CLINICAL STUDY PROTOCOL

PHASE 1/2, MULTICENTER, OPEN-LABEL, MULTIPLE DOSE, FIRST-IN-HUMAN STUDY OF U3-1402 IN SUBJECTS WITH HER3-POSITIVE METASTATIC BREAST CANCER

U31402-A-J101

VERSION 9.0, 8 NOV 2022

VERSION 8.0, 25 MAY 2022

VERSION 7.0, 28 OCT 2021

VERSION 6.0, 15 SEP 2020

VERSION 5.0, 05 SEP 2019

VERSION 4.0, 29 MAR 2019

VERSION 3.0, 26 JUN 2018

VERSION 2.0, 06 FEB 2018

VERSION 1.0, 10 AUG 2016

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Disclosure Agreement) without the prior written permission of an authorized representative of Daiichi Sankyo.

INVESTIGATOR AGREEMENT

PHASE 1/2, MULTICENTER, OPEN-LABEL, MULTIPLE DOSE, FIRST-IN-HUMAN STUDY OF U3-1402 IN SUBJECTS WITH HER3-POSITIVE METASTATIC BREAST CANCER

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo representative listed below.

PPD	
Print Name	**Signature**
PPD Global Oncology Research and Development	
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

SUMMARY OF CHANGES

Amendment Rationale:

The main purpose of this amendment is to revise the estimated study duration..

Changes to the Protocol:

Please refer to the comparison document for protocol Version 9.0 (dated 8 Nov 2022) versus protocol Version 8.0 (dated 25 May 2022) for actual changes in-text. The summary of changes below is a top-line summary and rationale of major changes in the U31402-A-J101 clinical study protocol (Version 9.0) by section.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES
All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes.
Minor edits, such as updates to language that do not alter original meaning, update to version numbering, formatting, change in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or changes in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
Section 3.1.1.3 Duration of the Study Section 17.2.2 Study Period Protocol Synopsis, Study Duration	Study period was updated from 6 years to 7 years (Nov 2016 to Dec 2023).	Study period was prolonged.

PROTOCOL SYNOPSIS

EudraCT:	NA
IND Number:	137503
Protocol Number:	U31402-A-J101
Investigational Product:	U3-1402
Active Ingredient(s)/INN:	U3-1402 consists of an antibody component (patritumab, U3-1287) covalently conjugated to a drug-linker (MAAA-1162a) containing a drug component (MAAA-1181a).
Study Title:	Phase 1/2, Multicenter, Open-label, Multiple Dose, First-in-human Study of U3-1402 in Subjects with HER3-Positive Metastatic Breast Cancer
Study Phase:	Phase 1/2
Indication Under Investigation:	U3-1402 will be evaluated in subjects with human epidermal growth factor receptor 3 (HER3)-positive, advanced/unresectable or metastatic breast cancer.
Study Objectives:	**Primary Objectives:** <u>Dose Escalation Part</u> 1. To assess safety and tolerability of U3-1402. 2. To determine the maximum tolerated dose (MTD) of U3-1402. <u>Dose Finding Part</u> 1. To assess safety and evaluate efficacy of U3-1402. 2. To assess the safety of alternative dosing schedule(s) of U3-1402. 3. To determine the recommended dose(s) for expansion (RDEs) of U3-1402. <u>Dose Expansion Part</u> 1. To assess safety and evaluate efficacy of U3-1402 at the RDEs in subjects with HER3-positive, human epidermal growth factor receptor 2 (HER2)-negative (including HR-positive and triple negative breast cancer [TNBC; HR-negative]) advanced/unresectable or metastatic breast cancers. **Secondary Objectives:** <u>Dose Escalation Part</u> 1. To assess the pharmacokinetics (PK) profiles of U3-1402, total anti-HER3 antibody, and MAAA-1181a. 2. To evaluate the efficacy of U3-1402. 3. To assess the incidence of anti-drug antibodies (ADAs) against U3-1402. <u>Dose Finding and Dose Expansion Parts</u> 1. To assess the PK profiles of U3-1402, total anti-HER3 antibody, and MAAA-1181a. 2. To assess the incidence of ADA against U3-1402. <u>Dose Expansion Part</u> 1. To determine the relationship between efficacy of U3-1402 and HER3 expression

	Exploratory Objectives: 1. To explore the concentration-corrected QT (QTc) relationships of U3-1402, total anti-HER3 antibody, and MAAA-1181a. 2. To identify biomarkers that correlate with U3-1402 response or toxicity.
Study Design:	This is a Phase 1/2, multicenter, open-label, multiple dose, first-in-human study of U3-1402 in subjects with HER3-positive advanced/unresectable or metastatic breast cancer. This study consists of 3 parts: Dose Escalation, Dose Finding, and Dose Expansion. In the Dose Escalation Part, eligible subjects with HER3-high breast cancer who have been refractory to or intolerant to standard treatment, or for whom standard treatment is no longer available, will be enrolled. In the Dose Finding Part, eligible subjects with HER3-high breast cancer who have received ≥2 and ≤6 prior chemotherapy regimens (including ≥2 regimens given in the advanced disease setting) will be enrolled. In the Dose Expansion Part, eligible subjects with HER3-positive, HER2-negative, HR-positive breast cancer who have received ≥2 and ≤6 prior chemotherapy regimens for breast cancer (including ≥2 regimens administered for the treatment of advanced/unresectable or metastatic disease), and eligible subjects with HER3-high TNBC who have received 1 to 2 prior chemotherapy regimens in the advanced disease setting will be enrolled. **Dose Escalation Part** Beginning with Cycle 1, Day 1, U3-1402 will be administered via intravenous (IV) infusion once every 3 weeks (Q3W), in 21-day cycles. The treatment will continue until unacceptable toxicity, progressive disease (PD), or withdrawal of consent. The starting dose for the Dose Escalation Part will be 1.6 mg/kg. Dose escalation will be guided by the modified Continuous Reassessment Method (mCRM) using a Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle. In this method, a decision to escalate to the next dose cohort will be based on review of all subjects who have completed the dose-limiting toxicity (DLT) evaluation period. This DLT evaluation period is defined as the 21 days of Cycle 1. A DLT-evaluable subject is defined as any subject who has received at least one dose of U3-1402, with the exception of those subjects for whom DLT evaluation could not be adequately conducted. The second subject in each dosing level should receive dosing at least 24 hours after the initial dosing of the first subject. This allows to check for acute toxicity such as an infusion-related reaction. The Dose Escalation Part will be conducted in Japan only. **Dose Finding Part** During the Dose Finding Part, subjects will be assigned into cohorts with multiple drug administration schedules, including up-titration of dose. The objectives of the Dose Finding Part are to assess safety and

evaluate efficacy of U3-1402. The Dose Finding Part will be conducted in Japan only.

The following Dose Finding Cohorts may be evaluated. These cohorts are provisional, and may change based on emerging safety, tolerability, and efficacy data:

Dose Finding Cohort 1

- U3-1402 at a dosage of 4.8 mg/kg administered via IV infusion Q3W in 21-day cycles.

Dose Finding Cohort 2

- U3-1402 at a dosage of 6.4 mg/kg administered via IV infusion Q3W in 21-day cycles.

Dose Finding Cohort 3

- U3-1402 administered via IV infusion Q3W in 21-day cycles with an up-titration of U3-1402 dose on Day 1 of the first 3 cycles as described below:
  - Cycle 1, Day 1: 3.2 mg/kg
  - Cycle 2, Day 1: 4.8 mg/kg
  - Cycle 3, Day 1 and subsequent cycles: 6.4 mg/kg

Dose Finding Cohort 4

- U3-1402 administered via IV infusion at a dosage of 4.2 mg/kg Q2W in 14-day cycles for 3 cycles, followed by a dosage of 6.4 mg/kg administered via IV infusion Q3W thereafter.

Dose Finding Cohort 5

- U3-1402 administered via IV infusion at a dosage of 3.2 mg/kg Q2W in 14-day cycles for 3 cycles, followed by a dosage of 4.8 mg/kg administered via IV infusion Q3W thereafter.

Additional Dose Finding Cohorts

- Additional dose levels equal to, or less than, the MTD (if attained or highest dose evaluated during the Dose Escalation Part) may be considered for the Dose Finding Part.
- Additional dose regimens, including up-titration of dose, may be considered for the Dose Finding Part based on emerging safety and efficacy data.

Dose Expansion Part

In the Dose Expansion Part, subjects will be assigned to cohorts as described below. The objectives of the Dose Expansion Part are to assess safety and evaluate efficacy of U3-1402 at the RDEs in subjects with HER3-positive, HER2-negative (including HR-positive and TNBC) advanced/unresectable or metastatic breast cancers. The Dose Expansion Part may include subjects from any participating country, including the United States (US) and Japan.

A total of approximately 110 subjects will be enrolled in the Dose Expansion Part among the following 4 cohorts:

	HER3-High, HR-Positive Cohorts Approximately 60 eligible subjects with HER3-high, HER2-negative, HR-positive breast cancer will be randomized into 1 of 2 cohorts. Subjects will receive U3-1402 at a dosage of either 4.8 mg/kg or 6.4 mg/kg administered via IV infusion Q3W. **HER3-Low, HR-Positive Cohort** Approximately 20 eligible subjects with HER3-low, HER2-negative, HR-positive breast cancer will be enrolled. U3-1402 at a dosage of 6.4 mg/kg will be administered via IV infusion Q3W. **HER3-High, TNBC Cohort** Approximately 30 eligible subjects with HER3-high, TNBC will be enrolled. U3-1402 at a dosage of 6.4 mg/kg will be administered via IV infusion Q3W. **Additional Expansion Cohort(s)** Additional cohorts may be considered for the Dose Expansion Part based on emerging safety and efficacy data.
Study Duration:	This study is expected to last approximately 7 years from the time the first subject is enrolled to the time the last subject is off the study. The end of the study is defined as the date of completion of the last visit or procedure shown in the Schedule of Events in the trial globally. Sponsor may terminate the study at any time due to administrative reason or at request from competent regulatory authorities. The number of treatment cycles is not limited in this study. Subjects will continue the study treatment until withdrawal of consent, PD, unacceptable toxicity, death, or termination of the study by Sponsor.
Study Sites and Location:	Approximately 20 study sites in Japan and the United States are planned for this study.
Subject Eligibility Criteria:	**Inclusion Criteria** Subjects must satisfy all of the following criteria to be included in the study: **Common Inclusion Criteria for Dose Escalation Part and Dose Finding Part** 1. Has a pathologically documented advanced/unresectable or metastatic breast cancer. 2. Has documented HER3-high expressing disease assessed using IHC testing by the central laboratory. 3. Is refractory to or intolerant to standard treatment, or for whom standard treatment is no longer available. 4. Male or female subjects aged ≥20 years in Japan. 5. Has an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1, with no deterioration over the previous 2 weeks. 6. Has left ventricular ejection fraction (LVEF) ≥ 50% by either echocardiography (ECHO) or multiple gated acquisition scan (MUGA) within 28 days prior to enrollment. 7. Has adequate bone marrow reserve and organ function within 7 days prior to enrollment, defined according to the following:

Item	Laboratory value
Platelet count	≥100 000/mm^3
Hemoglobin (Hb)	≥8.5 g/dL
Absolute neutrophil count (ANC)	≥1500/mm^3
Creatinine	≤1.5 × upper limit of normal (ULN), or creatinine clearance ≥60 mL/min as calculated using the Cockcroft-Gault equation
Serum aspartate aminotransferase (AST)/Serum alanine aminotransferase (ALT)	≤3 × ULN (if liver metastases are present, ≤5 × ULN)
Total bilirubin	≤1.5 × ULN

8. Has adequate treatment washout period before enrollment, defined according to the following:

Treatment	Washout period
Major surgery	≥3 weeks
Radiation therapy	≥3 weeks (or 2 weeks for palliative radiation for bone metastasis [excluding pelvic radiation] and brain metastasis, 1 week for stereotactic radiotherapy)
Hormonal therapy	≥2 weeks
Chemotherapy (including antibody drug therapy)	≥3 weeks (≥2 weeks for 5-fluorouracil-based agents, folinate agents, or weekly paclitaxel. ≥6 weeks for nitrosoureas or mitomycin C)
Immunotherapy	≥3 weeks
Cytochrome P450 (CYP) 3A4 strong inhibitor	≥3 elimination half-lives of the inhibitor
CYP3A4 strong inducer	≥2 weeks
QTc-prolonging medications	≥3 elimination half-lives of the medications
OATP1B inhibitor	≥3 elimination half-lives of the inhibitor

9. Has at least 1 measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 confirmed by the central laboratory.
10. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during the study and for at least 7 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception include:
    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal delivery).

b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable delivery).
c. Intrauterine device (IUD).
d. Intrauterine hormone-releasing system (IUS).
e. Bilateral tubal occlusion.
f. Vasectomized partner.
g. Complete sexual abstinence.

Non-childbearing potential is defined as pre-menopausal with documented tubal ligation or hysterectomy; OR postmenopausal with documented ≥12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] >40 mIU/mL and estradiol <40 pg/mL [<140 pmol/L] is confirmatory).

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to discontinue HRT and use 1 of the contraception methods outlined above for women of childbearing potential. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Use of HRT is not allowed during the study. Men who are fertile and sexually active should be willing to use highly effective methods of contraception if their partners are of reproductive potential.

Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration.

Female subjects must not donate or retrieve, for their own use, ova from the time of Screening and throughout the study treatment period, and for ≥7 months after the final dose of study drug.

11. Is able to provide written informed consent.
12. Has a life expectancy of ≥3 months.

Additional Inclusion Criterion for Dose Finding Part

13. Has received ≥2 and ≤6 prior chemotherapeutic regimens for breast cancer, ≥2 of which were administered for treatment of advanced/unresectable or metastatic disease. At least 1 prior chemotherapeutic regimen must have included a taxane (eg, paclitaxel, docetaxel), administered in the neoadjuvant, adjuvant, or advanced setting.

Inclusion Criteria for Dose Expansion Part

1. Has a pathologically documented advanced/unresectable or metastatic breast cancer.
2. Has documented HER3-positive (HER3-high or HER3-low) disease assessed by IHC assay by the central laboratory from archival tumor tissue or a screening tumor fresh biopsy sample.
3. Is able to submit a fresh tumor biopsy sample prior to starting study treatment. (If subjects have already submitted fresh tumor

biopsy sample for HER3 expression, resubmission is not necessary.)

4. Has documented HER2-negative expression according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines.
5. Has documented HR (estrogen and/or progesterone receptor) positive disease with exception of the TNBC cohort (see inclusion criterion #17 below).
6. Is refractory to or intolerant to standard treatment, or for whom standard treatment is no longer available.
7. With exception of the TNBC cohort (see inclusion criterion #18 below), has received ≥2 and ≤6 prior chemotherapeutic regimens for breast cancer, ≥2 of which were administered for treatment of advanced/unresectable or metastatic disease. At least 1 prior chemotherapeutic regimen must have included a taxane (eg, paclitaxel, docetaxel), administered in the neoadjuvant, adjuvant, or advanced setting.
8. Male or female subjects aged ≥20 years in Japan, ≥18 years in the United States.
9. Has an ECOG PS 0-1, with no deterioration over the previous 2 weeks.
10. Has LVEF ≥50% by either ECHO or MUGA within 28 days prior to enrollment.
11. Has adequate bone marrow reserve and organ function within 7 days prior to enrollment, defined according to the following:

Item	**Laboratory value**
Platelet count	≥100 000/mm^3
Hemoglobin (Hb)	≥9.0 g/dL
Prothrombin time (PT) or PT-international normalized ratio (INR) and partial thromboplastin time (PTT)	≤1.5 × ULN, except for subjects on coumarin-derivative anticoagulants or other similar anticoagulant therapy, who must have PT-INR within therapeutic range as deemed appropriate by the Investigator.
Absolute neutrophil count (ANC)	≥1500/mm^3
Creatinine	≤1.5 × upper limit of normal (ULN), or creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation
Serum aspartate aminotransferase (AST)/Serum alanine aminotransferase (ALT)	≤3 × ULN (if liver metastases are present, ≤5 × ULN)
Total bilirubin	≤1.5 × ULN (<3 × ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinemia] or liver metastases)

12. Has adequate treatment washout period before enrollment defined according to the following:

Treatment	Washout period
Major surgery	≥3 weeks
Radiation therapy	≥3 weeks (or 2 weeks for palliative radiation for bone metastasis [excluding pelvic radiation] and brain metastasis, 1 week for stereotactic radiotherapy)
Hormonal therapy	≥2 weeks
Chemotherapy (including antibody drug therapy)	≥3 weeks (≥2 weeks for 5-fluorouracil-based agents, folinate agents, or weekly paclitaxel. ≥6 weeks for nitrosoureas or mitomycin C)
Immunotherapy	≥3 weeks
CYP3A4 strong inhibitor	≥3 elimination half-lives of the inhibitor
QTc-prolonging medications	≥3 elimination half-lives of the medications
OATP1B inhibitor	≥3 elimination half-lives of the inhibitor

13. Has at least 1 measurable lesion based on RECIST version 1.1 confirmed by the central laboratory.
14. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during the study and for at least 7 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception include:
    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal delivery).
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable delivery).
    c. Intrauterine device (IUD).
    d. Intrauterine hormone-releasing system (IUS).
    e. Bilateral tubal occlusion.
    f. Vasectomized partner.
    g. Complete sexual abstinence.

    Non-childbearing potential is defined as pre-menopausal with documented tubal ligation or hysterectomy; OR postmenopausal with documented ≥12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] >40 mIU/mL and estradiol <40 pg/mL [<140 pmol/L] is confirmatory).

    Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to discontinue HRT and use 1 of the contraception methods outlined above for women of childbearing potential. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study

enrollment. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Use of HRT is not allowed during the study. Men who are fertile and sexually active should be willing to use highly effective methods of contraception if their partners are of reproductive potential.
Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration.
Female subjects must not donate or retrieve, for their own use, ova from the time of Screening and throughout the study treatment period, and for ≥7 months after the final dose of study drug.

15. Is able to provide written informed consent.
16. Has a life expectancy of ≥3 months.

Additional Inclusion Criteria for the HER3-high, TNBC Cohort

17. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER3-high, HR- (estrogen and progesterone receptor) negative disease and HER2-negative expression according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines.
18. Has progressed after receiving 1 to 2 prior chemotherapy regimens for advanced/unresectable or metastatic breast cancer.

Exclusion Criteria

Exclusion Criteria for Dose Escalation and Dose Finding Parts

Subjects who meet any of the following criteria will be disqualified from entering the study in Dose Escalation and Dose Finding Parts:

1. Prior treatment with an anti-HER3 antibody.
2. Prior treatment with an antibody-drug conjugate (ADC) which consists of an exatecan derivative that is a topoisomerase I inhibitor (eg, DS-8201a).
3. Has a medical history of symptomatic congestive heart failure (CHF) (New York Heart Association (NYHA) classes II-IV) or serious cardiac arrhythmia requiring treatment.
4. Has a medical history of myocardial infarction or unstable angina within past 6 months prior to enrollment.
5. Has a mean corrected QT by Fridericia's formula (QTcF) prolongation to >450 milliseconds (ms) in males and >470 ms in females in 3 successive screening measurements as assessed by central laboratory.
6. Has any history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis), has current ILD/pneumonitis, or is suspected to have such disease by imaging during screening.
7. Has clinically significant corneal disease.
8. Has an uncontrolled infection requiring IV injection of antibiotics, antivirals, or antifungals.
9. Has a positivity for human immunodeficiency virus (HIV), or active hepatitis B or C infection.

10. Is a lactating mother (women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days prior to enrollment.
11. Has clinically active spinal cord compression or brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic for 4 weeks before enrollment and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (1 week for stereotactic radiotherapy).
12. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, grade ≤1 or baseline. Subjects with chronic grade 2 toxicities may be eligible per the discretion of the Investigator.
13. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator.
14. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product.

Additional Exclusion Criteria for Dose Finding Part

15. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.

Exclusion Criteria for Dose Expansion Part

Subjects who meet any of the following criteria will be disqualified from entering the study in the Dose Expansion Part:

1. Prior treatment with an anti-HER3 antibody.
2. Prior treatment with an antibody-drug conjugate (ADC) which consists of a topoisomerase I inhibitor, exatecan derivative (eg, DS-8201a) or govitecan derivative (eg, IMMU-132).
3. Has a medical history of symptomatic congestive heart failure (CHF) (New York Heart Association (NYHA) classes II-IV) or serious cardiac arrhythmia requiring treatment.
4. Has a medical history of myocardial infarction or unstable angina within past 6 months prior to enrollment.
5. Has any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, second-degree heart block, or PR interval >250 ms.
6. Has a mean QTcF prolongation to >450 ms in males and >470 ms in females in 3 successive screening measurements as assessed by central laboratory.
7. Has any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as congenital long QT syndrome,

	family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives. 8. Has any history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis), has current ILD/pneumonitis, or is suspected to have such disease by imaging during screening. 9. Has clinically significant corneal disease. 10. Has any evidence of severe or uncontrolled systemic diseases (including uncontrolled hypertension, and active bleeding diatheses or active infection including hepatitis B, hepatitis C, and HIV infection), psychiatric illness/social situations, substance abuse, or other factors which in the Investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required. 11. Is a lactating mother (women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days prior to enrollment. 12. Has clinically active spinal cord compression or brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic for 4 weeks before enrollment and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (1 week for stereotactic radiotherapy). 13. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE version 5.0, grade ≤1 or baseline. Subjects with chronic grade 2 toxicities may be eligible per the discretion of the Investigator. 14. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator. 15. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product. 16. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.
Dosage Form, Dose and Route of Administration:	U3-1402 will be provided as a sterile, CCI [redacted] in an CCI [redacted]. Each vial will contain 50 mg of U3-1402 in a 2.5 mL solution. The selected dose of U3-1402 will be prepared by dilution of the required volume of the drug product (calculated from the subject's body weight) into a volume of 250 mL of 5% dextrose in water. U3-1402 will be infused as a continuous IV infusion over approximately 90 minutes on Day 1 of Cycle 1. If there are no infusion-related reactions after the initial dose, subsequent doses of U3-1402 will be infused over approximately 30 minutes on Day 1 of

	each cycle. An alternative drug administration schedule for dose finding may be considered upon review of human safety and PK parameters by the Investigators and Sponsor.
Study Endpoints:	Pharmacokinetic endpoints: Serum PK endpoints (area under the concentration-versus-time curve, from time 0 to the last measurable concentration as calculated by the linear-up log-down trapezoidal method [AUClast], AUC during dosing interval [AUCtau], maximum (peak) observed concentration [Cmax], time of maximum observed concentration [Tmax] and trough serum concentrations [Ctrough]) of U3-1402 for each subject will be estimated using standard noncompartmental methods. For total anti-HER3 antibody and MAAA-1181a, all parameters listed above will be estimated. Safety endpoints: Safety endpoints will include DLTs, serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings. Efficacy endpoints: Tumor response will be evaluated using RECIST version 1.1. Objective response rate (ORR) (the sum of CR rate and PR rate), disease control rate (DCR) (the sum of CR rate, PR rate, and stable disease [SD] rate), duration of response (DOR), clinical benefit rate (CBR; the proportion of subjects who achieved a best overall response of CR or PR or SD $\geq$ 6 months), time to response (TTR), progression free survival (PFS), overall survival (OS), and percent change in target lesion(s).
Planned Sample Size:	The Dose Escalation Part of this study consists of mCRM with EWOC design with at least 3 DLT-evaluable subjects per dose level. Sample size has been determined by practical considerations for the Dose Escalation Part. A total of approximately 12 subjects will be enrolled between Dose Escalation and Dose Finding for each of the Q3W Dosing Cohorts evaluated in Dose Finding. For the alternative dosing cohorts evaluated in Dose Finding, a total of approximately 12 subjects will be enrolled into each cohort. RDEs will be determined based on the risk and benefit assessment. For the Dose Expansion Part, there are 4 planned expansion cohorts: HER3-high, HR-positive (6.4 mg/kg), HER3-high, HR-positive (4.8 mg/kg), HER3-low, HR-positive (6.4 mg/kg) and HER3-high, TNBC (6.4 mg/kg): • Approximately 60 eligible subjects with HER3-high, HER2-negative, HR-positive disease will be randomized into 1 of 2 cohorts: 4.8 mg/kg or 6.4 mg/kg. • Subjects with HER3-low, HER2-negative, HR-positive breast cancer will not be randomized. Approximately 20 eligible subjects in this setting will be enrolled into a HER3-low, HR-positive (6.4 mg/kg) cohort.

