et al. (2019). "453PDSafety, anti-tumour activity, and biomarker results of the HER2-targeted bispecific antibody zanidatamab in HER2-expressing solid tumours." Annals of Oncology 30(Supplement_5).
4. Meric-Bernstam, F., et al. (2019). "Advances in HER2-Targeted Therapy: Novel Agents and Opportunities Beyond Breast and Gastric Cancer." Clin Cancer Res 25(7): 2033-2041.
5. Moasser, M. M. (2007). "The oncogene HER2: its signaling and transforming functions and its role in human cancer pathogenesis." Oncogene 26(45): 6469-6487.
6. Valle, J. W., et al. (2017). "New Horizons for Precision Medicine in Biliary Tract Cancers." Cancer Discov 7(9): 943-962.
7. Wolff A.C. et al. 2013. “Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update.” Journal of Clinical Oncology 31(31): 3997-401.

Appendix A: ECOG Performance Status Scale

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

Appendix B: Investigator Signature Page

Investigator Statement and Signature

I have read the attached protocol entitled “Expanded Access use of zanidatamab for the treatment of HER2-positive advanced solid tumors”.

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

Investigator Signature	Date
Investigator Name, Printed	

Submit completed form to Zymeworks.EAP@earlyaccesscare.com or your Early Access Care coordinator.