	• Subjects with HER3-high, TNBC will not be randomized. Approximately 30 eligible subjects in this setting will be enrolled into a HER3-high, TNBC (6.4 mg/kg) cohort. A total of approximately 110 subjects will be enrolled into the Dose Expansion Part. In HER3-high, HR-positive cohorts of the Dose Expansion Part, if target ORR is more than 10% (null hypothesis: ORR ≤0.10, alternative hypothesis: ORR >0.10), then the probability of no response out of 30 subjects will be less than 5%. The probability that more than 6 responders out of 30 subjects (ORR >20%) are observed will be less than 5% under the null hypothesis with ORR ≤0.10 but more than 80% under alternative hypothesis with ORR = 0.30. In the HER3-low, HR-positive cohort of the Dose Expansion Part, if target ORR is more than 10% (null hypothesis: ORR ≤0.10, alternative hypothesis: ORR >0.10), then the probability of no response out of 20 subjects will be less than 15%. The probability that more than 3 responders out of 20 subjects (ORR >15.0%) are observed will be less than 15% under the null hypothesis with ORR ≤0.10 but more than 75% under alternative hypothesis with ORR = 0.25. In the HER3-high, TNBC cohort of the Dose Expansion Part, if target ORR is more than 20% (null hypothesis: ORR ≤0.20, alternative hypothesis: ORR >0.20), then the probability of no response out of 30 subjects will be less than 5%. The probability that more than 9 responders out of 30 subjects (ORR >30.0%) are observed will be less than 10% under the null hypothesis with ORR ≤0.20 but more than 80% under alternative hypothesis with ORR = 0.40. The probability values for the sample size are derived based on binomial distribution using SAS® version 9.4.
Statistical Analyses:	The data cutoff for the primary analysis will occur after all subjects have either discontinued from the study or have been followed for at least 9 months following the first dose of study treatment, whichever is earlier. The primary analysis data cutoff may be extended if emerging data show responses are occurring later. The final analysis of the study will occur after all subjects have discontinued the study. Data collected beyond the primary analysis cut-off time point will be presented as appropriate in a Clinical Study Report addendum. Data analyses will also be conducted during the Dose Escalation and Dose Finding Parts. Descriptive statistics will be provided for selected demographic, safety, and PK data by cohort and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges (as well as geometric means and geometric coefficient of variation for Cmax and AUC PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. <u>Efficacy Analyses</u>: Efficacy variables will include ORR, DCR, DOR, CBR, TTR, PFS, using RECIST version 1.1 and OS.

	The efficacy variables will be listed and summarized. For ORR and DCR, point estimates and 2-sided 95% exact binomial confidence intervals will be provided. Time to event variables including DOR, TTR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method. PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic PD or death due to any cause. Censoring rules for the time-to-event endpoints such as PFS and OS analysis will be specified in the statistical analysis plan (SAP). Descriptive statistics for the best percent change in the sum of diameters of measurable tumors will be provided. A waterfall plot of the best percent change from screening in the sum of diameters for each subject will be presented. Safety Analyses: The safety profile will be based on TEAEs, SAEs, AESIs, clinical laboratory measurements, vital sign measurements, ECG recordings, physical examination findings, ECHO/MUGA findings, and ophthalmologic findings. In the Dose Escalation Part, the incidence of DLTs will also be evaluated. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the Dose Escalation Part, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized. Pharmacokinetic Analyses: PK analyses will be performed on the PK analysis set. Serum concentration-time data for U3-1402, total anti-HER3 antibody and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics at each point and in study period. PK parameters will be listed and summarized using descriptive statistics by dose and part. Biomarker and Exploratory Analyses: Exploratory analyses for biomarkers will be listed and summarized using descriptive statistics.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALP	serum alkaline phosphatase
ALT	serum alanine aminotransferase
ANC	absolute neutrophil count
AST	serum aspartate aminotransferase
BI	before infusion
BLRM	Bayesian logistic regression model
CBR	clinical benefit rate
CDISC	Clinical Data Interchange Standards Consortium
cfDNA	cell-free DNA
CFR	Code of Federal Regulations
cfRNA	cell-free RNA
CHF	congestive heart failure
COVID-19	coronavirus disease 2019
CR	complete response
CRF	case report form
CRO	contract research organization
CSF	colony stimulating factor
CT	computed tomography
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
EC	ethics committee
ECD	extracellular domain

ABBREVIATION	DEFINITION
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
ELISA	Enzyme-Linked Immunosorbent Assay
EOI	end of infusion
EOT	end of treatment
EWOC	escalation with overdose control
FDA	Food and Drug Administration
F/U	follow-up
GCP	Good Clinical Practice
Hb	hemoglobin
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2
HER3	human epidermal growth factor receptor 3
HER3ECD	human epidermal growth factor receptor 3 extracellular domain
hERG	human ether-a-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hormone receptor
HSD	human starting dose
ICF	informed consent form
ICH	International Council for Harmonisation
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
INN	International Non-proprietary Name
IO	immuno-oncology
IRB	institutional review board

ABBREVIATION	DEFINITION
IRT	interactive response technology
IV	intravenous
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
mCRM	modified continuous reassessment method
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
ms	millisecond
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NRU	neutral red uptake
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PS	performance status
Q2W	once every 2 weeks
Q3W	once every 3 weeks
QTc	corrected QT
QTcF	corrected QT by Fridericia's formula
QW	once every week
RDEs	recommended doses for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan

ABBREVIATION	DEFINITION
SAVER	serious adverse event report
SD	stable disease
SOP	standard operating procedure
SpO_2	oxygen saturation of peripheral artery
STD_{10}	severely toxic dose in 10% of the animals
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TK	toxicokinetic
TNBC	triple-negative breast cancer
TTR	time to response
ULN	upper limit of normal
US	United States

LIST OF PHARMACOKINETIC PARAMETERS

ABBREVIATION	DEFINITION
AUC	area under the plasma/serum concentration-time curve
AUClast	area under the plasma/serum concentration-time curve up to the last quantifiable time
AUCtau	AUC during dosing interval
CL	total body clearance
Cmax	maximum plasma/serum concentration
Ctrough	trough plasma/serum concentration
C_0	estimated plasma/serum concentration at time 0
Kel	elimination rate constant associated with the terminal phase
MRTinf	mean residence time to infinity
Tmax	time to reach maximum plasma/serum concentration
$T_{1/2}$	terminal elimination half-life
Vss	steady-state volume of distribution
Vz	volume of distribution based on the terminal phase

LIST OF DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
MAAA-1181a	The drug component of U3-1402 – a derivative of exatecan, a topoisomerase I inhibitor
MAAA-1162a	The drug-linker component of U3-1402: CCI [redacted]
U3-1287	Patritumab, the antibody component of U3-1402 – fully human anti-HER3 monoclonal IgG1 antibody

1. INTRODUCTION

1.1. Background

Globally, breast cancer is the most frequently diagnosed cancer in women, with 1.5 million women impacted each year.[1] In the United States (US), in 2016, there were an estimated 61,000 new cases of in situ disease, 246,660 cases of invasive disease, and 40,450 deaths due to breast cancer in women.[2]

In Japan, there were 89,400 estimated cases of breast cancer in 2015. Additionally, breast cancer represents 21% of all female cancers in Japan.[3] The number of cases is increasing every year.

Breast cancer is a heterogeneous disease with respect to molecular alterations, cellular composition, and clinical outcome. This diversity presents a challenge in developing tumor classifications that are clinically useful with respect to prognosis or prediction. Diagnosis by intrinsic subtype (eg, hormone receptor [HR] or human epidermal growth factor receptor 2 [HER2] status) adds significant prognostic and predictive information in breast cancer, particularly concerning the risk of relapse.[4] Among all breast cancer subtypes, HR-positive and HER2-negative tumors make up the majority of breast cancer patients. With regard to metastatic and relapsing breast cancer, the survival of patients with metastasis or relapse has gradually improved since the introduction of newer chemotherapeutic agents.[5, 6,7] However, despite these modest improvements, there is no single standard of care in late-line treatment for patients with metastatic/relapsing breast cancer and prognosis remains poor in this group.[8,9] In general, chemotherapies, which were not used in prior cancer treatments, are selected for treatment in late line, such as eribulin, capecitabine, vinorelbine, and so on. According to the Phase 3 study of eribulin in patients with metastatic breast cancer who received 2 to 5 previous chemotherapy regimens, including anthracyclines and taxanes, median progression-free survival (PFS) was 3.7 months and median overall survival (OS) was 13.1 months.[10]

In patients with advanced/unresectable or metastatic breast cancer classified as triple-negative breast cancer (TNBC; HER2-negative/HR-negative) chemotherapy remains the mainstay of treatment. While many drugs, including taxanes, anthracyclines, capecitabine, eribulin, S-1, and irinotecan, have shown activity, no standard of care has been established.[11, 12] Despite the treatment options presented by these agents, the prognosis for TNBC remains poor, with an estimated median overall survival of 10 to 18 months and post-progression survival of 6 months after first-line therapy.[13, 14] There is still an unmet medical need in advanced TNBC with disease progression after chemotherapy.

Considering the unmet medical need in breast cancer described here, an urgent need for the development of new therapy for advanced/unresectable or metastatic breast cancer is justified.

Preliminary data from Study U31402-A-J101 in patients with human epidermal growth factor receptor 3 (HER3)-positive, advanced/unresectable or metastatic breast cancer (N=42, total), including 10 subjects with TNBC, showed a persistent U3-1402 antitumor effect with a confirmed ORR of 42.9%, a DCR of 90.5%, and a median (range) PFS of 8.3 (1.2, 16.8) months (median follow-up of 10.5 months).

1.2. Data Summary

1.2.1. Physical, Chemical, Pharmaceutical Properties and Formulation

The U3-1402 drug product is an CCI sterile solution in CCI and is provided as a CCI U3-1402 is an antibody-drug conjugate (ADC) comprised of a recombinant fully human anti-human epidermal growth factor receptor 3 (HER3) immunoglobulin G1 (IgG1) monoclonal antibody covalently conjugated to a drug-linker, MAAA-1162a. The released drug is MAAA-1181a.

1.2.2. Nonclinical Studies

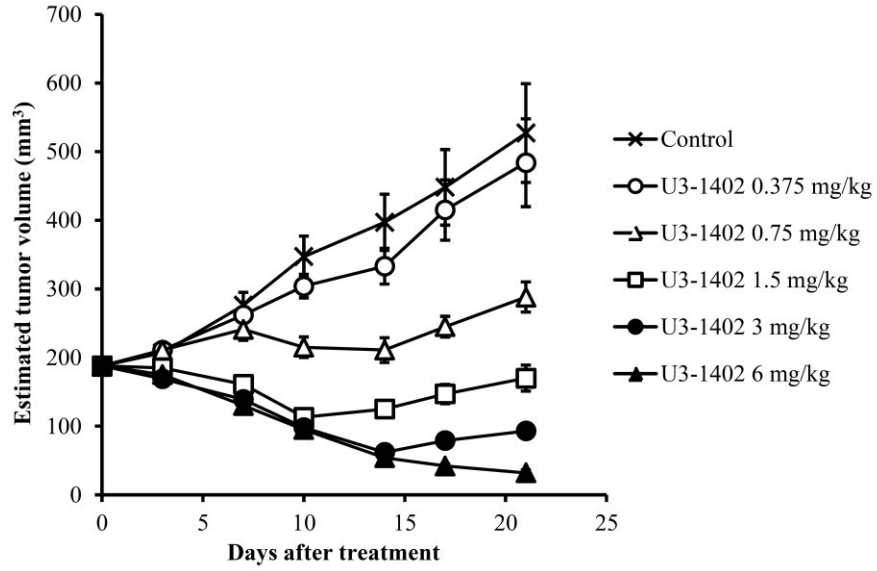
Additional information describing the U3-1402 nonclinical studies are available in the current Investigator's Brochure.

1.2.2.1. Pharmacology

U3-1402 bound specifically to human HER3 recombinant protein but did not bind to the other human HER family recombinant proteins. U3-1402 bound against human, cynomolgus monkey, rat, and mouse HER3. Cynomolgus monkey, rat, and mouse are therefore considered appropriate for the nonclinical pharmacokinetic (PK) and toxicological studies of U3-1402.

Significant dose-dependent antitumor activity of U3-1402 was shown in the MDA-MB-453 xenograft mouse model (Figure 1.1).

Figure 1.1: Tumor Growth of MDA-MB-453 Tumors Xenografted in Nude Mice



The mean estimated tumor volume and standard error (n = 10) are represented on the graph.

U3-1402 produced significant tumor regression in nude mice in HCC1569 (HER3 3+) and MDA-MB-453 (HER3 2+) human breast cancer xenograft models. U3-1402 showed inhibition of tumor proliferation in the NIBIO-G016 (HER3 1+) gastric cancer patient-derived xenograft model but did not show any anti-tumor effect in the MDA-MB-231 (HER3 0) human breast

cancer model. In conclusion, U3-1402 showed tumor regression in HER3 2+ and 3+ tumors, inhibition in HER3 1+ gastric tumour and no activity in HER3 0 tumors.

In addition, U3-1402 did not show antibody-dependent cellular cytotoxicity (ADCC) activity against HER3-expressing human breast cancer cell line. U3-1402 exerted specific cytotoxic activity against HER3-expressing cells, but did not exert cytotoxic activity against HER3-negative cells.

1.2.2.2. Safety Pharmacology

In telemetered male cynomolgus monkeys treated with single intravenous (IV) doses of U3-1402, no effects on the cardiovascular system, the respiratory system, or the central nervous system were observed at dose levels up to 30 mg/kg, the highest dose level tested. In addition, in human ether-a-go-go-related gene (hERG) studies of MAAA-1181a, the drug component, MAAA-1181a did not inhibit the hERG channel current at concentrations of up to 10 μmol/L (approximately 5000 ng/mL), the highest concentration level tested.

1.2.2.3. Pharmacokinetics and Drug Metabolism

In a single dose IV administration PK study of U3-1402 of 21 days duration in female nude mice, estimated plasma concentration at time 0 [C_0], area under the plasma concentration-time curve [AUC] and terminal elimination half-life [$T_{1/2}$] increased with increasing dose, and total body clearance [CL] decreased with increasing dose.

In a single dose IV administration PK study of 21 days duration in cynomolgus monkeys, plasma concentrations of U3-1402 were determined up until Day 7. The AUC for U3-1402 had more than a dose proportional increase from 0.1 to 1 mg/kg. The $T_{1/2}$ and mean residence time to infinity [MRTinf] values increased at 1 mg/kg, and the CL value trended towards a decrease with increasing dose. Anti-U3-1402 antibodies were detected in all animals on Days 14 and 21 after the dosing. MAAA-1181a was detected at low concentrations at 0.3 mg/kg (1 animal) and 1 mg/kg (3 animals) within 24 h after dosing.

The steady-state volume of distribution [Vss] value showed no apparent change with dose in mice and monkeys.

The plasma protein binding ratios of MAAA-1181a (10 ng/mL to 100 ng/mL) were 90.3% to 92.5% in mice, 94.2% to 96.7% in rats, 86.5% to 89.1% in monkeys, and 96.8% to 98.0% in humans.

The in vitro release rates of MAAA-1181a from U3-1402 in mouse, rat, monkey and human plasma, for 3 weeks were 5.9% or less.

MAAA-1181a was metabolized by cytochrome P450 (CYP) enzymes. CYP3A4 was the primary CYP isoform in the metabolism; however, CYP3A5 and CYP2D6 were also involved in the metabolism.

In rats, excretion of radioactivity from administered ^{14}C-labeled MAAA-1181a (^{14}C-MAAA-1181a) into feces via bile was predominant. Unchanged MAAA-1181a was the predominant component being excreted into urine, feces, and bile of the rat.

MAAA-1181a did not exhibit any potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (50% inhibitory concentration [IC_{50}] >50 μmol/L). MAAA-1181a did not exhibit any potential to induce CYP3A4, CYP1A2, and CYP2B6 up to 30 μmol/L. MAAA-1181a did not inhibit organic anion transporter (OAT) 3, organic cation transporter (OCT) 1, OCT2, organic anion transporting polypeptide (OATP) 1B3, multidrug and toxin extrusion (MATE) 1, MATE2-K, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and bile salt export pump (BSEP) (IC_{50} >30 μmol/L). MAAA-1181a was a substrate for organic anion transporting polypeptide (OATP) 1B1, OATP1B3, multidrug and toxin extrusion (MATE) 2-K, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated protein (MRP) 1 (but not MRP2 or MRP3). MAAA-1181a inhibited OAT1 and OATP1B1 with the IC_{50} values of 12.7 and 14.4 μmol/L, respectively, although the values were much higher than the observed plasma concentrations of MAAA-1181a in all the nonclinical in vivo studies. In addition, OATPs appeared to contribute to the human hepatic uptake of MAAA-1181a.

In the toxicokinetics (TK) evaluation of U3-1402 in rats (20, 60, and 194.3 mg/kg of U3-1402) and cynomolgus monkeys (3, 10, and 30 mg/kg of U3-1402), C_0, maximum plasma concentration [Cmax] and AUC values of U3-1402, or MAAA-1181a generally increased with increasing dose after the first dose. There were no clear sex differences. In rats, no apparent changes in TK parameters were noted after repeated dosing. In monkeys after the 4th dose, plasma concentrations of U3-1402 showed decreases in C_0 and AUC values. However, plasma concentrations of MAAA-1181a showed increases in the Cmax and AUC values in the 3 and 10 mg/kg groups.

Animals in which anti-U3-1402 antibody was detected tended to have lower AUC and $T_{1/2}$ values of U3-1402, and higher Cmax of MAAA-1181a on Day 64 compared to the corresponding animals on Day 1. Anti-U3-1402 antibody was not detected in rats given 20 and 60 mg/kg on Day 64. Anti-U3-1402 antibodies were detected in serum samples from several U3-1402-treated rats, and from 11 out of 12 of U3-1402-treated monkeys at 3 and 10 mg/kg. No marked differences were observed in PK and TK parameters in animals between U3-1402 and total antibody (drug conjugated and unconjugated antibody) before the occurrence of a positive reaction to anti-U3-1402 antibody. These in vivo and in vitro results indicate that U3-1402 is stable in plasma.

1.2.2.4. Toxicology

The binding profile of U3-1402 using an enzyme-linked immunosorbent assay (ELISA) showed that U3-1402 bound to the extracellular domain of HER3 in rats and cynomolgus monkeys. Therefore, for safety assessment, intermittent IV dosing studies were conducted in these 2 cross-reactive species for U3-1402. In a 12-week intermittent dose toxicity study of U3-1402 in rats, the animals received 20, 60, or 194.3 mg/kg of U3-1402 Q3W. The highest dose level selected for this study was the maximum feasible level, considering the tolerable range of dosing volume for rats and formulation concentration. In a 12-week intermittent dose toxicity study of U3-1402 in the monkey, the animals received 3, 10, or 30 mg/kg of U3-1402 Q3W based upon the results of a preliminary intermittent dose toxicity study (once every week [QW] dosing, 2 weeks). In the latter study, 30 mg/kg of U3-1402 and greater induced cardiotoxic changes and 80 mg/kg of U3-1402 induced moribundity. An in vitro tissue cross-reactivity study was

conducted using human, cynomolgus monkey, and rat tissues. No test-article related effects were observed in the 1- or 6-month intermittent dose toxicity study of U3-1287 in cynomolgus monkeys. A 4-week intermittent IV dosing study of MAAA-1181a was conducted in rats and cynomolgus monkeys to clarify the toxicity of MAAA-1181a. In addition, an in vitro 3T3 neutral red uptake (NRU) phototoxicity study was also conducted because MAAA-1181a has demonstrated photoabsorption in the UV-visible light range. No phototoxic reaction was noted in a single dose phototoxicity study of MAAA-1181a in pigmented rats at doses up to 3 mg/kg (the highest dose administered).

In the study of intermittent IV dosing of U3-1402 in the rat (Q3W dosing for 12 weeks at 20, 60, or 194.3 mg/kg), 1 male given 194.3 mg/kg in the toxicity evaluation group died and 1 female given 194.3 mg/kg in the TK evaluation group became moribund due to severe liver injury and severe suppression of lymphatic/hematopoietic systems. Myocardial necrosis was seen in the animal found dead and single cell necrosis of corneal epithelium was seen in the moribund animal. In the surviving animals, the major findings were hepatobiliary, thymic, gastrointestinal, reproductive organ, skin, and dental toxicity at dose levels of 20 mg/kg and greater, and renal, lymphatic/hematopoietic, pulmonary, and mammary gland toxicity at dose levels of 60 mg/kg and greater. At 194.3 mg/kg, treatment-related changes were observed in the mesenteric lymph node, urinary bladder (female only), accessory reproductive gland, tongue, harderian gland, salivary gland, and skeletal muscle. Except for the testicular changes, these changes showed recovery or a tendency of recovery after 6-week recovery period. Therefore, the severely toxic dose in 10% of the animals (STD_{10}) in the rat intermittent IV dosing study of U3-1402 was found to be 194.3 mg/kg because no severe or irreversible toxicity was seen in the surviving animals except for that in the testis and an incidence of death was substantially low.

In a 2-week preliminary intermittent IV dosing study of U3-1402 in cynomolgus monkeys (QW dosing), 1 male died and 1 female was sacrificed due to moribundity at 80 mg/kg, the highest dose level tested. The cause of the death or moribundity appeared to be sustained deterioration of the animals' physical conditions. The major findings of toxicity in the surviving animals in the 30 mg/kg and greater group were observed in the lymphatic/hematopoietic systems, digestive system, and heart. In the 80 mg/kg group, hepatotoxicity, renal, pancreas, and skin toxicity were also observed.

In the intermittent IV dosing study of U3-1402 in cynomolgus monkeys (Q3W, 12 weeks at 0, 3, 10, or 30 mg/kg), there were no deaths or moribund animals. The major findings of toxicity were observed in the thymus and ovary at 10 mg/kg and greater, and in the bone marrow leading to suppression of hematopoiesis and in the skin at 30 mg/kg. Emetic action, immunogenicity including anti-U3-1402 antibody production, and increased inflammatory parameters were also observed at 3 mg/kg and greater. By the end of the 6-week recovery period, all the treatment-related changes observed during the dosing period had disappeared or shown a trend of reversibility. Therefore, the highest non-severely toxic dose (HNSTD) was considered to be 30 mg/kg in the Q3W dosing regimen because no severe or irreversible toxicity was seen at up to 30 mg/kg.

An intermittent dose toxicity study of U3-1402 for cardiotoxic assessment was additionally conducted in cynomolgus monkeys at 30 mg/kg in the QW dosing regimen for 2 weeks. One male out of 4 monkeys was sacrificed moribund with severe deterioration of physical conditions 6 days after the second dose. This animal had necrosis of cardiac myocytes with notable

increase in plasma cardiac troponin I (cTnI) concentration detected just before autopsy. Higher MAAA-1181a concentration in the heart tissue was also observed in this animal in comparison with those of the other 3 animals. Plasma cTnI was increased transiently in the other 2 out of 3 monkeys after the first dosing; however, no histopathological changes in their heart were observed at the end of 2-week dosing period.

In the intermittent IV dose toxicity studies of U3-1287 in cynomolgus monkeys (QW dosing for 1 or 6 months), the no observed adverse effect level (NOAEL) was 200 mg/kg, the highest dose tested, because of no significant changes in any examination.

In an intermittent IV dose toxicity study of MAAA-1181a (QW dosing for 4 weeks) in the rat, there was no death or moribundity at up to 30 mg/kg. Toxicity findings in the lymphatic/hematopoietic system, intestinal tract, and the cornea of the eye were observed at 3 mg/kg and greater. Findings similar to those in rats were observed in cynomolgus monkeys at dose levels of 1 mg/kg and greater in a toxicity study of MAAA-1181a with the same dose regimen. In addition, 1 female died and 1 male was sacrificed moribund at 12 mg/kg. Although effects on the heart (focal myocardial cell degeneration/necrosis) were found in the moribund male, there were no abnormal heart findings in the female found dead. Both animals exhibited worsening clinical conditions associated with sustained decreases in food consumption, bone marrow toxicity, and intestinal toxicity. These changes were considered to be the cause of the death and moribundity.

The common target organs of toxicity of U3-1402 and MAAA-1181a were the lymphatic/hematopoietic systems, intestine, cornea, liver and heart. For U3-1402 treatment, there were treatment-related toxicities in the lung, kidney, reproductive organ, skin, thymus, pancreas, mesenteric lymph node, urinary bladder, accessory reproductive gland, harderian gland, salivary gland, and skeletal muscle.

Tissue-cross reactivity studies of U3-1402 with human and monkey tissue panels showed no U3-1402-specific immunoreactivity in any tissues. In rats, there was U3-1402 specific staining in red blood cells, bone marrow, and spleen, with staining of mast cells in a variety of tissues.

In an in vitro 3T3 NRU phototoxicity study, MAAA-1181a was found to be phototoxic to Balb/c 3T3 mouse fibroblasts. However, in an in vivo single dose phototoxicity study of MAAA-1181a in pigmented rats, no phototoxic reaction was noted at 3 mg/kg, the highest dose tested.

1.2.3. Clinical Experience

This is a first-in-human study of U3-1402.

As of the 25 Aug 2018 data cut-off, 56 subjects had received U3-1402 as part of Study U31402-A-J101: 34 subjects in the Dose Escalation Part, 8 subjects in the Dose Finding Part, and 14 subjects in the Dose Expansion Part. At the time of the data cut-off, 41 subjects were receiving treatment, 13 subjects had discontinued treatment due to disease progression, 1 subject had discontinued treatment due to Grade 2 pneumonitis, and 1 subject had withdrawn consent.

Fifty-four (96.4%) of the 56 treated subjects had experienced at least 1 TEAE. All 54 subjects had also experienced at least 1 TEAE considered by the investigator as related to study drug. Among all treated subjects, the most frequent (>20%) TEAEs, all grades, regardless of causality

and noted in descending order of frequency, included nausea (47 subjects [83.9%]), decreased appetite (36 subjects [64.3%]), platelet count decreased (36 subjects [64.3%]), white blood cell count decreased (30 subjects [53.6%]), neutrophil count decreased (29 subjects [51.8%]), vomiting (25 subjects [44.6%]), aspartate aminotransferase (AST) increased (23 subjects [41.1%]), alanine aminotransferase (ALT) increased (22 subjects [39.3%]), anemia (19 subjects [33.9%]), stomatitis (17 subjects [30.4%]), alopecia (15 subjects [26.8%]), diarrhea (15 subjects [26.8%]), fatigue (12 subjects [21.4%]), and malaise (12 subjects [21.4%]).

Eighteen (32.1%) of the 56 treated subjects had developed treatment-emergent SAEs, including 12 subjects (21.4%) with study drug-related SAEs. The treatment-emergent SAEs, in descending order of frequency, included platelet count decreased (6 subjects [10.7%]); decreased appetite (3 subjects [5.4%]); and atelectasis, cellulitis, cholecystitis acute, dehydration, dyspnea, implant site infection, malaise, myalgia, pneumonia, pneumothorax, pseudomembranous colitis, thrombocytopenia, and urinary tract infection (1 subject [1.8%] each).

Additional data describing the clinical experience of U3-1402 are available in the current Investigator's Brochure.

1.3. Study Rationale

U3-1402 is an ADC that targets HER3 and is comprised of a fully human anti-HER3 monoclonal IgG1 antibody (U3-1287) covalently linked to MAAA-1162a (CCI [redacted] linker and a topoisomerase I inhibitor [MAAA-1181a]). The drug MAAA-1181a, a derivative of exatecan,[15,16,17] is released after internalization of U3-1402 and leads to apoptosis of the target tumor cells by inhibition of topoisomerase I.

In nonclinical studies, the fact that U3-1402 binds specifically to the HER3 extracellular domain (ECD) and does not bind to other HER family proteins has been confirmed. In vivo studies indicate that U3-1402 exhibits HER3 expression-dependent cell growth inhibition activity, moreover, no growth inhibition was observed in HER3-negative cells, thus confirming the HER3 specificity of U3-1402. U3-1402 showed significant tumor regression in human breast cancer xenograft models.

In summary, U3-1402 is hypothesized to show anticancer activity with a manageable safety profile in HER3-positive cancer.

High HER3 expression was reported in breast cancer patients.[18,19,20] Therefore, U3-1402 is being developed as an ADC targeting HER3-positive breast cancer, NSCLC and potentially other solid tumors expressing HER3.

1.4. Risks and Benefits for Study Subjects

U3-1402 is being developed for the treatment of HER3-expressing malignant tumors. The product is in the early stages of development.

Nonclinical studies have demonstrated the antitumor activity of U3-1402 in HER3 tumor-bearing mouse models. Thus, U3-1402 is hypothesized to demonstrate efficacy in HER3-expressing tumors in patients.

In nonclinical toxicology studies, toxicity of intestinal, lymphatic/hematopoietic, skin, pulmonary, reproductive and accessory organ, hepatic, cardiovascular, and renal systems were

found in association with the administration of U3-1402. As with any therapeutic antibodies, there is a possibility of infusion-related reactions and immune responses causing allergic or anaphylactic reactions to U3-1402. Considering the toxicity data from the nonclinical studies, the potential risks of QT prolongation, left ventricular ejection fraction (LVEF) decreased, potential Hy's Law, ILD, pneumonitis, infusion-related reaction, dry eye, keratitis, photosensitivity, stomatitis, alopecia, dry skin, rash, rash maculopapular, and skin pigmentation in humans from exposure to U3-1402 have been closely monitored and evaluated in the U3-1402 clinical development program.

Based on the preliminary clinical safety data from the ongoing U3-1402 studies, nausea, decreased appetite, platelet count decreased/thrombocytopenia, white blood cell count decreased/leukopenia, neutrophil count decreased/neutropenia, vomiting, anemia, diarrhea and interstitial lung disease/pneumonitis are identified risks and will continue to be closely monitored and evaluated in the U3-1402 clinical development program.

In conclusion, based on the efficacy and safety data from the nonclinical studies and the preliminary clinical efficacy and safety data from the ongoing studies, the benefit/risk balance supports continued clinical development of U3-1402.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

2.1.1.1. Dose Escalation Part

The primary objectives are as follows:

1. To assess safety and tolerability of U3-1402.
2. To determine the maximum tolerated dose (MTD) of U3-1402.

2.1.1.2. Dose Finding Part

The primary objectives are as follows:

1. To assess safety and evaluate efficacy of U3-1402.
2. To assess safety of alternative dosing schedule(s) of U3-1402.
3. To determine the recommended dose(s) for expansion (RDEs) of U3-1402.

2.1.1.3. Dose Expansion Part

The primary objective is as follows:

1. To assess safety and evaluate efficacy of U3-1402 at the RDEs in subjects with HER3-positive, HER2-negative (including HR-positive and TNBC) advanced/unresectable or metastatic breast cancers.

2.1.2. Secondary Objectives

2.1.2.1. Dose Escalation Part

The secondary objectives are as follows:

1. To assess the PK profiles of U3-1402, total anti-HER3 antibody, and MAAA-1181a.
2. To evaluate efficacy of U3-1402.
3. To assess the incidence of human anti-drug antibodies (ADAs) against U3-1402.

2.1.2.2. Dose Finding and Dose Expansion Parts

The secondary objective is as follows:

1. To assess the PK profiles of U3-1402, total anti-HER3 antibody, and MAAA-1181a.
2. To assess the incidence of ADA against U3-1402.

2.1.2.3. Dose Expansion Part

1. To determine the relationship between efficacy of U3-1402 and HER3 expression.

2.1.3. Exploratory Objectives

The exploratory objectives for the Dose Escalation Part, Dose Finding Part, and Dose Expansion Part are as follows:

1. To explore the concentration-corrected QT (QTc) relationships of U3-1402, total anti-HER3 antibody, and MAAA-1181a.
2. To identify biomarkers that correlate with U3-1402 response or toxicity.

2.2. Study Hypotheses

U3-1402 will have anticancer activity in breast cancer patients whose tumors express HER3 and will be well-tolerated with acceptable PK properties.

2.3. Study Endpoints

The endpoints for the study include the following:

- Pharmacokinetic endpoints:

  Serum PK endpoints (area under the concentration-versus-time curve, from time 0 to the last measurable concentration as calculated by the linear-up log-down trapezoidal method [AUClast], AUC during dosing interval [AUCtau], Cmax, time of maximum observed concentration [Tmax] and trough serum concentrations [Ctrough]) of U3-1402 for each subject will be estimated using standard noncompartmental methods. For total anti-HER3 antibody and MAAA-1181a, all parameters listed above will be estimated.

- Safety endpoints:

  Safety endpoints will include dose-limiting toxicities (DLTs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, electrocardiogram (ECG) parameters, echocardiography (ECHO)/multiple gated acquisition scan (MUGA) findings and ophthalmologic findings.

- Efficacy endpoints:

  Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Objective response rate (ORR) (the sum of complete response [CR] rate and partial response [PR] rate), disease control rate (DCR) (the sum of CR rate, PR rate, and stable disease [SD] rate), duration of response (DOR), clinical benefit rate (CBR; the proportion of subjects who achieved a best overall response of CR or PR or SD $\geq$ 6 months), time to response (TTR), PFS, OS, and percent change in target lesion(s).

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

3.1.1.1. Study Type

This is a Phase 1/2, multicenter, open-label, multiple dose, first-in-human study of U3-1402 in subjects with HER3-positive metastatic breast cancer. The Dose Escalation and Dose Finding Parts will be conducted in Japan only. The Dose Expansion Part may include subjects from any participating country, including the US and Japan.

3.1.1.2. Treatment Groups

Dose Escalation Part

In the Dose Escalation Part, eligible subjects with HER3-high breast cancer who have been refractory to or intolerant to standard treatment, or for whom standard treatment is no longer available, will be enrolled. Subjects will receive U3-1402 at varying dose levels based on their assigned cohort to identify the MTD of U3-1402. Refer to Section 3.1.3 for further details.

Dose Finding Part

In the Dose Finding Part, eligible subjects with HER3-high breast cancer will be enrolled. Cohorts with multiple drug doses and/or administration schedules, including up-titration of dose, will be selected by the Sponsor for further evaluation. Doses evaluated for alternative administration schedules, including up-titration of dose, will be equal to or less than the MTD (or highest dose evaluated) of U3-1402 administered via IV infusion Q3W. Refer to Section 3.1.4 for details.

Dose Expansion Part

In the Dose Expansion Part, eligible subjects with HER3-positive (HER3-high or HER3-low), HER2-negative, HR-positive breast cancer who have received ≥2 and ≤6 prior chemotherapy regimens for breast cancer (including ≥2 regimens administered for the treatment of advanced/unresectable or metastatic disease) and those with HER3-high, TNBC who have received 1 to 2 prior chemotherapy regimens in the advanced disease setting will be enrolled to evaluate safety and efficacy of U3-1402 at the RDEs. In the Dose Expansion Part, multiple expansion cohorts will be evaluated as described in Section 3.1.5.

3.1.1.3. Duration of the Study

This study is expected to last approximately 7 years from the time the first subject is enrolled to the time the last subject is off the study. The end of the study is defined as the date of completion of the last visit or procedure shown in the Schedule of Events (Section 17.8) in the trial globally.

Sponsor may terminate the study at any time due to administrative reason or at request from competent regulatory authorities.

3.1.1.4. Duration of Subject Participation

The number of treatment cycles is not limited in this study. Subjects will continue study treatment until withdrawal of consent, progressive disease (PD), unacceptable toxicity, death, or termination of the study by Sponsor.

There is an end-of-treatment (EOT) Visit which occurs within 7 days after the date of discontinuation. A 28-Day F/U Visit (- 7 days) takes place 28 days after the last U3-1402 administration. If the subject begins another anticancer therapy before the end of the 28 days (– 7 days), every effort will be made to complete all of the F/U assessments prior to starting the new therapy. For further details concerning assessments performed at the EOT and F/U Visits refer to Section 6.7 and Section 6.8, respectively.

For subjects with positive ADA at F/U visit (or EOT visit if F/U visit was not performed), additional serum ADA samples should be collected every 3 months (± 1 month) for up to 1 year after the last dose of U3-1402, unless one of the following occurs sooner; the ADA becomes negative; the ADA titer falls below baseline if ADA was measurable prior to first dose of U3-1402; the subject starts another therapy for cancer; or the subject withdraws consent from the study.

After discontinuation from study treatment, follow-up information for survival and subsequent anticancer therapy, if available, should be collected approximately every 3 months; refer to Section 6.9 for details.

3.1.2. Dose Escalation Process and Dose Selection

The study will enroll subjects into cohorts during dose escalation by modified continuous reassessment method (mCRM) with escalation with overdose control (EWOC) principle as outlined in Section 3.1.3). The starting dose will be 1.6 mg/kg (see Section 3.2.1 for justification of the human starting dose).

In the Dose Escalation Part, the second subject in each dosing level should start dosing at least 24 hours after the initial dosing of the first subject to check the acute toxicity such as infusion-related reaction.

In the Dose Finding Part, subjects will be enrolled to multiple Dose Finding cohorts equal to or less than the MTD (if attained, or the highest dose evaluated) to determine the RDEs (Section 3.1.4). Doses evaluated for alternative administration schedules, including up-titration of dose, will be equal to or less than the MTD (or highest dose evaluated) of U3-1402 administered via IV infusion Q3W.

In the Dose Expansion Part, subjects will be enrolled to multiple Dose Expansion cohorts as described in Section 3.1.5.

3.1.3. Dose Escalation Part

Dose escalation of U3-1402 to determine the MTD will be guided by the mCRM using a Bayesian logistic regression model (BLRM) following EWOC principle. The proposed human starting dose of U3-1402 is 1.6 mg/kg, based on 1/6 human equivalent dose (HED) of HNSTD in monkey (30 mg/kg). The following planned dose levels will be assessed in the Dose Escalation Part (Table 3.1). U3-1402 will be administered via IV infusion Q3W in 21-day cycles in the Dose Escalation Part.

Table 3.1: Dose Escalation Cohorts

Dose Cohort[a]	U3-1402 Dosage (21-day cycles)
1	1.6 mg/kg IV infusion Q3W
2	3.2 mg/kg IV infusion Q3W
3	4.8 mg/kg IV infusion Q3W
4	6.4 mg/kg IV infusion Q3W
5	8.0 mg/kg IV infusion Q3W
6	9.6 mg/kg IV infusion Q3W

IV = intravenous; Q3W = once every 3 weeks

[a] Additional dose levels may also be considered based on review of available safety, tolerability, and pharmacokinetic data in this and other studies with the investigational agent.

Dose level increment during Dose Escalation Part by mCRM with EWOC

- The dose level increment should be no more than 100% even if the model suggests a higher dose than 100% for the next cohort.

The escalation by mCRM with EWOC principle will be based on a BLRM. The logistic regression model for the dose-response (DLT rate) relationships will include 2 parameters, the intercept, and slope. After at least 3 subjects of each cohort complete DLT evaluation during Cycle 1, posterior distributions of DLT rate are derived for all dose levels based on the BLRM using DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The posterior probability of DLT rate in the following 4 intervals at each dose level: 0% ≤DLT rate ≤16% as DLT rate interval for under-dosing, 16% <DLT rate ≤33% as target DLT rate interval, 33% <DLT rate ≤60% as DLT rate interval for excessive toxicity, and 60% <DLT rate ≤100% as DLT rate interval for unacceptable toxicity will then be calculated, and used for dose recommendation for the next cohort according to the EWOC principle. The EWOC principle requires that the mCRM recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval of 16% <DLT rate ≤33% among all doses fulfilling the overdose control constraint: there is less than 25% of probability for DLT rate >33% (probability for excessive or unacceptable toxicity).

The dose for the next cohort will be chosen by the Sponsor based on the dose recommendation by the mCRM, clinical assessment of toxicity profiles, and PK information observed thus far.

Cohorts of at least 3 DLT evaluable subjects will be enrolled and assessed for DLT during the dose escalation process. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 DLT evaluable subjects in the cohort experience DLT before the enrollment of the third subject. Enrollment of subjects to a new higher dose cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed DLT evaluation nor experienced DLT will be censored and not included in the BLRM update. In the event when subjects in the previous cohort experience DLTs after enrollment of subjects to a new cohort has begun, dose level assignment of the next

subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed doses. Subject ongoing will continue treatment at their assigned dose level.

Subjects can be backfilled (added) to lower doses previously proven to be safe at any point during dose escalation.

To better understand the safety, tolerability, PK or preliminary activity of U3-1402, additional patients may be enrolled to preceding dose levels, or to intermediate dose level before or while proceeding with further dose escalation.

The Dose Escalation Part will be stopped according to the following rules:

i. at least 6 evaluable subjects have been enrolled at the MTD level with at least 18 evaluable subjects in total enrolled in the Dose Escalation Part

ii. at least 9 evaluable subjects have been enrolled at a particular dose level, the model recommends continuing at the same dose level, and the posterior probability of the DLT rate falling within the target DLT interval is ≥50%. The target DLT interval is defined as 16% <DLT rate ≤33%

iii. DLT assessment with at least 3 evaluable subjects at the maximum possible dose level with upper limit of 95% credible interval for posterior probability of DLT rate is lower than 33%

iv. the initial dose level is too toxic.

Cohorts may be expanded at any dose level or at the MTD for further elaboration of safety, or PK parameters as required.

3.1.4. Dose Finding Part

In the Dose Finding Part, subjects will be enrolled into cohorts with multiple drug doses and/or administration schedules, including up-titration of dose. Doses evaluated for alternative administration schedules, including up-titration of dose, will be equal to or less than the MTD (or highest dose evaluated) of U3-1402 administered via IV infusion Q3W. The objectives of the Dose Finding Part are to assess the safety and evaluate the efficacy of U3-1402 and determine the RDEs for the Dose Expansion Part. A total of approximately 12 subjects will be enrolled between Dose Escalation and Dose Finding for each of the Q3W Dosing Cohorts evaluated in Dose Finding. For the alternative dosing cohorts evaluated in Dose Finding, a total of approximately 12 subjects will be enrolled into each cohort.

Dose Finding Cohorts

The following cohorts may be evaluated during the Dose Finding Part. These cohorts are provisional and may change based on emerging safety, tolerability, and efficacy data.

Dose Finding Cohort 1 (Q3W Dosing)

U3-1402 at a dosage of 4.8 mg/kg administered via IV infusion Q3W in 21-day cycles.

Dose Finding Cohort 2 (Q3W Dosing)

U3-1402 at a dosage of 6.4 mg/kg administered via IV infusion Q3W in 21-day cycles.

Dose Finding Cohort 3 (Q3W Dosing with Up-titration)

U3-1402 administered via IV infusion Q3W in 21-day cycles with an up-titration of U3-1402 dose on Day 1 of the first 3 cycles as described below.

Table 3.2: Dose Finding Cohort 3 Dosing Schedule

Cycle	U3-1402 Dosage
1	3.2 mg/kg IV infusion Q3W
2	4.8 mg/kg IV infusion Q3W
3	6.4 mg/kg IV infusion Q3W
Subsequent cycles	6.4 mg/kg IV infusion Q3W

IV = intravenous; Q3W = once every 3 weeks.

Dose Finding Cohort 4 (Q2W Dosing)

U3-1402 at a dosage of 4.2 mg/kg administered via IV infusion once every 2 weeks (Q2W) in 14-day cycles for the first 3 cycles of treatment, followed by a dosage of 6.4 mg/kg administered via IV infusion Q3W thereafter.

Table 3.3: Dose Finding Cohort 4 Dosing Schedule

Cycle	U3-1402 Dosage
Cycle 1, 2, and 3	4.2 mg/kg IV infusion Q2W
Subsequent cycles	6.4 mg/kg IV infusion Q3W

IV = intravenous; Q2W = once every 2 weeks; Q3W = once every 3 weeks.

Dose Finding Cohort 5 (Q2W Dosing)

U3-1402 at a dosage of 3.2 mg/kg administered via IV infusion Q2W in 14-day cycles for the first 3 cycles of treatment, followed by a dosage of 4.8 mg/kg administered via IV infusion Q3W thereafter.

Table 3.4: Dose Finding Cohort 5 Dosing Schedule

Cycle	U3-1402 Dosage
Cycle 1, 2, and 3	3.2 mg/kg IV infusion Q2W
Subsequent cycles	4.8 mg/kg IV infusion Q3W

IV = intravenous; Q2W = once every 2 weeks; Q3W = once every 3 weeks.

Additional Dose Finding Cohorts

- Additional dose levels equal to, or less than, the MTD (if attained or highest dose evaluated during the Dose Escalation Part) may be considered for the Dose Finding Part.
- Additional dose regimens, including up-titration of dose, may be considered for the Dose Finding Part based on emerging safety and efficacy data.

3.1.5. Dose Expansion Part

In the Dose Expansion Part, subjects will be enrolled into cohorts as described below based on HER3 status and breast cancer molecular subtype. The primary objective of the Dose Expansion Part is to assess safety and evaluate efficacy of U3-1402 at the RDE in subjects with

HER3-positive, HER2-negative (including HR-positive and TNBC) advanced/unresectable or metastatic breast cancer. The Dose Expansion Part may include subjects from any participating country, including the US and Japan.

A total of approximately 110 subjects will be enrolled in the Dose Expansion Part.

HER3-High, HR-Positive Cohorts

Approximately 60 eligible subjects with HER3-high, HER2-negative, HR-positive breast cancer will be randomized into 1 of 2 cohorts. U3-1402 at a dosage of either 4.8 mg/kg or 6.4 mg/kg will be administered via IV infusion Q3W in 21-day cycles.

HER3-Low, HR-Positive Cohort

Approximately 20 eligible subjects with HER3-low, HER2-negative, HR-positive breast cancer will be enrolled. U3-1402 at a dosage of 6.4 mg/kg will be administered via IV infusion Q3W in 21-day cycles.

HER3-High, TNBC Cohort

Approximately 30 eligible subjects with HER3-high, TNBC will be enrolled. U3-1402 at a dosage of 6.4 mg/kg will be administered via IV infusion Q3W.

Additional Expansion Cohort(s)

Additional cohorts may be considered for the Dose Expansion Part based on emerging safety and efficacy data.

3.1.6. Study Stopping Criteria

The study treatment will be continued according to the dosing criteria to derive clinical benefit in the absence of withdrawal of subject consent, PD, unacceptable toxicity, or death. If the study treatment is delayed more than 4 weeks from the planned date of administration (ie, 49 days from the last infusion date), the subject may be withdrawn from the study (see Sections 5.4 and 5.7).

The study may be terminated any time at the Sponsor's discretion.

3.1.7. Dose-limiting Toxicities

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the DLT evaluation period (Day 1 to Day 21 in Cycle 1 of Dose Escalation Part) and is Grade 3 or above according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, with the exceptions as defined below:

For hematological toxicities, a DLT is defined as follows:

- Grade 4 neutrophil count decreased lasting >7 days, neutrophil count decreased that requires standard therapies, such as colony stimulating factor (CSF)
- Grade ≥3 febrile neutropenia
- Grade 4 anemia
- Grade 4 platelet count decreased

- Grade ≥3 platelet count decreased lasting >7 days
- Grade ≥3 platelet count decreased with clinically significant hemorrhage
- Grade 4 lymphocyte count decreased lasting ≥14 days

For hepatic organ toxicities, a DLT is defined as follows:

- Serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) >20 × upper limit of normal (ULN)
- AST or ALT >5 × ULN, if accompanied by blood bilirubin >1.5 × ULN
- In subjects without liver metastases, AST or ALT >5 × ULN lasting >3 days
- In subjects with liver metastases, AST or ALT >5 × ULN lasting >3 days, if the baseline level was ≤3 × ULN
- In subjects with liver metastases, AST or ALT >8 × ULN lasting >3 days, if the baseline level was >3 × ULN

For non-hematological, non-hepatic major organ toxicities, a DLT is defined as follows:

- Symptomatic congestive heart failure (CHF)
- Left ventricular ejection fraction (LVEF) decline to <40% or >20% drop from baseline
- Other Grade ≥3 non-hematological, non-hepatic major organ toxicities

The following TEAEs are NOT considered DLTs:

- Grade 3 fatigue lasting <7 days
- Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to Grade ≤2 within 3 days
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 serum alkaline phosphatase (ALP) increased, hyperuricemia, serum amylase increased, and lipase increased, and Grade 3 hyponatremia lasting <72 hours developed from Grade 1 at baseline
- Grade 3 lymphocyte count decreased

If any of the above toxicities is observed during the DLT evaluation period, whether the toxicity is regarded as DLT will be determined based on consultation between the Investigator and Sponsor.

In addition, with regard to other toxicities that impact the conduct of the scheduled study treatment, anemia with blood transfusion, or platelet count decreased with platelet transfusion, whether they are regarded as DLT will be determined based on consultation between the Investigator and Sponsor.

The premedication, which is a treatment before study drug administration to avoid adverse event (AE), is prohibited during the DLT evaluation period.

However, the supportive therapy for the treatment is permitted after study drug administration:

For example:

- Nausea, vomiting: Antiemetics

3.1.8. Maximum Tolerated Dose and Recommended Dose for Expansion Definition

Once the dose escalation stopping criteria are met, the MTD estimated by mCRM + EWOC will be the dose with the highest posterior probability of the DLT rate in the target DLT rate interval of 16% <DLT rate ≤33% among all doses fulfilling the overdose control constraint: there is less than 25% probability of a DLT rate >33% (probability for excessive or unacceptable toxicity) (Section 3.1.3). The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the mCRM and on an overall assessment of safety data from subsequent cycles and PK information collected at all different doses tested.

Multiple drug doses less than the MTD (if attained, or the highest dose evaluated) and/or administration schedules, including up-titration of dose, will be selected by the Sponsor for further evaluation in the Dose Finding Part. Doses evaluated for alternative administration schedules, including up-titration of dose, will be equal to or less than the MTD (or highest dose evaluated) of U3-1402 administered via IV infusion Q3W. Based on the safety, PK, and efficacy profiles of U3-1402 obtained from the Dose Escalation and Dose Finding Parts, multiple dosing regimens may be selected by the Sponsor for further evaluation in the Dose Expansion Part.

The study team will actively monitor all safety data within the EDC database on a regular basis. Study drug interruption and modification guidelines are in place for this study and described here in the protocol (Section 5.4). During the Dose Expansion Part, Safety Review Meetings will occur as needed to assess safety and tolerability of the selected RDEs.

3.1.9. Management of Subjects with Adverse Events

See Section 5.4.

3.2. Discussion of Study Design

3.2.1. Human Starting Dose

For the first in human, dose escalation clinical trial with U3-1402, the proposed human starting dose (HSD) is 1.6 mg/kg. This dose was selected based on the following rationale:

In the 12-week intermittent dose toxicity study in rats, no severe and irreversible toxicity was seen in surviving males and females except for testis effects at 194.3 mg/kg, although 1 of 15 males died in the 194.3 mg/kg group after the 4th administration. Therefore, under the conditions of this study, the STD_{10} of the animals was considered to be 194.3 mg/kg, which was also the highest (maximum feasible) dose level tested. By determining 1/10 of the STD_{10} and taking the HED of this conversion results in a HSD of 3.1 mg/kg.

In the 12-week intermittent dose toxicity study in monkeys, the HNSTD was 30 mg/kg, which was the highest dose level tested. By determining 1/6 of the HNSTD and taking the HED of this conversion results in a HSD of 1.6 mg/kg.

With regard to the interests of patients for considering the safety, 1.6 mg/kg was determined as the HSD, which was also the maximum recommended starting dose. At the proposed HSD,

estimated human U3-1402 AUC (<43.7 µg·d/mL), which was calculated based on the hypothesis that human PK is the same as monkey, is greater than mouse AUC at 1.5 mg/kg (27.8 µg·d/mL), which showed the regression of tumor size from the initiation of dosing in a subcutaneous xenograft model using the MDA-MB-453 cell line (HER3-expressing). In case that the efficacy in human is expected to the same as that to the xenograft model, 1.6 mg/kg is considered to be efficacious for the cancer therapy.

3.2.2. Treatment Schedule

Based on the result of nonclinical toxicology studies (Section 1.2.2.4), death or moribundity were observed in once weekly dosing. The cause of the death or moribundity appeared to be sustained deterioration of the animal physical conditions. Therefore, Q3W and Q2W dosing schedules were selected.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

4.1.1. Common Inclusion Criteria for Dose Escalation and Dose Finding Parts

1. Has a pathologically documented advanced/unresectable or metastatic breast cancer.
2. Has documented HER3-high expressing disease assessed using immunohistochemistry (IHC) by the central laboratory.
3. Is refractory to or intolerant to standard treatment, or for whom standard treatment is no longer available.
4. Male or female subjects aged ≥20 years in Japan.
5. Has an ECOG PS 0-1, with no deterioration over the previous 2 weeks.
6. Has LVEF ≥50% by either ECHO or MUGA within 28 days prior to enrollment.
7. Has adequate bone marrow reserve and organ function within 7 days prior to enrollment, defined according to the following:

Item	Laboratory value
Platelet count	≥100 000/mm^3
Hemoglobin (Hb)	≥8.5 g/dL
Absolute neutrophil count (ANC)	≥1500/mm^3
Creatinine	≤1.5 × ULN, or creatinine clearance ≥60 mL/min as calculated using the Cockcroft-Gault equation
AST/ALT	≤3 × ULN (if liver metastases are present, ≤5 × ULN)
Total bilirubin	≤1.5 × ULN

8. Has adequate treatment washout period before enrollment, defined according to the following:

Treatment	Washout period
Major surgery	≥3 weeks
Radiation therapy	≥3 weeks (or 2 weeks for palliative radiation for bone metastasis [excluding pelvic radiation] and brain metastasis, 1 week for stereotactic radiotherapy)
Hormonal therapy	≥2 weeks
Chemotherapy (including antibody drug therapy)	≥3 weeks (≥2 weeks for 5-fluorouracil-based agents, folinate agents, or weekly paclitaxel. ≥6 weeks for nitrosoureas or mitomycin C)
Immunotherapy	≥3 weeks
CYP3A4 strong inhibitor	≥3 elimination half-lives of the inhibitor
CYP3A4 strong inducer	≥2 weeks
QTc-prolonging medications	≥3 elimination half-lives of the medications
OATP1B inhibitor	≥3 elimination half-lives of the inhibitor

9. Has at least 1 measurable lesion based on RECIST version 1.1 confirmed by the central laboratory.

10. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during the study and for at least 7 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception include:

    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal delivery).
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable delivery).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Bilateral tubal occlusion.
    - Vasectomized partner.
    - Complete sexual abstinence.

    Non-childbearing potential is defined as pre-menopausal with documented tubal ligation or hysterectomy; OR postmenopausal with documented ≥12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] >40 mIU/mL and estradiol <40 pg/mL [<140 pmol/L] is confirmatory).

    Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to discontinue HRT and use 1 of the contraception methods outlined above for women of childbearing potential. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Use of HRT is not allowed during the study. Men who are fertile and sexually active should be willing to use highly effective methods of contraception if their partners are of reproductive potential.

    Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration.

    Female subjects must not donate or retrieve, for their own use, ova from the time of Screening and throughout the study treatment period, and for ≥7 months after the final dose of study drug.

11. Is able to provide written informed consent.

12. Has a life expectancy of ≥3 months.

4.1.2. Additional Inclusion Criterion for Dose Finding Part

13. Has received ≥2 and ≤6 prior chemotherapeutic regimens for breast cancer, ≥2 of which were administered for treatment of advanced/unresectable or metastatic disease. At least 1 prior chemotherapeutic regimen must have included a taxane (eg, paclitaxel, docetaxel), administered in the neoadjuvant, adjuvant, or advanced setting.

4.1.3. Inclusion Criteria for Dose Expansion Part

1. Has a pathologically documented advanced/unresectable or metastatic breast cancer.
2. Has documented HER3-positive (HER3-high or HER3-low) disease assessed by IHC assay by the central laboratory from archival tumor tissue or a screening tumor fresh biopsy sample.
3. Is able to submit a fresh tumor biopsy sample prior to starting study treatment. (If subjects have already submitted fresh tumor biopsy sample for HER3 expression, resubmission is not necessary.)
4. Has documented HER2-negative expression according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines.
5. Has documented HR (estrogen and/or progesterone receptor) positive disease with exception of the TNBC cohort (see inclusion criterion #17 below).
6. Is refractory to or intolerant to standard treatment, or for whom standard treatment is no longer available.
7. With the exception of the TNBC cohort (see inclusion criterion #18 below), has received ≥2 and ≤6 prior chemotherapeutic regimens for breast cancer, ≥2 of which were administered for treatment of advanced/unresectable or metastatic disease. At least 1 prior chemotherapeutic regimen must have included a taxane (eg, paclitaxel, docetaxel), administered in the neoadjuvant, adjuvant, or advanced setting.
8. Male or female subjects aged ≥20 years in Japan, ≥18 years in the US.
9. Has an ECOG PS 0-1, with no deterioration over the previous 2 weeks.
10. Has LVEF ≥50% by either ECHO or MUGA within 28 days prior to enrollment.
11. Has adequate bone marrow reserve and organ function within 7 days prior to enrollment, defined according to the following:

Item	Laboratory value
Platelet count	≥100 000/mm^3
Hemoglobin (Hb)	≥9.0 g/dL
Prothrombin time (PT) or PT- international normalized ratio (INR) and partial thromboplastin time (PTT)	≤1.5 × ULN, except for subjects on coumarin-derivative anticoagulants or other similar anticoagulant therapy, who must have PT-INR within therapeutic range as deemed appropriate by the Investigator.
Absolute neutrophil count (ANC)	≥1500/mm^3
Creatinine	≤1.5 × ULN, or creatinine clearance ≥50 mL/min as calculated using the Cockcroft-Gault equation
AST/ALT	≤3 × ULN (if liver metastases are present, ≤5 × ULN)
Total bilirubin	≤1.5 × ULN (<3 × ULN in the presence of documented Gilbert's Syndrome [unconjugated hyperbilirubinemia] or liver metastases)

12. Has adequate treatment washout period before enrollment, defined according to the following:

Treatment	Washout period
Major surgery	≥3 weeks
Radiation therapy	≥3 weeks (or 2 weeks for palliative radiation for bone metastasis [excluding pelvic radiation] and brain metastasis, 1 week for stereotactic radiotherapy)
Hormonal therapy	≥2 weeks
Chemotherapy (including antibody drug therapy)	≥3 weeks (≥2 weeks for 5-fluorouracil-based agents, folinate agents, or weekly paclitaxel. ≥6 weeks for nitrosoureas or mitomycin C)
Immunotherapy	≥3 weeks
CYP3A4 strong inhibitor	≥3 elimination half-lives of the inhibitor
QTc-prolonging medications	≥3 elimination half-lives of the medications
OATP1B inhibitor	≥3 elimination half-lives of the inhibitor

13. Has at least 1 measurable lesion based on RECIST version 1.1 confirmed by the central laboratory.

14. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during the study and for at least 7 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception include:

    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal delivery).

b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable delivery).
c. Intrauterine device (IUD).
d. Intrauterine hormone-releasing system (IUS).
e. Bilateral tubal occlusion.
f. Vasectomized partner.
g. Complete sexual abstinence.

Non-childbearing potential is defined as pre-menopausal with documented tubal ligation or hysterectomy; OR postmenopausal with documented ≥12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] >40 mIU/mL and estradiol <40 pg/mL [<140 pmol/L] is confirmatory).

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to discontinue HRT and use 1 of the contraception methods outlined above for women of childbearing potential. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks must elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Use of HRT is not allowed during the study. Men who are fertile and sexually active should be willing to use highly effective methods of contraception if their partners are of reproductive potential.

Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration.

Female subjects must not donate or retrieve, for their own use, ova from the time of Screening and throughout the study treatment period, and for ≥7 months after the final dose of study drug.

15. Is able to provide written informed consent.

16. Has a life expectancy of ≥3 months.

4.1.4. Additional Inclusion Criteria for the HER3-high, TNBC Cohort

17. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER3-high, HR- (estrogen and progesterone receptor) negative disease and HER2-negative expression according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines.

18. Has progressed after receiving 1 to 2 chemotherapy regimens for advanced/unresectable or metastatic breast cancer.

4.2. Exclusion Criteria

4.2.1. Exclusion Criteria for Dose Escalation and Dose Finding Parts

Subjects who meet any of the following criteria will be disqualified from entering the study in Dose Escalation and Dose Finding Parts:

1. Prior treatment with an anti-HER3 antibody.
2. Prior treatment with an ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor (eg, DS-8201a).
3. Has a medical history of symptomatic CHF (New York Heart Association (NYHA) classes II-IV) or serious cardiac arrhythmia requiring treatment.
4. Has a medical history of myocardial infarction or unstable angina within past 6 months prior to enrollment.
5. Has a mean corrected QT by Fridericia's formula (QTcF) prolongation to >450 milliseconds (ms) in males and >470 ms in females in 3 successive screening measurements as assessed by central laboratory.
6. Has any history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis), has current ILD/pneumonitis, or is suspected to have such disease by imaging during screening.
7. Has clinically significant corneal disease.
8. Has an uncontrolled infection requiring IV of antibiotics, antivirals, or antifungals.
9. Has a positivity for human immunodeficiency virus (HIV), or active hepatitis B or C infection.
10. Is a lactating mother (women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days prior to enrollment.
11. Has clinically active spinal cord compression or brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic for 4 weeks before enrollment and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (1 week for stereotactic radiotherapy).
12. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE version 5.0, grade ≤1 or baseline. Subjects with chronic grade 2 toxicities may be eligible per the discretion of the Investigator.
13. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator.
14. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product.

4.2.2. Additional Exclusion Criteria for Dose Finding Part

15. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.

4.2.3. Exclusion Criteria for Dose Expansion Part

Subjects who meet any of the following criteria will be disqualified from entering the study in the Dose Expansion Part:

1. Prior treatment with an anti-HER3 antibody.
2. Prior treatment with an antibody-drug conjugate (ADC) which consists of a topoisomerase I inhibitor, exatecan derivative (eg, DS-8201a) or govitecan derivative (eg, IMMU-132).
3. Has a medical history of symptomatic CHF (New York Heart Association [NYHA] classes II-IV) or serious cardiac arrhythmia requiring treatment.
4. Has a medical history of myocardial infarction or unstable angina within past 6 months prior to enrollment.
5. Has any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, second-degree heart block, or PR interval >250 ms.
6. Has a mean QTcF prolongation to >450 ms in males and >470 ms in females in 3 successive screening measurements as assessed by central laboratory.
7. Has any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first-degree relatives.
8. Has any history of interstitial lung disease (including pulmonary fibrosis or radiation pneumonitis), has current ILD/pneumonitis, or is suspected to have such disease by imaging during screening.
9. Has clinically significant corneal disease.
10. Has any evidence of severe or uncontrolled systemic diseases (including uncontrolled hypertension, and active bleeding diatheses or active infection including hepatitis B, hepatitis C and HIV infection), psychiatric illness/social situations, substance abuse, or other factors which in the Investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.
11. Is a lactating mother (women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days prior to enrollment.
12. Has clinically active spinal cord compression or brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic for 4 weeks before enrollment and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment (1 week for stereotactic radiotherapy).

13. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE version 5.0, grade ≤1 or baseline. Subjects with chronic grade 2 toxicities may be eligible per the discretion of the Investigator.
14. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator.
15. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product.
16. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatment Group(s)/Sequences and Blinding

5.1.1. Treatment Group(s)/Sequences

See Section 3.1.1.1 to 3.1.1.4.

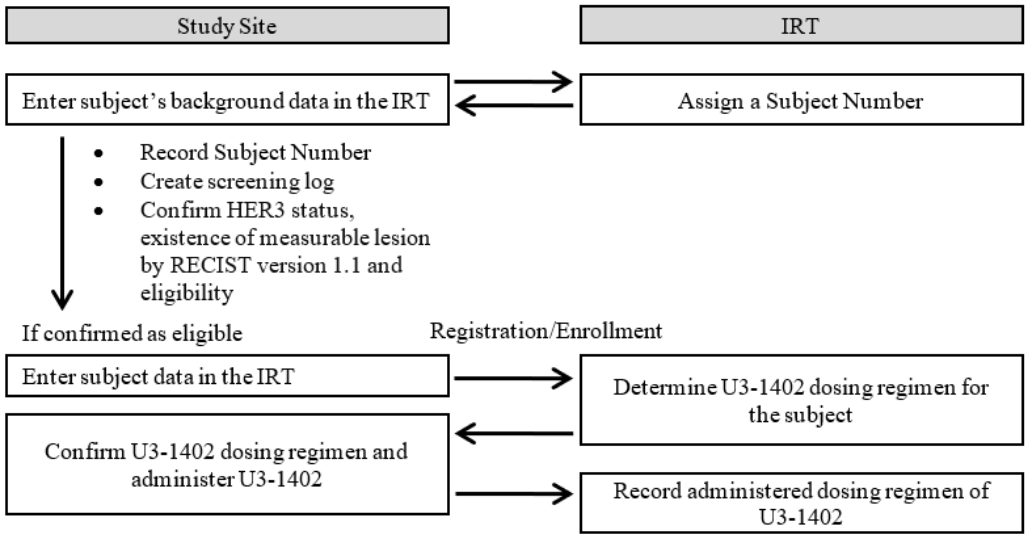
5.1.2. Method of Treatment Group(s)/Sequences Allocation

See Section 3.1.1.1 to 3.1.1.4.

5.1.2.1. Enrollment

Subject enrollment is conducted at central interactive response technology (IRT). Enrollment process is described in Figure 5.1.

Figure 5.1: Subject Enrollment Process



HER3 = human epidermal growth factor receptor 3; IRT = interactive response technology; RECIST = Response Evaluation Criteria in Solid Tumors

Investigators will maintain a confidential screening log of all potential study subjects that includes limited information of the subjects, date and outcome of screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled and screen failed in the study indicating their assigned Subject Number. The unique Subject Number will be assigned by IRT for all subjects who provide written informed consent for tumor screening.

Each subject will be provided with information about the study, will have all questions answered to their satisfaction, and will sign and date an ICF. This must be completed before any study-specific procedures are performed. Separate Informed consent must be obtained for the examination of HER3 expression in the tumor tissue. Additional information about informed consent procedures is provided in Section 15.3.

After obtaining an informed consent for tumor screening, the Investigator or designee should perform a tumor biopsy or should request archive tumor tissue. Tumor tissue (fresh or archived) must be sent to a central laboratory selected by the Sponsor to determine HER3 expression. Results of HER3 IHC testing will be reported to the Investigator by the central laboratory. During the Dose Expansion Part, subjects with HER3 positive expression determined using an archived tumor tissue sample will require a fresh tumor biopsy prior to study treatment. Fresh tumor tissue obtained from this biopsy must be sent to the central laboratory selected by the Sponsor to determine HER3 expression; these results are not required for study eligibility. The Investigator or designee must also send all computed tomography (CT) or magnetic resonance imaging (MRI) scans performed within 28 days of enrollment to the central imaging CRO selected by the Sponsor for confirmation of measurable disease per RECIST version 1.1. The central imaging CRO review results will be reported to the Investigator to confirm eligibility.

After obtaining written informed consent (Section 15.3), the Investigator or designee must determine if all inclusion and exclusion criteria have been satisfied, including obtaining a fresh tumor biopsy, if required. A subject is considered enrolled in the study once the Investigator enters all required data of eligible subjects into the IRT (IWRS). After the confirmation of the eligibility of the subject, the Investigator or designee enters subject data in the IRT. The date of enrollment is defined as the date that the subject is confirmed eligible in the IRT.

When the subject is enrolled, administration dose and dosing schedule will be assigned by the IRT. Investigators must confirm the dosing regimen assigned by the IRT before administration of U3-1402.

For screen fail subjects, Investigators must explain the reason of screen failure to the subject and then record the date of screen failure and the reason of failure in the IRT.

Electronic case report form (eCRF) will be created for all subjects who have signed informed consent for participation in the study. An eCRF will not be created for subjects who have signed informed consent for examination of the tumor only. Data for all study visits will be recorded on the eCRF for subjects who receive study drug. Only minimal data will be recorded as screening failures on the eCRF for subjects who do not meet eligibility and/or do not receive study drug. Further data, such as AEs, will not be collected from subjects once they are considered screen failures or have decided to withdraw prior to receiving study drug.

5.1.3. Blinding

This study is open-label and no blinding will be performed.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug(s)

5.2.1. Description

The head of the study center in Japan or the Investigator must ensure that the investigational product will be used only in accordance with the protocol.

The U3-1402 drug product is an [redacted] containing 50 mg of U3-1402 in 2.5 mL solution in a [redacted] and is provided as a [redacted]

It is supplied in single-use [redacted] of sterile drug product solution. It is not to be used to treat more than 1 subject.

5.2.2. Labeling and Packaging

U3-1402 will be supplied by the Sponsor. Study drug supplies will be packaged in cartons containing 10 vials of U3-1402 Injection 50 mg/2.5 mL. The packaging will be clearly labeled "For Clinical Study Use Only" and will show the display name of the investigational product, the lot number, storage condition and other required information in accordance with local regulations.

5.2.3. Preparation

The drug for IV infusion is prepared by dilution of the required volume of the drug product (calculated based on the subject's body weight) in a volume of 250 mL 5% dextrose in water (D5W). Prepared medicinal solutions should be used immediately. The preparation will be conducted in accordance with the Pharmacy Instruction provided by the Sponsor. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study site.

5.2.4. Administration

U3-1402 will be infused as a continuous IV infusion over approximately 90 minutes on Day 1 of Cycle 1. If there are no infusion-related reactions after the initial dose, subsequent doses of U3-1402 will be infused over approximately 30 minutes on Day 1 of each subsequent cycle. Refer to Table 5.2 for additional information on drug administration following infusion related reactions. The subject's weight at Screening (baseline) will be used to calculate the initial dose. The subject's weight will be determined at the beginning of each cycle. If the subject's weight changes more than 10% from the baseline weight, the dose will be recalculated using the new weight. This weight will become the new baseline weight for dosing.

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the storage conditions listed below:

- Stored [redacted]

If storage conditions are not maintained per specified requirements, Sponsor or Contract research organization (CRO) should be contacted.

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, and check the drug expiration date. In addition, the Investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the investigational product. The record must be kept current and should contain the dates and quantities of drug received, subject's information for whom the investigational product was dispensed, the date and quantity of investigational product dispensed and the remaining quantity.

At the end of the study, or as directed, all unused U3-1402 will be returned to a designee as instructed by Sponsor or will be destroyed. Investigational Product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of Investigational Product must be documented, and the documentation included in the shipment. At the end of the study, a final Investigational Product reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the supervisor of investigational products in Japan and Investigator in the US when approved in writing by Sponsor, and after the Sponsor has received copies of the site's drug handling and disposition SOPs.

All investigational product inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The supervisor of investigational products in Japan and Investigator in the US are responsible for the accountability of all used and unused study supplies at the site.

5.2.7. Retention Samples

Not applicable.

5.3. Control Treatment

Not applicable.

5.4. Dose Interruptions and Reductions

Specific criteria for dose interruption, re-initiation, reduction and/or discontinuation of U3-1402 are listed in Table 5.2. Doses may also be interrupted for other AEs per Investigator discretion, and supportive therapy may be administered in accordance with local practice guidelines. All dose interruptions or dose modifications must be recorded on the AE and drug administration eCRF pages.

Dose modifications are applicable only to TEAEs that are assessed as related to use of U3-1402 by the Investigator(s). For non-drug-related TEAEs, follow standard clinical practice. Appropriate external experts such as a cardiologist, pulmonologist, etc, should be consulted as deemed necessary.

5.4.1. Dose Interruptions

The dose can be interrupted for up to 4 weeks from the planned date of administration (ie, 49 days from the last infusion date). If a subject is assessed as requiring a dose delay longer than 4 weeks, the subject may be withdrawn from the study following discussion and agreement between the Investigator and Sponsor.

5.4.2. Dose Reductions

Two dose reductions of U3-1402 may be permitted. Further dose reductions may be considered after discussion and agreement between the Investigator and Sponsor. Dose reductions below 1.6 mg/kg (or equivalent Q2W dose level; Table 5.1) will not be permitted.

Dose Reduction(s) for Q3W Dosing Schedule

If dose reduction is required, U3-1402 dosing should be reduced by 1 dose level at a time (Table 5.1). Once the dose of U3-1402 has been reduced due to an AE, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required.

Dose Reduction(s) for Q3W Dosing Schedule with Up-Titration Cohorts

If dose reduction is required, U3-1402 dosing should be reduced by 1 dose level at a time (Table 5.1). Once the dose of U3-1402 has been reduced due to an AE, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. In addition, no further up-titration will be permitted.

Dose Reduction(s) for Q2W Dosing Schedule

If dose reduction is required during the Q2W dosing period, U3-1402 dosing should be reduced by 1 dose level (Table 5.1); all subsequent cycles during the Q2W dosing period should be administered at the reduced dose level and the equivalent Q3W dosing level should be used from Cycle 4 and beyond, unless further dose reduction is required.

Table 5.1: Dose Levels for U3-1402

Dose Level	Q3W Dose Schedule (21-day cycles)	Q2W Dose Schedule (14-day cycles)
1[a]	1.6 mg/kg IV infusion Q3W	1.0 mg/kg IV infusion Q2W
2	3.2 mg/kg IV infusion Q3W	2.1 mg/kg IV infusion Q2W
3	4.8 mg/kg IV infusion Q3W	3.2 mg/kg IV infusion Q2W
4	6.4 mg/kg IV infusion Q3W	4.2 mg/kg IV infusion Q2W
5	8.0 mg/kg IV infusion Q3W	5.3 mg/kg IV infusion Q2W
6	9.6 mg/kg IV infusion Q3W	6.4 mg/kg IV infusion Q2W

IV = intravenous; Q2W = once every 2 weeks; Q3W = once every 3 weeks.
[a] Dose reductions below Dose Level 1 will not be permitted.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
General disorders and administration site conditions		
Infusion related reaction	Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during infusion, the rate should be reduced by 50% and subjects should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
	Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV injection fluids); prophylactic medications indicated for ≤24 hours	U3-1402 infusion should be interrupted. Symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids). If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. Upon restart, if Grade 2 symptoms recur, no further U3-1402 should be administered at that visit. The amount of U3-1402 infused must be recorded in the eCRF. Subsequent infusions must be conducted at the 50% reduced infusion rate (ie, same reduced rate as previous infusion).
	Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4 Life-threatening consequences; urgent intervention indicated	Administration of U3-1402 should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, corticosteroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation etc, must be administered as clinically indicated.
Fatigue/ Asthenia	Grade 3	Delay dose until resolved to ≤Grade 1 or baseline values, then: If resolved to ≤Grade 1 or baseline values in ≤14 days, resume U3-1402. If resolved to ≤Grade 1 or baseline values in >14 days, U3-1402 may be resumed after discussion and agreement reduce U3-1402 by 1 dose level and resume.
Blood and lymphatic system disorders		
Neutrophil count decreased	Grade 3 (500 to <1000/mm^3; 0.5-1 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then resume U3-1402.
	Grade 4 (<500/mm^3; <0.5 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then reduce U3-1402 by 1 dose level.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Febrile neutropenia (ANC <1000/mm^3; <1 × 10^9/L, fever >38.3°C or a sustained temperature of ≥38°C for more than 1 hour)	Grade 3	Delay dose until resolved; then resume U3-1402. Consider reducing U3-1402 by 1 dose level. Consider administration of granulocyte colony-stimulating factor as prophylaxis for all subsequent cycles and according to local guidelines.
	Grade 4	Delay dose until resolved, then reduce U3-1402 by 1 dose level and resume. Administer granulocyte colony-stimulating factor as prophylaxis for all subsequent cycles and according to local guidelines.
Anemia	Grade 3 (Hemoglobin <8.0 g/dL)	Delay dose until resolved to ≤Grade 2 or baseline; then resume U3-1402. For recurrent anemia, delay dose until resolved ≤Grade 2 or baseline, then reduce U3-1402 by 1 dose level and resume. Consider packed red blood cell transfusion according to institutional guidelines.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Delay dose until resolved to ≤Grade 2 or baseline, then reduce U3-1402 by 1 dose level and resume. Consider transfusion according to institutional guidelines.
Platelet count decreased	Grade 3 (Platelet <50 - 25 × 10^9/L)	Delay dose until resolved to ≤Grade 1, then: If resolved in ≤14 days, resume U3-1402. If resolved in >14 days, U3-1402 may be resumed. Consider reducing U3-1402 by 1 dose level. Consider platelet transfusion according to institutional guidelines.
	Grade 4 (Platelet <25 × 10^9/L)	Delay dose until resolved to ≤Grade 1, then reduce U3-1402 by 1 dose level and resume. Consider transfusion according to institutional guidelines.
Lymphocyte Count Decreased	Grade 4 (<0.2 × 10^9/L)	Delay dose until resolved to ≤Grade 2, then: If resolved in ≤14 days, resume U3-1402. If resolved in >14 days, reduce U3-1402 by 1 dose level and resume.
Cardiac disorders		
Heart failure	Grade ≥2 (Symptoms with moderate activity or exertion)	Cardiologist consult as necessary. Delay dose until resolved to ≤Grade 1, then reduce U3-1402 by 1 dose level.
Ejection fraction decreased	Decrease in LVEF 10% to 20% (absolute value), but LVEF >45%	Continue treatment with U3-1402.
	LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline	Continue treatment with U3-1402. Repeat LVEF assessment within 3 weeks.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
	LVEF 40% to ≤45% and decrease is ≥10% to 20% (absolute value) from baseline	Delay U3-1402 dosing. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment.
	LVEF <40% or >20% drop from baseline	Delay U3-1402 dosing. Repeat LVEF assessment within 3 weeks; if LVEF <40% or >20% (absolute value) drop from baseline is confirmed, discontinue U3-1402. Cardiologist consult as necessary.
Cardiac troponin increased	Grade 1 (Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer) In subjects without symptoms suggestive of acute coronary syndrome	Perform additional troponin I testing by central laboratory, at 3 hours (± 1 hour) after initial local troponin test. Follow institutional guidelines for management of detectable troponin testing. Otherwise: Repeat troponin testing at 3 (± 1 hour) after initial troponin test. If levels at 3 hours (6 hours post-infusion) rise significantly, perform ECG in triplicate and repeat troponin testing 6 (± 1 hour) or 24 (± 1 hour) after initial troponin test. If acute myocardial infarction is ruled out, continue U3-1402. If acute myocardial infarction is confirmed, discontinue subject from U3-1402.
	Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer) In subjects without symptoms suggestive of acute coronary syndrome	Follow institutional guidelines for management of detectable troponin testing. Perform 12-lead ECG in triplicate. Perform additional troponin I testing by central laboratory at 6 and 12 hours (± 1 hour) after initial local troponin test. Cardiologist consult as necessary. If acute myocardial infarction is ruled out, resume U3-1402. If acute myocardial infarction is confirmed, discontinue subject from U3-1402.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
	Grade 1 (Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer) in subjects with symptoms suggestive of acute coronary syndrome	Repeat levels should be obtained every 6 to 8 hours to identify a rising and/or falling pattern of values. Perform 12-lead ECG in triplicate. Perform additional troponin I testing by central laboratory at 6 and 12 hours (± 1 hour) after initial local troponin test. Follow institutional guidelines for management of detectable troponin testing. Cardiologist consult as necessary. If acute myocardial infarction is ruled out, resume U3-1402. If acute myocardial infarction is confirmed, discontinue subject from U3-1402.
	Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer) in subjects with symptoms suggestive of acute coronary syndrome	Discontinue subject from U3-1402. Follow institutional guidelines for management of detectable troponin testing. Repeat levels should be obtained every 6 to 8 hours to identify a rising and/or falling pattern of values. Perform 12-lead ECG in triplicate. Perform additional troponin I testing by central laboratory at 6 and 12 hours (± 1 hour) after initial local troponin test. Cardiologist consult as necessary.
Electrocardiogram QT corrected interval prolonged	Grade 3 (Average QTcF ≥501 ms; >60 ms change from baseline)	Delay U3-1402 until resolved to ≤Grade 1 (QTcF ≤480 ms). Determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected. If QTcF prolongation is attributed to U3-1402, then reduce U3-1402 by 1 dose level. Cardiologist consult as necessary.
	Grade 4 (Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia)	Discontinue subject from U3-1402. Cardiologist consult as necessary

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Respiratory, thoracic and mediastinal disorders		
Pulmonary toxicity	See next column	If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If ILD/pneumonitis is suspected, delay U3-1402 dosing pending further evaluation and start corticosteroid treatment promptly unless clinically contraindicated. Evaluations must include CT (preferably high-resolution CT), and pulmonologist consultation (when the Investigator is not a pulmonologist). The following evaluations must also be obtained, as indicated: • Infectious disease consultation as clinically indicated • Blood culture and CBC (other blood tests could be considered as needed) • Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests • Pulse oximetry (SpO_2) • Arterial blood gases, as clinically indicated • Diffusing capacity of the lungs for carbon monoxide (DLCO), as clinically indicated • One blood sample collection for PK analysis as soon as ILD is suspected, if feasible • Other tests, as clinically indicated If a noninflammatory/infectious etiology is confirmed by the Investigator, treat accordingly and resumption of U3-1402 may occur after discussion between the Investigator and Sponsor. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Pulmonary toxicity	Grade 1	The administration of U3-1402 must be delayed. U3-1402 can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤28 days from day of onset, maintain dose. • If resolved in >28 days from day of onset, reduce dose 1 level. Toxicity Management: • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry. • Consider follow-up imaging in 1 to 2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, at least 0.5-mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines (if subject is asymptomatic, then subject must still be considered as Grade 1 even if steroid treatment is given).
	Grade 2	Permanently discontinue subject from study treatment. Toxicity Management: • Promptly start systemic steroids (eg, at least 1-mg/kg/day prednisone or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT findings, followed by gradual taper over at least 4 weeks. • Monitor symptoms closely. • Reimage as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, – Consider increasing dose of steroids (eg, 2-mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone). – Reconsider additional work-up for alternative etiologies as described previously. Escalate care as clinically indicated.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Pulmonary toxicity	Grade 3 or 4	Permanently discontinue subject from study treatment. Toxicity Management: • Hospitalization is required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for a minimum of 14 days or until complete resolution of clinical symptoms and chest CT findings, followed by gradual taper over at least 4 weeks. • Reimage as clinically indicated. • If still no improvement within 3 to 5 days, – Reconsider additional work-up for alternative etiologies as described above. – Consider other immuno-suppressants and/or treat per local practice.
Endocrine disorders		
Endocrine disorders	Grade 3	Delay dose until resolved to ≤Grade 2, then: If resolved in ≤14 days, resume U3-1402. If resolved in >14 days, U3-1402 may be resumed after discussion and agreement between the Investigator and Sponsor.
	Grade 4	Discontinue subject from U3-1402.
Eye disorders		
Ocular	Grade 3	Delay dose until resolved to ≤Grade 2, then: If resolved in ≤7 days, resume U3-1402. If resolved in >7 days, then reduce U3-1402 by 1 dose level. Ophthalmologist consultation as clinically indicated.
	Grade 4	Discontinue subject from U3-1402. Ophthalmologist consult as necessary.
Renal and urinary disorders		
Creatinine increased	Grade 3 (>3.0 × baseline; >3.0 - 6.0 × ULN)	Delay dose until resolved to ≤Grade 1 or baseline, then reduce U3-1402 by 1 dose level.
	Grade 4 (>6.0 × ULN)	Discontinue subject from U3-1402.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Hepatobiliary disorders		
AST or ALT increased without TBL increased	Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	Continue U3-1402. In subjects **without** liver metastasis, monitor AST/ALT 24 to 72 hours later, and continue regular monitoring until resolution.
	Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level was ≤ 3 × ULN.	Delay U3-1402 dose until resolved to ≤Grade 1, then: If resolved in ≤7 days, resume U3-1402. If resolved in >7 days, then reduce U3-1402 by 1 dose level.
	>8.0-20.0 × ULN if baseline was normal; >8.0-20.0 × baseline level if baseline level was abnormal In subjects with liver metastases, if the baseline level was > 3 × ULN.	Delay U3-1402 dose until resolved to ≤baseline level, then: If resolved in ≤7 days, resume U3-1402; If resolved in >7 days, then reduce U3-1402 by 1 dose level.
	Grade 4 (>20.0 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from U3-1402. Gastroenterologist or hepatologist consult as necessary.
TBL increased	Grade 2 (>1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 × baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay U3-1402 until resolved to ≤Grade 1, then: If resolved in ≤7 days, resume U3-1402; If resolved in >7 days, reduce U3-1402 by 1 dose level. If documented Gilbert's syndrome or liver metastases at baseline, continue U3-1402.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
TBL increased	Grade 3 (>3.0-10.0 × ULN if baseline level was normal; >3.0-10.0 × baseline level if baseline level was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay U3-1402 dose until resolved to ≤Grade 1, then: • If resolved in ≤7 days, reduce U3-1402 by 1 dose level; • If resolved in >7 days, discontinue subject from U3-1402. If documented Gilbert's syndrome or liver metastases at baseline, delay U3-1402 dose until resolved to ≤Grade 2, then: • If resolved in ≤7 days, reduce U3-1402 by 1 dose level; • If resolved in >7 days, discontinue subject from U3-1402.
	Grade 4 (>10.0 × ULN if baseline was normal; >10.0 × baseline if baseline was abnormal)	Discontinue subject from U3-1402.
AST or ALT increased and TBL increased	AST or ALT ≥3 × ULN with simultaneous TBL >2 × ULN	Delay U3-1402 until drug-induced liver injury can be ruled out. The Investigator should consult with a gastroenterologist or hepatologist as needed, and the subject should be treated accordingly. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as viral or autoimmune hepatitis, alcoholic liver injury, biliary tract disorders, or hemodynamic abnormalities. Results from diagnostic workup (including, for example: INR, direct bilirubin, serologic tests for hepatitis A, B, and C; alcohol use, ultrasound, MRI, CT scan, concomitant medication use, immunoglobulin levels, ECHO) must be recorded within the eCRF. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of U3-1402 may occur after discussion between the Investigator and Sponsor. U3-1402 will be permanently discontinued if drug induced liver injury cannot be ruled out from diagnostic workup.

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
AST or ALT> 3.0 × ULN (if liver metastases are present, >5 × ULN) with known Hepatitis B and/or Hepatitis C infection at baseline	--	Delay U3-1402 until reactivation of Hepatitis B and/or Hepatitis C can be ruled out. Perform HBV DNA and/or HCV RNA to rule out reactivation of Hepatitis B and/or Hepatitis C, respectively. Hepatologist and infectious disease consultations are recommended. If reactivation of Hepatitis B and/or Hepatitis C is confirmed, permanently discontinue U3-1402.
Gastrointestinal disorders		
Nausea	Grade 3 (Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated)	Delay U3-1402 until resolved ≤Grade 1, and consider treatment with antiemetics and/or corticosteroids as per Investigators judgement and local practice/guidelines, then: If resolved to ≤Grade 1 in ≤14 days, resume U3-1402. If does not resolve to ≤Grade 1 in >14 days, reduce U3-1402 by 1 dose level.
Vomiting	Grade 3 (Tube feeding, TPN, or hospitalization indicated)	Delay U3-1402 until resolved ≤Grade 1, and consider treatment with antiemetics and/or corticosteroids as per Investigators judgement and local practice/guidelines, then: If resolved to ≤Grade 1 in ≤7 days, resume U3-1402. If does not resolve to ≤Grade 1 in >7 days, reduce U3-1402 by 1 dose level.
	Grade ≥4	Discontinue subject from U3-1402
Based on currently available clinical safety data for U3-1402, it is recommended that patients receive premedication with antiemetic agents. Suggested agents include a 5-HT3 blocker in combination with another antiemetic or corticosteroid approximately 30 minutes prior to U3-1402 infusion. Choice of agents is based on Investigator's discretion as per local/institutional guidelines. Investigators must also consider providing patients with an antiemetic regimen for subsequent use as needed.		

Table 5.2: Dose Delay Criteria and Dose Reduction for U3-1402 (Continued)

	Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for U3-1402
Diarrhea/ Colitis	Grade 3	Delay U3-1402 until resolved ≤Grade 1, and consider treatment per local practice/guidelines, then: If resolved to ≤Grade 1 in ≤7 days, resume U3-1402. If resolved to ≤Grade 1 in >7 days, then reduce U3-1402 by 1 dose level
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from U3-1402.
Mucositis oral	Grade 3	Delay U3-1402 until resolved ≤Grade 1, and consider treatment per local practice/guidelines, then: If resolved to ≤Grade 1 in ≤14 days, resume U3-1402; If resolved to ≤Grade 1 in >14 days, then reduce U3-1402 by 1 dose level.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from U3-1402.
Other Adverse Events (Nonlaboratory or Laboratory)	Grade 3	Delay U3-1402 until resolved ≤Grade 1 or baseline level, then: If resolved in ≤7 days, resume U3-1402; If resolved >7 days, then reduce U3-1402 by 1 dose level.
	Grade 4 (Life-threatening consequences; urgent intervention indicated)	Discontinue subject from U3-1402.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram, eCRF = electronic case report form; g/dL = grams per deciliter; HBV DNA = hepatitis B virus DNA (a measure of the hepatitis B viral load in the blood); HCV DNA = hepatitis C virus DNA (a measure of the hepatitis C viral load in the blood); ILD = interstitial lung disease, INR = international normalized ratio; IV = intravenous; L = liter; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs = nonsteroidal anti-inflammatory drugs; QTcF = corrected QT using Fridericia's formula; SpO_2 = oxygen saturation of peripheral artery; TBL = total bilirubin; ULN = upper limit of normal.

5.5. Method of Assessing Treatment Compliance

All drugs used for the study treatment will be administered by the Investigator or other designated study personnel. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for the administration of study treatment.

5.6. Prior and Concomitant Medications

5.6.1. Prior Medications

All prior anticancer treatments or procedures for breast cancer (eg, surgery, radiation therapy, TKI therapy, chemotherapy, and immune checkpoint inhibitor therapy) will be recorded.

5.6.2. Concomitant Medications

Medications used from Day 1 of Cycle 1 to the follow-up (F/U) visit or 28 days after the last dose of U3-1402 (if the F/U visit is not performed), will be recorded. If the subject begins another anticancer therapy, medications used after these anticancer therapies will not be record. All concomitant medications will be recorded on the eCRF.

Prophylactic treatment for expected toxicities may be administered per Investigator discretion and institution guidelines.

Hematopoietic growth factors may be used per clinical judgment of the Investigator and according to prescribing information and institutional guidelines.

Bisphosphonates (eg, pamidronate or zoledronate) or denosumab for control of bone pain, treatment of bony metastases, or treatment of osteoporosis, may be used per clinical judgment of the Investigator and according to prescribing information and institutional guidelines.

Supportive treatment including management of study drug-related adverse events will be per Investigator discretion.

Subjects taking warfarin should be monitored regularly for changes in prothrombin time or INR.

5.6.3. Prohibited Concomitant Medications/Activities

The following medications and products will be prohibited from Day 1 of Cycle 1 until end of treatment (EOT):

- Other anticancer therapy, including cytotoxic agents, targeted agents, immunotherapy or endocrine therapy.
- Radiotherapy, except for palliative radiation to known metastatic sites (as long as it does not affect assessment of tumor response). Whenever possible, subject should have a tumor assessment of the lesion(s) prior to receiving radiotherapy in order to rule out progression of disease. In case of Progressive Disease (PD), subjects should be discontinued from the U3-1402 J101 protocol.
- Hormonal replacement therapy.
- Concomitant medications that prolong the QTc interval including but not limited to: antipsychotics, tricyclic/tetracyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), macrolide antibiotics, fluoroquinolone antibacterials, azole antifungals, antimalarials, and antiprotozoals.
  - If the concomitant medication(s) that prolong the QTc interval is unavoidable, consider delaying U3-1402 treatment until such drug has cleared from circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If the

drug which prolongs the QTc interval is co-administered and U3-1402 treatment cannot be delayed, patients should be closely monitored for adverse reactions.

- Other investigational agents.
- Chloroquine and hydroxychloroquine
- CYP3A4 strong inhibitors including but not limited to: boceprevir, clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, telaprevir, telithromycin, voriconazole.
  - If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying U3-1402 treatment until the strong CYP3A4 inhibitors have cleared from circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is co-administered and U3-1402 treatment cannot be delayed, patients should be closely monitored for adverse reactions.
- [Dose Escalation and Dose Finding Parts Only] Avoid CYP3A4 strong inducers (eg, carbamazepine, phenytoin, and rifampin).
- Organic anion transporting polypeptide (OATP)1B inhibitors including but not limited to: atazanavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir, rifampin, ritonavir, simeprevir. Consult with your local resources as needed to evaluate potential OATP1B inhibitors.
  - If concomitant use of OATP1B inhibitors is unavoidable, consider delaying U3-1402 treatment until the OATP1B inhibitors have cleared from circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If an OATP1B inhibitor is co-administered and U3-1402 treatment cannot be delayed, patients should be closely monitored for adverse reactions.

5.6.4. Dietary and Lifestyle Restrictions

The following foods and products will be prohibited from 14 days before Day 1 of Cycle 1 until EOT:

- Foods containing hypericum perforatum (Saint John's wort)

The following foods and products will be prohibited from Day 1 of Cycle 1 until EOT:

- Foods or beverages containing grapefruit

For Japanese sites, subjects will be hospitalized during Day 1 to Day 21 on Cycle 1 of the Dose Escalation Part.

Female subjects of child bearing potential or those who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of childbearing potential and required along with the partner of subject enrolled in study to both use adequate contraceptive methods (eg, concomitant use of a spermatocidal agent and barrier contraceptive, intrauterine contraceptive, which are approved or certificated in Japan [for Japanese subjects] and US [for US subjects]) during the study and for at least 7 months after the last dose of U3-1402.

Subjects who wear contact lenses must discontinue wearing their lenses if they have any mild to moderate symptoms (CTCAE Grade ≤2) while receiving treatment until at least 1 week after symptoms have resolved. If a subject has a recurrence of eye symptoms or experiences any severe (CTCAE Grade ≥3) ocular events they must discontinue wearing their contact lenses until at least 1 week after treatment is permanently discontinued. Subjects must not use any eye drops or ointment for treatment of eye symptoms, unless agreed by a study doctor, at any time during the study and ≥1 week after permanent discontinuation of study treatment.

Subjects must avoid using tanning lights and booths. When in the sun, subject should cover their skin and use sunscreen as possible.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal

Any subject who discontinues from the study treatment for any reason will have their study treatment discontinuation recorded.

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

- Progressive disease (PD) per RECIST version 1.1
- Clinical progression: provide date (ie, definitive clinical signs of disease progression, but a recent radiographic assessment did not meet the criteria for PD according to RECIST version 1.1)
- AE
- Death
- Pregnancy
- Withdrawal of consent by subject
- Lost to follow-up
- Protocol violation (specify)
- Study terminated by Sponsor
- Other, specify (eg, Investigator discretion)

If there is evidence that the subject is receiving benefit from treatment even though the subject has met a criterion for discontinuation as listed above, the subject may remain on study treatment after discussion with and approval from the Sponsor.

Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

5.7.2. Withdrawal Procedures

If a subject is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized as possible. All subjects who are withdrawn from the study and received study treatment should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will involve an EOT visit and a F/U visit 28 days (− 7 days) after the last administration of U3-1402. Protocol-specified withdrawal procedures are the same as those to be performed at the EOT visit and the F/U visit (Section 6.7 and Section 6.8).

If the subject is withdrawn due to reasons other than death, withdrawal of consent, loss to follow-up, or study closure, and received study treatment, disease progression should be followed until PD or starting new anticancer therapy, whichever occurs first regardless of Follow-up period (Section 6.4.2).

If the subject is withdrawn due to reasons other than death, withdrawal of consent, loss to follow-up, or study closure, and received study treatment, follow-up for survival and subsequent anticancer therapy, if available (Section 6.9).

5.7.3. Subject Replacement

Subject replacement is not allowed for this study.

5.7.4. Subject Re-screening Procedures

The study will allow re-screening for any subject who failed to meet eligibility criteria upon initial screening. A new Subject Number will be assigned at re-screening. The initial screening information and the reason why the subject was ineligible for the initial evaluation will be recorded on the Screening Log.

5.8. Criteria for Suspending Study Treatment

The subject should be discontinued from the study under the following conditions:

1. If a subject is assessed as requiring a dose delay longer than 4 weeks (See Section 5.4), after discussion with the Sponsor.
2. If a subject is assessed PD (per RECIST version 1.1) or clinical progression by the Investigator.
3. If a subject presents any significant AE, as determined by the Investigator.
4. If any major protocol violation occurred, at the discretion of Investigator and Sponsor.
5. If becomes clear that the subject did not meet the inclusion/exclusion criteria, after discussion with the Sponsor.
6. If the subject withdraws consent.
7. If the study is terminated by the Sponsor.
8. At the discretion of Investigator, according to the condition of subject.

6. STUDY PROCEDURES

Study visit schedules in tabular format are provided in Table 17.7, Table 17.8, Table 17.9, and Table 17.10.

6.1. Screening

Obtain a signed and dated ICF for the study before any study-related procedures or assessments. Informed consent for tumor screening should be obtained in a separate ICF.

In this study, enrollment will be performed as described in Section 5.1.2.1.

The following activities and/or assessments will be performed during the screening period:

Tumor Screening

The following procedures should be conducted:

Before enrollment

- Obtain a separate signed and dated ICF for tumor screening before any study-related procedures or assessments are performed.
- Perform a tumor biopsy OR request archive tumor tissue sample.
- Send tumor tissue to the central laboratory for assay of the HER3 status. Refer to the Laboratory Manual for information regarding archived and/or fresh tumor tissue requirements and shipping.

  If HER3 status to determine eligibility was assessed with archived tumor tissue sample:

  – A fresh tumor biopsy may be performed for subjects with HER3-negative tissue that was assayed using an archived tumor tissue samples. Tumor tissue obtained by this fresh biopsy should be sent to the central laboratory for the re-assay of HER3 status. Tumor samples must be obtained after the date of informed consent for tumor screening.

  – In the Dose Finding Part, perform an **optional** fresh tumor biopsy for subjects with HER3-positive tumor tissue that was assayed using an archived tumor tissue sample. Tumor tissue from this fresh biopsy should be sent to the central laboratory for analysis of HER3 IHC; these results are not required for study entry.

  – In the Dose Expansion Part, perform a fresh tumor biopsy for subjects with HER3-positive tumor tissue that was assayed using an archived tumor tissue sample. Tumor tissue from this fresh biopsy should be sent to the central laboratory for analysis of HER3 IHC; these results are not required for study eligibility.

Within 28 days prior to enrollment

- Perform tumor assessment by CT or MRI scans of the brain, chest, abdomen, pelvis, and any other sites of disease. A bone scan will be required at screening (Section 17.4). Send all CT or MRI scans to the central imaging CRO selected by the Sponsor for confirming the existence of at least 1 measurable lesion per RECIST version 1.1. Confirmation of measurable disease by central imaging review is required for subject eligibility.

Eligibility Screening

Before enrollment

- Have the subject sign the ICF before any study-related procedures or assessments are performed.
- Record Subject Number.
- Record demographics (eg, birth date, sex, race, ethnicity), primary breast cancer history (only for Dose Expansion TNBC subjects, include BRCA genomic testing results if subject has consented to release this information), significant medical history, and history of prior cancer treatment.
- Confirm eligibility of the subject.
- Assess for AEs.

Within 28 days prior to enrollment

- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, fundoscopy, and tonometry.
- Perform either ECHO or MUGA (LVEF). The same test should be used for the subject throughout the study.
- Perform a complete physical examination and record weight.
- Perform a 12-lead ECG in triplicate*.

  *: ECGs will be taken in close succession, a few minutes apart, after being in a supine/semi-recumbent position for 5 minutes. All ECG data collected will be sent to the central laboratory for ECG analysis.

Within 7 days prior to enrollment

- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential. For postmenopausal subjects (no childbearing potential, as indicated by an elapse of at least 12 months after the last menstruation) or female subjects who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of childbearing potential and required to undergo the pregnancy test.
- Assess functional status using the ECOG PS Scale (Section 17.3).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories and cardiac troponin T (cTnT) (alternatively cTnI) (Section 8.8).
- Obtain blood sample for cTnI to be sent to central laboratory (Section 6.10.5).
- [In the Dose Escalation and Dose Finding Parts] Obtain blood samples for human epidermal growth factor receptor 3 extracellular domain (HER3ECD) (Section 6.10.5).

Before the first dose of study drug administration

- Record height.

When the subject is confirmed as ineligible during the screening period, Investigators will notify the subject and promptly terminate the study-related procedures. The following will be recorded in the eCRF; and a F/U visit should not be performed.

- Informed Consent Date
- Demographics (eg, birth date, sex, race, ethnicity)
- Date and reason of screen failure

6.2. Subject Management

In consideration of subject safety, subjects will be hospitalized from Day 1 to Day 21 on Cycle 1 of the Dose Escalation Part to allow for careful safety monitoring. However, a temporary stay outside the hospital is permitted at the Investigator's discretion. The Investigator should examine the subject carefully before granting permission and the study site should give subjects instructions for emergency contact. Subjects should be instructed to refrain from prolonged exposure to ultraviolet rays. Additional safety assessments should be conducted as needed at the Investigator's discretion.

6.3. Randomization

6.3.1. Dose Escalation Part

Not applicable.

6.3.2. Dose Finding Part

Eligible subjects will be randomized into open Dose Finding cohorts during the Dose Finding Part, if applicable.

6.3.3. Dose Expansion Part

Approximately 60 eligible subjects with HER3-high metastatic breast cancer will be randomized into 1 of 2 cohorts: 4.8 mg/kg and 6.4 mg/kg.

Eligible subjects with HER3-low metastatic breast cancer will not be randomized.

6.4. Treatment Period

6.4.1. Administration of U3-1402

See Sections 3.1.3, 3.1.4, 3.1.5, and 5.2.4.

6.4.2. Tumor Assessment

Tumor assessments of the chest, abdomen, pelvis, and other areas where scans were performed at screening or where new disease is suspected should be performed every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1 and every 12 weeks (± 7 days) thereafter. Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1 and should continue until PD or until a new anticancer therapy is started, whichever occurs first.

CT or MRI scans of the chest, abdomen, and pelvis are mandatory. The same methodology (CT or MRI) and scan acquisition techniques (including use or nonuse of IV contrast) that were used for the screening assessments should be used throughout the study for all assessments for each subject, unless prior approval is obtained from the Sponsor. Unscheduled tumor assessments may be conducted if progression is suspected. Tumor assessments should be performed per RECIST version 1.1 (Section 17.4).

A brain scan (CT of the brain with contrast or MRI of the brain pre- and post-gadolinium) should be performed at screening. During the treatment period, CT or MRI of the brain should be performed in subjects with baseline brain metastases or where clinically indicated, and within a target of 1 week (+ 1 week) after a subject achieves CR.

A bone scan should be performed at screening. In subjects whose body CT/MRI scans indicate that CR has been achieved, a bone scan (within a target of 1 week [+ 1 week]) will be required at confirmation of CR to exclude new bone metastases.

All images including CT and MRI must be submitted to the central imaging CRO selected by the Sponsor for independent tumor assessment.

6.4.3. ECG Measurement

Triplicate ECGs should be taken in close succession, a few minutes apart, after the subject has been in a supine/semi-recumbent position for 5 minutes. All ECG data that are collected will be sent to the central laboratory for ECG analysis.

Table 6.1: ECG Measurement Time Points

			Dose Escalation Part	Dose Finding Part			Dose Expansion Part
				Q3W Dosing	Q3W Dosing with Up-Titration	Q2W Dosing	
Screening[a]			●	●	●	●	●
Cycle 1	Day 1	BI[b]	●[c]	●[c]	●	●	●[c]
		EOI[d]	●[c]	●[c]			●[c]
		2H[e]	●[c]				
		4H[e]	●[c]	●[c]			●[c]
		7H[e]	●[c]				
	Day 2[f]		●[c]				
	Day 4 (± 1D)		●[c]				
	Day 8 (± 1D)			●[c]			●[c]
	Day 22[h] (+ 2D)		●[c]			NA	
Cycle 2	Day 1[b,i]		●[c]	●	●	●	●
Cycle 3	Day 1	BI[b]	●[c]	●[c]	●	●	●[c]
		EOI[d]	●[c]	●[c]			●[c]
		2H[e]	●[c]				
		4H[e]	●[c]	●[c]			●[c]
		7H[e]	●[c]				
	Day 2[j]		●[c]				
	Day 4 (± 1D)		●[c]				
	Day 8 (± 2D)			●[c]			●[c]
	Day 22[h] (± 2D)		●[c]			NA	
Cycle 4	Day 1		●[c,b,i]	●[g]	●[g]	●[g]	●[g]
Cycle 5, and subsequent cycles	Day 1		●[g]	●[g]	●[g]	●[g]	●[g]
EOT[k]			●	●	●	●	●

BI = before infusion; EOI = end of infusion; EOT = end of treatment; D = day; H = hour; NA = not applicable; Q2W = once every 3 weeks; Q3W = once every 3 weeks.

[a] Within 28 days prior to enrollment
[b] Within 8 hours of the start of infusion
[c] Blood for PK should be collected within 15 minutes of the end of ECG measurement.
[d] Within 30 minutes post-infusion
[e] ± 15 minutes after the start of infusion.
[f] 24 hours (± 2 hours) after the start of Day 1 administration.
[g] Within 3 days of infusion
[h] If dosing for the next cycle is delayed for ≥3 days, including if the subject cannot continue onto the next cycle.
[i] If triplicate ECGs were collected on Day 22 of the previous cycle, then triplicate ECGs should also be performed BI (−8 hours), if possible.
[j] 24 hours (- 2 to + 4 hours) after the start of Day 1 administration.
[k] The date of discontinuation of treatment is defined as the date of decision by Investigator. Triplicate ECGs should be performed at EOT visit (within 7 days after the date of discontinuation).

6.4.4. Cycle 1, Day 1 (All Parts)

Pre-infusion

The following procedures must be completed pre-infusion. If assessments at screening are performed within this period, they can be considered to be Day 1 data and there is no need to repeat them.

- Assess for AEs.

Within 3 days prior to infusion

- Perform a complete physical examination and record weight.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, body temperature, and oxygen saturation of peripheral artery [SpO_2]).
- Obtain blood samples for safety laboratories (Section 8.8).

Within 8 hours prior to infusion

- Perform a 12-lead ECG in triplicate as indicated in Table 6.1.
- Obtain PK blood sample as indicated (Section 6.10.3).
- Obtain blood sample for ADA (Section 6.10.6).
- [Dose Expansion Part Only] Obtain blood samples for HER3ECD, cell-free DNA (cfDNA), and cell-free RNA (cfRNA) (Section 6.10.5).

Administration

- Administer U3-1402 via IV infusion and record start and stop times.
- Refer to Pharmacy Instruction for preparation information of U3-1402.
- Refer to Section 5.2.4 for information regarding administration of U3-1402.
- Refer to Table 5.2 for information regarding infusion reactions.

Post-infusion

The following procedures will be completed post-infusion:

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature).
- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples as indicated in Section 6.10.3.
- Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety and repeat as needed (see Table 5.2). The test used to detect troponin should remain the same for the subject throughout the study.

- Obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory. Repeat testing if indicated as described in Table 5.2.
- Record concomitant medications.
- Assess for AEs.

6.4.5. Cycle 1, Day 2 (Dose Escalation, Dose Finding [Q3W Dosing Cohorts], and Dose Expansion Parts)

The following procedures will be performed on Cycle 1, Day 2 during the Dose Escalation, Dose Finding (Q3W Dosing Cohorts), and Dose Expansion Parts:

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature).
- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- [Dose Escalation Part Only] Obtain blood samples for safety laboratories (Section 8.8).
- Record concomitant medications.
- Assess for AEs.

6.4.6. Cycle 1, Day 4 (Dose Escalation, Dose Finding [Q3W Dosing Cohorts and Q2W Dosing Cohorts], and Dose Expansion Parts)

The following procedures will be performed on Cycle 1, Day 4 (± 1 day) during the Dose Escalation, Dose Finding (Q3W Dosing Cohorts and Q2W Dosing Cohorts), and Dose Expansion Parts:

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature).
- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Record concomitant medications.
- Assess for AEs.

6.4.7. Cycle 1, Day 8 (All Parts)

The following procedures will be performed on Cycle 1, Day 8:

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature).
- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.

- Obtain blood samples for safety laboratories (Section 8.8).
- Obtain blood sample for ADA (Section 6.10.6).
- Record concomitant medications.
- Assess for AEs.

6.4.8. Cycle 1, Day 15 (All Parts)

The following procedures will be performed on Cycle 1, Day 15:

Cycle 1, Day 15 (± 1 day) for Dose Escalation, Dose Finding (Q3W Dosing Cohorts and Q3W Dosing with Up-titration Cohorts), and Dose Expansion Parts

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature).
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain blood samples for safety laboratories (Section 8.8).
- Record concomitant medications.
- Assess for AEs.

Cycle 1, Day 15 (+ 2 days; if applicable) for Dose Finding Part (Q2W Dosing Cohorts)

- If the dose of U3-1402 is delayed for ≥3 days, including if the subject cannot continue onto the next cycle, the following procedures should be performed on Day 15 (+ 2 days):
  - Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
  - Assess for AEs.
  - Record concomitant medications.

6.4.9. Cycle 1, Day 22 (if Applicable; for Dose Escalation, Dose Finding [Q3W Dosing Cohorts and Q3W Dosing with Up-titration Cohorts], and Dose Expansion Parts)

- If the dose of U3-1402 is delayed for ≥3 days, including if the subject cannot continue onto the next cycle, the following procedures will be performed on Day 22 (+ 2 days).
  - Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
  - Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
  - Record concomitant medications.
  - Assess for AEs.

6.4.10. Cycle 2, Day 1 (All Parts)

The following procedures must be completed pre-infusion:

Pre-infusion

- Record concomitant medications.
- Assess for AEs.

Within 7 days prior to infusion

- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, fundoscopy and tonometry. Investigators must ensure results of ophthalmologic assessments are available for review prior to dosing on corresponding cycle visits. Repeat ophthalmologic assessments are not required in the event of dose delays that occur after examination if there were no abnormal findings. Ophthalmologic assessments may be repeated per Investigator discretion.

Within 3 days prior to infusion

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Perform either ECHO or MUGA (LVEF). Investigators must ensure results of ECHO/MUGA are available for review prior to dosing on corresponding cycle visits. Repeat ECHO/MUGA assessments are not required in the event of dose delays that occur after examination if there are no abnormal findings. ECHO or MUGA may be repeated per Investigator discretion.
- Obtain blood samples for safety laboratories (Section 8.8).

Within 8 hours prior to infusion

- Perform a 12-lead ECG in triplicate as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain a blood sample for ADA (Section 6.10.6).

Administration

- Administer U3-1402 via IV infusion and record start and stop times.
- Refer to Pharmacy Instruction for preparation information of U3-1402.
- Refer to Section 5.2.4 for information regarding administration of U3-1402.
- Refer to Table 5.2 for information regarding infusion reactions.

Post-infusion

The following procedures will be completed at post-infusion on Cycle 2, Day 1:

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety and repeated as needed (see Table 5.2). The test used to detect troponin should remain the same for the subject throughout the study.
- Obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory. Repeat testing if indicated as described in Table 5.2.
- Record concomitant medications.
- Assess for AEs.

6.4.11. Cycle 2, Day 3 (Dose Expansion Part Only)

[Optional] An optional on-study tumor biopsy may be performed approximately 48 to 72 hours after the end of infusion of U3-1402 on Cycle 2, Day 1 (Section 7.3). Additionally, a blood sample for HER3ECD, cfDNA, cfRNA, and PK should be collected ± 4 hours from the time of this optional tumor biopsy, if obtained. Consent for this biopsy should be documented in the tissue consent portion of the ICF. Tumor tissue from this biopsy may be obtained from primary tumor or a metastatic site.

6.4.12. Cycle 2, Day 8 (All Parts)

The following procedures will be performed Cycle 2, Day 8:

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain blood samples for safety laboratories (Section 8.8).
- Record concomitant medications.
- Assess for AEs.

6.4.13. Cycle 2, Day 15 (± 2 days; Dose Escalation, Dose Finding [Q3W Dosing Cohorts, Q3W Dosing with Up-Titration Cohorts], and Dose Expansion Parts)

The following procedures will be performed Cycle 2, Day 15:

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.

- Obtain blood samples for safety laboratories (Section 8.8).
- Record concomitant medications.
- Assess for AEs.

6.4.14. Cycle 2, Day 22 (if Applicable; for Dose Escalation and Dose Finding [Q3W Dosing with Up-titration] Parts)

If the dose of U3-1402 is delayed for ≥3 days, including if the subject cannot continue onto the next cycle, the following procedures will be performed on Cycle 2, Day 22 (± 2 days):

- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Record concomitant medications.
- Assess for AEs.

6.4.15. Cycle 3, Day 1 (All Parts)

Pre-infusion

The following procedures must be completed at pre-infusion:

- Record concomitant medications.
- Assess for AEs.

Within 3 days prior to infusion

- Perform a complete physical examination and record weight.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, body temperature, and SpO_2).
- Perform either ECHO or MUGA (LVEF). Investigator must ensure results of ECHO/MUGA are available for review prior to dosing on corresponding cycle visits. If there is a delay after an ECHO/MUGA assessment with no clinically significant findings, then repeat assessments are not required but may be repeated per Investigator discretion.
- Obtain blood samples for safety laboratories (Section 8.8).

Within 8 hours prior to infusion

- Perform a 12-lead ECG in triplicate as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.

Administration

- Administer U3-1402 via IV infusion and record start and stop times.
- Refer to Pharmacy Instruction for preparation information of U3-1402.
- Refer to Section 5.2.4 for information regarding administration of U3-1402.

- Refer to Table 5.2 for information regarding infusion reactions.

Post-infusion

The following procedures will be completed at post-dose on Cycle 3, Day 1:

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety and repeat as needed (see Table 5.2). The test used to detect troponin should remain the same for the subject throughout the study.
- Obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory. Repeat testing if indicated as described in Table 5.2.
- Record concomitant medications.
- Assess for AEs.

6.4.16. Cycle 3, Day 2 (Dose Escalation Part Only)

The following procedures will be performed on Cycle 3, Day 2 of the Dose Escalation Part only:

- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Record concomitant medications.
- Assess for AEs.

6.4.17. Cycle 3, Day 4 (Dose Escalation and Dose Finding [Q2W Dosing Cohort] Only)

The following procedures will be performed on Cycle 3, Day 4 (± 1 day) of the Dose Escalation and Dose Finding (Q2W Dosing Cohort) Parts:

- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Record concomitant medications.
- Assess for AEs.

6.4.18. Cycle 3, Day 8 (All Parts)

The following procedures will be performed on Cycle 3, Day 8:

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature).

- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain blood samples for safety laboratories (Section 8.8).
- Record concomitant medications.
- Assess for AEs.

6.4.19. Cycle 3, Day 15 (All Parts)

The following procedures will be performed on Cycle 3, Day 15:

Cycle 3, Day 15 (± 2 days) for Dose Escalation, Dose Finding (Q3W Dosing Cohorts and Q3W Dosing with Up-titration Cohorts), and Dose Expansion Parts

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain blood samples for safety laboratories, if applicable, as indicated in Section 8.8.
- Record concomitant medications.
- Assess for AEs.

Cycle 3, Day 15 (± 2 days; if Applicable) for Q2W Dosing Schedules

- If the dose of U3-1402 is delayed for ≥3 days, including if the subject cannot continue onto the next cycle, the following procedures should be performed on Cycle 3, Day 15 (± 2 days):
  - Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
  - Assess for AEs.
  - Record concomitant medications.

6.4.20. Cycle 3, Day 22 (if Applicable; for Dose Escalation, Dose Finding [Q3W Dosing and Q3W Dosing with Up-titration], and Dose Expansion Parts)

If the dose of U3-1402 is delayed for ≥3 days, including if the subject cannot continue onto the next cycle, the following procedures will be performed on Cycle 3, Day 22 (± 2 days):

- Perform a 12-lead ECG in triplicate, if applicable, as indicated in Table 6.1.
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Record concomitant medications.
- Assess for AEs.

6.4.21. Cycle 4 and Subsequent Cycles, Day 1 (All Parts)

Pre-infusion

The following procedures must be completed pre-infusion:

- Record concomitant medications.
- Assess for AEs.
- Perform a 12-lead ECG in triplicate as indicated in Table 6.1.

Within 7 days prior to infusion

- Day 1 of Cycle 5 and every 4 cycles thereafter to EOT (eg, Day 1 of Cycle 5, 9, 13...)
- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, fundoscopy and tonometry. Investigators must ensure results of ophthalmologic assessments are available for review prior to dosing on corresponding cycle visits. Repeat ophthalmologic assessments are not required in the event of dose delays that occur after examination if there were no abnormal findings. Ophthalmologic assessments may be repeated per Investigator discretion.

Within 3 days prior to infusion

- Perform a complete physical examination and record weight.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, body temperature, and SpO_2).
- Perform either ECHO or MUGA (LVEF). Investigators must ensure results of ECHO/MUGA are available for review prior to dosing on corresponding cycle visits. Repeat ECHO/MUGA assessments are not required in the event of dose delays that occur after examination if there were no abnormal findings. ECHO or MUGA may be repeated per Investigator discretion.
- Obtain blood samples for safety laboratories (Section 8.8).

Within 8 hours prior to infusion

- Cycle 4, Day 1; Cycle 5, Day 1; Cycle 6, Day 1; and Cycle 8, Day 1 only
  - Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Cycle 4, Day 1 and every 2 cycles thereafter to EOT (eg, Day 1 in Cycle 4, 6, 8, 10)
  - Obtain blood sample for ADA (Section 6.10.6).

COVID-19 Sample

- Cycle 5, Day 1 and every 4 cycles thereafter, and at EOT (Day 1 in Cycle 5, 9, etc.)
  - Obtain a serum sample for coronavirus disease 2019 (COVID-19) testing from each subject who provides consent (Appendix 17.9).

Administration

- Administer U3-1402 via IV infusion and record start and stop times.
- Refer to Pharmacy Instruction for preparation information of U3-1402.
- Refer to Section 5.2.4 for information regarding administration of U3-1402.
- Refer to Table 5.2 for information regarding infusion reactions.

Post-Infusion

The following procedures will be completed at post-dose on Day 1:

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature; only in Cycle 4, Day 1 of Q2W Dosing Cohorts).
- Cycle 4, Day 1; Cycle 5, Day 1; and Cycle 6, Day 1 only
  - Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety and repeat as needed (see Table 5.2). The test used to detect troponin should remain the same for the subject throughout the study.
- Obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory. Repeat testing if indicated as described in Table 5.2.
- Record concomitant medications.
- Assess for AEs.

6.4.22. Cycle 4, Day 8 (± 2 days) for Dose Finding (Q2W Dosing Cohort) Part

The following procedures will be performed on Cycle 4, Day 8 (± 2 days):

- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, and body temperature).
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Obtain blood samples for safety laboratories (Section 8.8).
- Record concomitant medications.
- Assess for AEs.

6.4.23. Cycle 4, Day 15 (± 2 days) for Dose Finding (Q2W Dosing Cohort) Part

The following procedures will be performed on Cycle 4, Day 15 (± 2 days):

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.

- Obtain blood samples for safety laboratories, if applicable, as indicated in Section 8.8.
- Record concomitant medications.
- Assess for AEs.

6.4.24. Cycle 4, Day 22 (± 2 days) for Dose Finding (Q2W Dosing Cohort) Part

If the dose of U3-1402 is delayed for ≥3 days, including if the subject cannot continue onto the next cycle, the following procedures will be performed on Cycle 4, Day 22 (± 2 days):

- Obtain PK blood samples, if applicable, as indicated in Section 6.10.3.
- Record concomitant medications.
- Assess for AEs.

6.5. Washout

Not applicable.

6.6. Check-out or Early Termination

See Section 5.7.

6.7. End of Treatment

The date of discontinuation of treatment is defined as the date of decision by Investigator. The following assessments will be performed at the EOT Visit (within 7 days after the date of discontinuation). If the EOT assessment is performed in the treatment period, then it may be considered as EOT data and need not be repeated.

- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential. For postmenopausal subjects (no childbearing potential, as indicated by an elapse of at least 12 months after the last menstruation) or female subjects who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of childbearing potential and required to undergo the pregnancy test.
- Perform a complete physical examination and record weight.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Obtain vital sign measurements (systolic and diastolic blood pressures, pulse rate, body temperature, and SpO_2).
- Perform a 12-lead ECG in triplicate.
- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination fundoscopy and tonometry.
- Perform either ECHO or MUGA (LVEF).

- Obtain blood samples for ADA (Section 6.10.6).
- Obtain blood samples for safety laboratories and cTnT (alternatively cTnI) (Section 8.8).
- Obtain blood sample for cTnI to be sent to central laboratory (Section 6.10.5).
- Obtain a serum sample for COVID 19 testing from each subject who provides consent (Appendix 17.9).
- [Dose Expansion Part Only] Obtain blood samples for HER3ECD, cfDNA, and cfRNA (Section 6.10.5).
- [Dose Expansion Part Only] **Optional** tumor biopsy should be obtained from primary tumor or a metastatic site, preferably from a site of recent radiographic progression, within 30 days of the date of discontinuation and prior to starting any new anticancer treatment.
- Perform same imaging tumor assessment as at the time of screening by CT or MRI scans. If the previous tumor assessment was performed within the last 21 days, this assessment does not need to be performed. CT or MRI scans of the chest, abdomen and pelvis are mandatory. CT or MRI of the brain should be performed in subjects with baseline brain metastases or if clinically indicated.
- Record concomitant medications.
- Assess for AEs.
- Record reason for treatment discontinuation.

6.8. Follow-up

The F/U visit should occur 28 days (– 7 days) after the last administration of U3-1402. If the subject begins another anticancer therapy before the end of the 28 days (– 7 days), every effort will be made to complete all the F/U assessments prior to commencing the new therapy. In case of unresolved AEs, the Investigator will follow the AEs until the event has resolved or the condition has stabilized as possible. If assessments at EOT or in the treatment period are performed within this period, they can be considered as the F/U data and there is no need to repeat them. If discontinuation of treatment is decided later than 28 days after the last administration of U3-1402, there is no need to perform the F/U visit.

The following information will be collected at this F/U visit:

- Perform a complete physical examination and record weight.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories (Section 8.8) and ADA* (Section 6.10.6).

  *For subjects with positive ADA at F/U visit (or EOT visit if F/U visit was not performed), additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing

ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

- Record concomitant medications.
- Assess for AEs.

6.9. New Cancer Treatment and Survival Follow-up

After discontinuation from all study treatment, follow-up information for survival and subsequent anticancer therapy, if available, will be obtained approximately every 3 months from the date of F/U visit or Safety Follow-up, whichever is later, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first. If direct contacts are not possible due to withdrawal of consent or loss to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws.

Subsequent anticancer treatment and survival follow-up information will not be collected after the implementation of protocol Version 8.0, which occurs upon the IRB approval of protocol Version 8.0 at study sites.

6.10. Pharmacokinetics, Pharmacodynamics, Exploratory Biomarkers, and Anti-drug Antibodies

6.10.1. Blood Sampling

Blood samples for PK, exploratory biomarkers (eg, HER3ECD, cfDNA, cfRNA and cTnI), and ADA will be collected into blood sampling tubes supplied by the Sponsor. The collected blood will be centrifuged to separate the serum/plasma. The serum samples will be shipped to a central laboratory.

Refer to the Laboratory Manual for information regarding the handling of blood samples and shipping of serum samples.

6.10.2. Tumor Sampling

In the Dose Expansion part, for those subjects with HER3-positive tissue assayed using an archived tumor tissue sample, a fresh tumor biopsy should be collected before the first dose of U3-1402. This fresh tumor biopsy is **optional** for the Dose Finding Part.

It is recommended (although optional) to perform a tumor biopsy approximately 48 to 72 hours after the end of infusion of U3-1402 on Cycle 2, Day 1 in the Dose Expansion Part. Additionally, blood samples for HER3ECD, cfDNA, cfRNA, and PK assessments should be collected ± 4 hours from the time of this optional biopsy, if obtained. A minimum of 20 subjects in the HER3-high, HR-positive cohorts, a minimum of 6 subjects in the HER3-low, HR-positive cohort and a minimum of 9 subjects in the HER3-high, TNBC cohort will be required to submit on-treatment biopsies during the Dose Expansion Part.

An **optional** tumor biopsy may be performed at EOT in the Dose Expansion Part.

Tissue from these biopsies will be examined for biomarkers, mutational status (DNA/RNA), and gene expression analysis (RNA) to elucidate mechanism of action and resistance to study drug.

Refer to the Laboratory Manual for information regarding archived and/or fresh tumor tissue requirements.

Any SAEs directly related to a tumor biopsy procedure performed after signing the appropriate ICF should be reported according to Section 8.5.

6.10.3. Pharmacokinetic

Blood samples of approximately 5 mL for PK analyses will be collected at the time points as specified in Table 6.2, Table 6.3, Table 6.4, Table 6.5, and Table 6.6.

The actual time of study drug administration and the exact time of blood sampling must be recorded in source document and the eCRF.

6.10.3.1. Dose Escalation Part Pharmacokinetic Sampling Time Points

Table 6.2: Pharmacokinetic Sampling Time Points (Dose Escalation Part)

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	• BI (– 8 hours)[a] • EOI (within 30 minutes after EOI)[a] • 2 hours after the start of infusion (± 15 minutes)[a] • 4 hours after the start of infusion (± 15 minutes)[a] • 7 hours after the start of infusion (± 15 minutes)[a]
	Day 2	24 hours after the start of infusion (± 2 hours)[a]
	Day 4	3 days after the start of infusion (± 1 day)[a]
	Day 8	7 days after the start of infusion (± 1 day)
	Day 15	14 days after the start of infusion (± 1 day)
	Day 22[b]	21 days after the start of infusion (+ 2 days)[a]
Cycle 2	Day 1	• BI (– 8 hours)[a,c] • EOI (within 30 minutes after EOI)
	Day 8	7 days after the start of infusion (± 2 days)
	Day 15	14 days after the start of infusion (± 2 days)
	Day 22[b]	21 days after the start of infusion (± 2 days)
Cycle 3	Day 1	• BI (– 8 hours)[a] • EOI (within 30 minutes after EOI)[a] • 2 hours after the start of infusion (± 15 minutes)[a] • 4 hours after the start of infusion (± 15 minutes)[a] • 7 hours after the start of infusion (± 15 minutes)[a]
	Day 2	24 hours after the start of infusion (- 2 to + 4 hours, within 15 minutes after the end of ECG measurement)[a]
	Day 4	3 days after the start of infusion (± 1 day)[a]
	Day 8	7 days after the start of infusion (± 2 days)
	Day 15	14 days after the start of infusion (± 2 days)
	Day 22[b]	21 days after the start of infusion (± 2 days)[a]
Cycle 4	Day 1	BI (– 8 hours)[a,c]
Cycle 6 and Cycle 8	Day 1	BI (– 8 hours)

BI = before infusion; ECG = electrocardiogram; EOI = end of infusion; PK = pharmacokinetic.

[a] Blood for PK should be collected within 15 minutes of the end of ECG measurement.

[b] If dosing for the next cycle is delayed for ≥3 days, including if the subject cannot continue onto the next cycle.

[c] If blood for PK was collected on Day 22 of the previous cycle, a PK blood sample should be collected BI (−8 hours), if possible.

6.10.3.2. Dose Finding Part Pharmacokinetic Sampling Time Points

Table 6.3: Q3W Dosing Cohorts

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	• BI (– 8 hours)[a] • EOI (within 30 minutes after EOI)[a] • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes)[a] • 7 hours after the start of infusion (± 15 minutes)
	Day 2	24 hours after the start of infusion (± 2 hours)
	Day 4	3 days after the start of infusion (± 1 day)
	Day 8	7 days after the start of infusion (± 1 day)[a]
	Day 15	14 days after the start of infusion (± 1 day)
	Day 22[b]	21 days after the start of infusion (+ 2 days)
Cycle 2	Day 1	• BI (– 8 hours)[c] • EOI (within 30 minutes after EOI)
Cycle 3	Day 1	• BI (– 8 hours)[a] • EOI (within 30 minutes after EOI)[a] • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes)[a] • 7 hours after the start of infusion (± 15 minutes)
	Day 8	7 days after the start of infusion (± 2 days)[a]
	Day 15	14 days after the start of infusion (± 2 days)
	Day 22[b]	21 days after the start of infusion (± 2 days)
Cycle 4	Day 1	BI (– 8 hours)[c]
Cycle 5	Day 1	• BI (– 8 hours) • EOI (within 30 minutes of the EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
Cycle 6 and Cycle 8	Day 1	BI (– 8 hours)

BI = before infusion; ECG = electrocardiogram; EOI = end of infusion; PK = pharmacokinetic.
[a] Blood for PK should be collected within 15 minutes of the end of ECG measurement.
[b] If dosing for the next cycle is delayed for ≥3 days, including if the subject cannot continue onto the next cycle.
[c] If blood for PK was collected on Day 22 of the previous cycle, a PK blood sample should be collected BI (−8 hours), if possible.

Table 6.4: Q3W Dosing with Up-titration Cohorts

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	• BI (– 8 hours) • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
	Day 8	7 days after the start of infusion (± 1 day)
	Day 15	14 days after the start of infusion (± 1 day)
	Day 22[a]	21 days after the start of infusion (+ 2 days)
Cycle 2	Day 1	• BI (– 8 hours)[b] • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
	Day 8	7 days after the start of infusion (± 2 days)
	Day 15	14 days after the start of infusion (± 2 days)
	Day 22[a]	21 days after the start of infusion (± 2 days)
Cycle 3	Day 1	• BI (– 8 hours)[b] • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
	Day 8	7 days after the start of infusion (± 2 days)
	Day 15	14 days after the start of infusion (± 2 days)
	Day 22[a]	21 days after the start of infusion (± 2 days)
Cycle 4	Day 1	BI (– 8 hours)[b]
Cycle 5	Day 1	• BI (– 8 hours) • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
Cycle 6 and Cycle 8	Day 1	BI (– 8 hours)

BI = before infusion; EOI = end of infusion; PK = pharmacokinetic.

[a] If dosing for the next cycle is delayed for ≥3 days, including if the subject cannot continue onto the next cycle.

[b] If blood for PK was collected on Day 22 of the previous cycle, a PK blood sample should be collected BI (−8 hours), if possible.

Table 6.5: Q2W Dosing Cohorts

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	• BI (– 8 hours) • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
	Day 4	3 days after the start of infusion (± 1 day)
	Day 8	7 days after the start of infusion (± 1 day)
	Day 15[a]	14 days after the start of infusion (+ 2 day)
Cycle 2	Day 1	• BI (– 8 hours)[b] • EOI (within 30 minutes after EOI)
Cycle 3	Day 1	• BI (– 8 hours) • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
	Day 4	3 days after the start of infusion (± 1 day)
	Day 8	7 days after the start of infusion (± 2 days)
	Day 15[a]	14 days after the start of infusion (± 2 days)
Cycle 4	Day 1	• BI (– 8 hours)[b] • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
	Day 8	7 days after the start of infusion (± 2 day)
	Day 15	14 days after the start of infusion (± 2 days)
	Day 22[a]	21 days after the start of infusion (± 2 days)
Cycle 5	Day 1	BI (– 8 hours)[c]
Cycle 6	Day 1	• BI (– 8 hours) • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
Cycle 8	Day 1	BI (– 8 hours)

BI = before infusion; EOI = end of infusion; PK = pharmacokinetic.

[a] If dosing for the next cycle is delayed for ≥3 days, including if the subject cannot continue onto the next cycle.

[b] If blood for PK was collected on Day 15 of the previous cycle, a PK blood sample should be collected BI (−8 hours), if possible.

[c] If blood for PK was collected on Day 22 of the previous cycle, a PK blood sample should be collected BI (−8 hours), if possible.

6.10.3.3. Dose Expansion Part Pharmacokinetic Sampling Time Points

Table 6.6: Pharmacokinetic Sampling Time Points (Dose Expansion Part)

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	• BI (– 8 hours)[a] • EOI (within 30 minutes after EOI)[a] • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes)[a] • 7 hours after the start of infusion (± 15 minutes)
	Day 2	24 hours after the start of infusion (± 2 hours)
	Day 4	3 days after the start of infusion (± 1 day)
	Day 8	7 days after the start of infusion (± 1 day)[a]
	Day 15	14 days after the start of infusion (± 1 day)
	Day 22[b]	21 days after the start of infusion (+ 2 days)
Cycle 2	Day 1	• BI (– 8 hours)[c] • EOI (within 30 minutes after EOI)
	Day 3	± 4 hours from the time of optional biopsy, if obtained
Cycle 3	Day 1	• BI (– 8 hours)[a] • EOI (within 30 minutes after EOI)[a] • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes)[a] • 7 hours after the start of infusion (± 15 minutes)
	Day 8	7 days after the start of infusion (± 2 days)[a]
	Day 15	14 days after the start of infusion (± 2 days)
	Day 22[b]	21 days after the start of infusion (± 2 days)
Cycle 4	Day 1	BI (– 8 hours)[c]
Cycle 5	Day 1	• BI (– 8 hours) • EOI (within 30 minutes after EOI) • 2 hours after the start of infusion (± 15 minutes) • 4 hours after the start of infusion (± 15 minutes) • 7 hours after the start of infusion (± 15 minutes)
Cycle 6 and Cycle 8	Day 1	BI (– 8 hours)

BI = before infusion; ECG = electrocardiogram; EOI = end of infusion; PK = pharmacokinetic.
[a] Blood for PK should be collected within 15 minutes of the end of ECG measurement.
[b] If dosing for the next cycle is delayed for ≥3 days, including if the subject cannot continue onto the next cycle.
[c] If blood for PK was collected on Day 22 of the previous cycle, a PK blood sample should be collected BI (−8 hours), if possible.

6.10.4. Pharmacodynamics

Not applicable.

6.10.5. Exploratory Biomarkers

Based on the evaluation of pre-treatment tumor sample, the levels of HER3 in fresh biopsies will be assessed by IHC. The exploratory biomarkers (eg, HER3ECD, mRNA, cfDNA, cTnI, and PD-L1) will be assessed accordingly, at pre-treatment, on-treatment, and post-treatment time points. Tissue biopsy samples will be used for analyses of IHC, and mRNA; and liquid biopsy will be used for analyses of proteins, mRNA, cfRNA, and cfDNA.

The purpose of the HER3ECD assay is to determine its potential to be a predictive marker of drug efficacy or a surrogate for IHC.

A variety of assays may be used to help us to understand U3-1402 mechanism of action (ie, tumor cell apoptosis, immune profiling), mechanism of resistance (ie, downregulation / mutation of HER3, loss of ADC internalization, attenuation of cathepsin levels/activity, upregulation of drug export, etc.) and correlation of biomarkers with clinical activity (ie, HER3ECD, mutational profiling of cfDNA, cfRNA, and mRNA).

cTnI will be assessed as an exploratory biomarker for drug safety.

Blood samples of approximately 4 mL for HER3ECD analyses will be collected at the time points specified in Table 6.7.

Table 6.7: HER3ECD Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Screening (Dose Escalation and Dose Finding Parts Only)	-	Latest data within 7 days prior to enrollment
Cycle 1 (Dose Expansion Part Only)	Day 1	BI (– 8 hours)
Cycle 2 (Dose Expansion Part Only, if optional tumor biopsy is obtained)	Day 3	±4 hours from time of biopsy, if obtained
EOT (Dose Expansion Part Only)	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days)

EOT = end of treatment; BI = before infusion.

Refer to the Laboratory Manual for information regarding the handling and shipping of blood samples.

Blood samples of approximately 10 mL for cfDNA analyses and 10 mL for cfRNA analyses will be collected at the time points specified in Table 6.8.

Table 6.8: cfDNA and cfRNA Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1 (Dose Expansion Part Only)	Day 1	BI (– 8 hours)
Cycle 2 (Dose Expansion Part Only, if optional tumor biopsy is obtained)	Day 3	± 4 hours from time of optional biopsy, if obtained
EOT (Dose Expansion Part Only)	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days)

EOT = end of treatment; BI = before infusion.

Refer to the Laboratory Manual for information regarding the handling and shipping of whole blood samples.

Blood samples of approximately 4 mL for cTnI analyses will be collected at the time points specified in Table 6.9.

Table 6.9: cTnI Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Screening	-	Latest data within 7 days prior to enrollment
At every cycle	Day 1	3 hours after EOI (± 1 hour)
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days)

EOI = end of infusion; EOT = end of treatment.

Refer to the Laboratory Manual for information regarding handling and shipping of serum samples.

Exploratory biomarker (HER3ECD, cfDNA, cfRNA) samples will not be collected after the implementation of protocol Version 8.0, which occurs upon the IRB approval of protocol Version 8.0 at study sites.

6.10.6. Anti-Drug Antibodies

Blood samples for ADA of approximately 4 mL analyses will be collected at the time points specified in Table 6.10. Serum concentrations of U3-1402 and/or total anti-HER3 antibody may be measured using the same ADA samples for purpose of anti-drug antibody assessment.

Refer to the Laboratory Manual for information regarding the handling and shipping of serum samples.

Table 6.10: ADA Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1 Day 8	BI (– 8 hours) 7 days after infusion (± 1 day)
Cycle 2	Day 1	BI (– 8 hours)
After Cycle 4 at every 2 cycles (eg, Cycle 4, 6, 8, 10, 12...)	Day 1	BI (– 8 hours)
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days)
F/U visit[a]	-	28 days (− 7 days) after the last study drug administration or until starting new anticancer treatment, whichever comes first

BI = before infusion; EOT = end of treatment; F/U = follow up.

[a] For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

7. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

7.1. Pharmacokinetic Assessment(s)

The serum PK parameters listed in Table 7.1 of U3-1402, total anti-HER3 antibody and MAAA-1181a for each subject will be estimated using standard noncompartmental methods. The other PK parameters (elimination rate constant associated with the terminal phase [Kel], $T_{1/2}$, CL, volume of distribution based on the terminal phase [Vz], and Vss) will be calculated if data permits. Population PK and exposure-response analyses for U3-1402, total anti-HER3 antibody and MAAA-1181a will be performed to characterize the relationships between dose and exposure and between exposure and efficacy and/or safety endpoints. If performed, results of population PK or exposure-response analyses will be reported separately (ie, not in the Clinical Study Report).

Table 7.1: Pharmacokinetic Parameters

Analyte	PK parameters
U3-1402, total anti-HER3 antibody and MAAA-1181a	AUClast, AUCtau, Cmax, Tmax, Ctrough

7.2. Pharmacodynamic Assessment(s)

Not applicable.

7.3. Biomarker and Exploratory Assessment(s)

Subjects will be requested to provide a tumor sample for assessing HER3 expression at study entry and optionally at some additional time points during the course of clinical study.

Clinical samples, including tumor tissue and blood, will be retained until the end of the defined storage period and may be analyzed for exploratory research purposes. The sample collection information should be recorded in the eCRF.

Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the Laboratory Manual.

All subjects will be asked to provide written consent to supply tumor tissue (archival tissue or fresh tumor biopsy) and blood samples for research purposes prior to study entry.

7.3.1. HER3 expression

The level of HER3 expression will be assessed by IHC using archival or fresh biopsy provided by the patient. In the Dose Expansion Part, the level of HER3 expression in pre-study treatment, on-study treatment and post-study treatment will be assessed with the biopsy sample.

7.3.1.1. Tumor Sample Collection

Refer to the Laboratory Manual for instructions regarding archived and fresh tumor tissue handling and shipping.

Study Entry

Tissue to analyze for HER3 expression for study eligibility may be obtained from fresh tumor biopsy or from archived tumor samples.

- A fresh tumor biopsy may be requested from subjects with a HER3-negative tissue result that was assayed using an archived tumor tissue sample. Tumor tissue obtained from this fresh biopsy should be sent to the central laboratory for the re-assay of the HER3 status. Tumor samples must be obtained after the date of informed consent for tumor screening.

Pre-treatment Biopsy

- For the Dose Finding Part, perform an **optional** tumor biopsy for subjects with HER3-positive tissue that was assayed using an archived tumor tissue sample. Tumor tissue from the fresh biopsy should be sent to the central laboratory for analysis of HER3 IHC; these results are not required for study entry.
- For the Dose Expansion Part, perform a tumor biopsy for subjects with HER3-positive tumor tissue that was assayed using an archived tumor tissue sample. Tumor tissue from this fresh biopsy should be sent to the central laboratory for analysis of HER3 IHC; these results are not required for study entry.

On-study Biopsy (Dose Expansion Part Only)

An **optional** on-study tumor biopsy may be performed approximately 48 to 72 hours after the end of the U3-1402 infusion on Cycle 2, Day 1. Additionally, blood for HER3ECD, cfDNA, cfRNA, and PK should be collected ± 4 hours from the time of this optional biopsy, if obtained. A minimum of 20 subjects in the HER3-high, HR-positive cohorts, a minimum of 6 subjects in the HER3-low, HR-positive cohort, and a minimum of 9 subjects in the HER3-high, TNBC cohort will be required to submit on-treatment biopsies during the Dose Expansion Part. Consent for this biopsy should be documented in the tissue consent portion of the ICF. Tumor tissue from this biopsy should be obtained from the primary tumor or metastatic site.

End-of-treatment Biopsy (Dose Expansion Part Only)

An **optional** end-of-treatment tumor biopsy may be performed at the time of progression or discontinuation from study treatment. Consent for this biopsy should be documented in the tissue consent portion of the appropriate ICF. Tumor biopsy should be obtained from the primary tumor or a metastatic site, preferably from a site of recent radiographic progression, within 30 days of the date of discontinuation, and prior to starting any new anticancer treatment.

Any SAEs directly related to a tumor biopsy procedure and performed after signing the appropriate ICF should be reported according to Section 8.5.

7.3.2. Biomarker Assessments in Tumor Tissue and Blood Samples

The biomarkers will be analyzed with the intent of identifying those subjects who will most likely derive clinical benefit from treatment with U3-1402. Further exploratory tissue or blood-based biomarkers may be analyzed based on emerging scientific knowledge to better understand the target disease and also possibly the effects of study treatment.

Exploratory analysis will be done to assess the status of some biomarkers (eg, HER3ECD, mRNA, cfDNA, cfRNA, PD-L1 and cTnI).

During the study, in addition to the biomarkers specified above, other exploratory biomarker research may be conducted on tissue and/or blood samples. These studies would extend the search for other potential biomarkers relevant to the effects of U3-1402, cancer, and/or resistance to the treatment. This may include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

The results from exploratory biomarker research may be pooled with biomarker data from other studies with the investigational product to generate hypotheses to be verified in future studies.

7.4. Immunogenicity

Blood samples will be obtained at the time points specified in Section 17.1. The details on immunogenicity blood sample collection, handling and shipment are described in the Laboratory Manual. The immunogenicity testing will be performed using a validated anti-drug antibodies (ADA) assay which is comprised of tiered steps including screening, confirmatory as well as titer determination. ADA samples confirmed positive will be banked until availability of a neutralizing anti-drug antibody assay.

Immunogenicity will be assessed through characterization of incidence and titer of ADA. The number and percentage of subjects will be calculated for the presence or absence of development of ADA after the start of administration, defining subjects who are negative for ADA at all time points as negative and subjects who are positive for ADA at least 1 time point as positive. The raw values and change from baseline for ADA titers will be summarized by time point and treatment group using descriptive statistics.

7.5. Pharmacogenomic Analysis

7.5.1. Genomic or Genetic Banking and Analysis

7.5.1.1. Genomic or Genetic Banking and Analysis

In the Dose Expansion Part, a single blood sample (20 mL) for cfDNA (10 mL) and cfRNA (10 mL) analysis will be collected pretreatment on Cycle 1, Day 1; on treatment Cycle 2, Day 3; and at EOT from subjects who provide consent.

Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of the study drug. Additionally, samples may be analyzed for genes involved in study drug-related signaling pathways, or to examine diseases or physiologic processes related to the study drug. Subject samples will not be sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

7.5.1.2. Collection of Specimens for Genomic or Genetic Banking and Analysis

Instructions for collection of specimens for genomic or genetic banking and analysis are included in the Laboratory Manual.

7.5.1.3. Disclosure of the Results of Genomic or Genetic Analysis

Because the nature and value of future pharmacogenomic research cannot be known at this time, any results obtained from research involving pharmacogenomic samples will not be disclosed to the subject or Investigators now or in the future.

7.5.1.4. Storage and Disposal of Specimens for Genomic or Genetic Banking and Analysis

Samples will be retained until exhausted, or 15 years if required by local regulations, or until the Sponsor requests disposition.

If the subject withdraws consent, the banked tumor and blood samples will be promptly managed regarding proper disposition. However, the data will not be discarded if genetic analysis has been completed before the subject withdraws consent.

8. SAFETY EVALUATION AND REPORTING

8.1. Assessment of Safety Endpoint Event(s)

Safety endpoints will include DLTs, SAEs, TEAEs, AESIs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic assessments. Dose escalation will be determined by the incidence of DLTs.

8.2. Adverse Event Collection and Reporting

All clinical AEs occurring after the subject signs the ICF and up to F/U visit after the last dose of study drug (ie, the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event Case Report Form (CRF) page. Medical conditions (including clinical laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history.

All AEs, AESIs, events of overdose, and SAEs are to be reported according to the procedures in Section 8.5.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal clinical laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each time point, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each time point. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 8.4. The Investigator's assessment must be clearly documented in the study site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 8.4.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Progressive disease is a study endpoint and consequently, should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, "Progressive disease" should be reported as an SAE. In addition, any serious, untoward event that may occur

subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE. The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

8.3. Adverse Events of Special Interest

Based on the available preclinical data, review of the cumulative literature, and reported AEs for agents of the same class of ADC components of monoclonal antibody or payload of U3-1402; the events described below are considered to be AESIs. AESIs will be collected through targeted questionnaires within the eCRF or via paper form (in the event an eCRF is unavailable). Please refer to the IB for additional information.

8.3.1. Cardiotoxicity (Cardiac-related Events Including QT Prolongation and LVEF Decreased)

LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs must be evaluated by the Investigator or a delegated physician for monitoring cardiac function. The same modality (ECHO or MUGA) should be used for the subject throughout the study. In addition, standard ECG parameters will be measured, including RR, PR, and QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or a delegated physician for the presence of abnormalities. In this study, cTnI testing will be used as an exploratory biomarker in parallel with standard clinical assessments of cardiac function (eg, ECHO/MUGA and ECG).

8.3.2. Pulmonary Toxicity (Interstitial Lung Disease/Pneumonitis)

If a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If ILD/pneumonitis is suspected, delay U3-1402 dosing pending further evaluation. Refer to Table 5.2 for guidance on further evaluation and management of ILD/pneumonitis.

8.3.2.1. Interstitial Lung Disease Adjudication Committee

An independent ILD Adjudication Committee for U3-1402 is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This data collection will be triggered for adverse events reported using MedDRA preferred terms (PT) from the current ILD Standard MedDRA Query (SMQ) and the PTs of acute respiratory failure and respiratory failure.

8.3.3. Hepatotoxicity (Potential Hy's Law)

All hepatic events (both serious and non-serious, and clinical laboratory results) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur simultaneously or at different time points during the study, regardless of whether these hepatic events are symptomatic, lead to study drug discontinuation, dose reduction or dose interruption, require corrective treatment, constitute an AE in the Investigator's clinical judgment and/or are related to disease progression.

8.4. Adverse Event

8.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal clinical laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Council for Harmonization (ICH) E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal clinical laboratory findings which should be considered AEs.

8.4.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

8.4.3. Severity Assessment

All AEs will be graded (1 to 5; see below) according to the NCI-CTCAE version 5.0:

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

Severity vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

8.4.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

    or
  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study or its chemical group or is predicted by known pharmacology.
- Unrelated:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

8.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study product was permanently stopped.
- Dose Reduced: The dosage of study product was reduced.
- Drug Interrupted: The study product was temporarily stopped.
- Not Applicable

8.4.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or OTC medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

8.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed.
- Recovering/Resolving
  - The AE improved but has not fully resolved.
- Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- Unknown

8.5. Serious Adverse Events Reporting – Procedure for Investigators

All AEs, AESIs, events of overdose, and SAEs will be reported in the CRF.

Serious events that are also efficacy endpoints (disease progression) will be exempted from SAE processing and expedited reporting. Disease progression should not be reported as an AE/SAE. However, if a subject dies from disease progression with no other immediate causes, “disease progression” should be reported as an SAE and captured on designated eCRF.

The following types of events should be reported by the Investigator in electronic data capture (EDC) within 24 hours of awareness:

- SAEs (see Section 8.4.2 for definition)

- All potential ILD/pneumonitis cases should be reported within 24 hours; including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is defined by the Event Adjudication Site Manual List of Preferred Terms [PTs]).
- All hepatic events (both serious and non-serious, and clinical laboratory results) which meet the potential Hy's Law criteria defined as an elevated ALT or AST ≥3 × ULN and an elevated total bilirubin >2 × ULN that may occur simultaneously or at different time points during the study, regardless of whether these hepatic events are symptomatic, lead to study drug discontinuation, dose reduction or dose interruption, require corrective treatment, constitute an AE in the Investigator's clinical judgment and/or are related to disease progression (see Section 8.3 for details).
- Overdose, defined as the accidental or intentional administration of any dose of study drug that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs, and is considered by the Investigator as clinically relevant, ie, poses an actual or potential risk to the subject.

All events (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed and include the results if available. Source documents (including medical reports) will be retained at the study center and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries and follow-up information such as those upgraded to fatal/life threatening case must be followed up and addressed promptly. The investigator will submit any updated SAE data to the CRO/sponsor within 24 hours of receipt of the information. Other follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up. In the event that eCRF is unavailable, report SAEs on a Serious Adverse Event Report (SAVER) form. All completed SAVER forms must be signed by the Investigator and e-mailed or faxed to the Sponsor or the CRO using the provided fax transmittal form and the appropriate fax number provided for your country.

Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

8.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

Daiichi Sankyo and/or CRO will inform Investigators, IRBs/Ethics Committees (ECs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs)

occurring in other sites as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the investigational product, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

In Japan, it is the Sponsor's responsibility to report all the fatal/life-threatening adverse reactions to the regulatory authorities regardless of expectedness, and SUSARs to the regulatory authorities and IRB/ECs.

8.7. Exposure in Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject or partner of a male subject who becomes pregnant while receiving or within 7 months of discontinuing the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject or a partner of a male subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The Investigator should make every effort to follow the subject or partner until completion of the pregnancy and complete the EIU Reporting form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 8.5.

8.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

Laboratory tests	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), mean platelet volume, reticulated platelet fraction[a]
Chemistry	Total protein, albumin, ALP, ALT, AST, total bilirubin, BUN, Ca, Cl, serum creatinine, lactate dehydrogenase (LDH), K, Na, Mg
Coagulation (only at Screening in Dose Expansion Part)	Prothrombin time, PT international normalized ratio (INR), partial thromboplastin time

[a] if available

In addition, the following laboratory tests will be performed at the visits indicated in Appendix 17.8.

- Cardiac troponin T (alternatively cardiac troponin I)

- Pregnancy test (serum or urine) for all female subjects of childbearing potential must be performed during the Screening Period. A positive urine pregnancy test result must be confirmed immediately using a serum test.

All laboratory values must be appraised by the Investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered clinically significant by the Investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, it should be reported by the Investigator with a targeted questionnaire is in-built as an eCRF or a SAVER form within 24 hours of awareness and other relevant procedures must be followed (see Section 8.5). Abnormal laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

8.9. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure and pulse rate and body temperature. Additionally, SpO_2 will be measured before administration on Day 1 of each cycle and EOT.

8.10. Electrocardiograms

Standard 12-lead ECGs in triplicate will be performed as described in the Schedule of Events (Table 17.7, Table 17.8, Table 17.9, and Table 17.10). Triplicate ECGs should be taken in close succession, a few minutes apart, after being in a supine/semi-recumbent position for 5 minutes. Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. All ECG data collected will be sent to the central laboratory for ECG analysis.

8.11. Physical Examinations

Physical examination findings including ECOG PS will evaluate the following body systems/organs: general appearance; dermatological; head and eyes; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/extremities; and neurological. Weight and height will also be recorded in kilograms and centimeters, respectively.

8.12. Other Examinations

Ophthalmologic assessments will include visual acuity testing, slit lamp examination, fundoscopy and tonometry. Ophthalmologic assessments must be evaluated by the Investigator or delegated physician.

LVEF will be measured by either ECHO or MUGA, as described in the Schedule of Events. All ECHO/MUGA assessments must be evaluated by the Investigator or delegate. The same modality (ECHO or MUGA) should be used for the subject throughout the study.

Additional safety assessments should be conducted as needed, per Investigator's discretion.

9. EFFICACY ASSESSMENTS

Efficacy endpoints will include ORR (the sum of CR rate and PR rate), DCR (the sum of CR rate, PR rate, and SD rate), DOR, CBR, TTR, PFS, OS, and percentage change in target lesion(s).

Tumor response will be evaluated using RECIST version 1.1 (Section 17.4) by the Investigator and the independent central imaging CRO selected by the Sponsor. Tumor assessments will be performed at screening and every 6 weeks in the first 24 weeks after Day 1 of Cycle 1 and every 12 weeks thereafter, independent of dosing schedule. Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1 and should continue until progressive disease or until a new anticancer therapy is started, whichever occurs first.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The primary analysis is to assess the efficacy, safety, and tolerability of U3-1402 in subjects with HER3-positive metastatic breast cancer and to determine the MTD/RDE or establish the safety and tolerability of the maximum administered dose of U3-1402.

The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or have been followed for at least 9 months following the first dose of study treatment, whichever is earlier. The primary analysis data cutoff may be extended if emerging data show responses are occurring later. The final analysis of the study will occur after all subjects have discontinued from the study. Data collected beyond the primary analysis cut-off time point will be presented as appropriate in a Clinical Study Report (CSR) addendum.

The data analyses will also be conducted during the Dose Escalation and Dose Finding Parts.

Descriptive statistics will be provided for selected demographic, safety, and PK data by cohort and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges (as well as geometric means and geometric coefficient of variation for Cmax and AUC PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last nonmissing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

Safety analyses will be performed based on the safety analysis set. Analysis of PK parameters will be based on the PK analysis set and biomarker analyses will be based on the Full Analysis Set (FAS). Efficacy endpoints will be analyzed based on the FAS. Data will be summarized by cohort, RDE cohort(s) (Dose Escalation and Dose Finding Parts), and overall.

A detailed Statistical Analysis Plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized before database lock. Statistical methods described within this document may be changed based on advances in research.

11.2. Analysis Sets

11.2.1. Full Analysis Set

The FAS will include all subjects enrolled in the study who received at least 1 dose of U3-1402.

11.2.1.1. Dose-Limiting Toxicity Evaluable Set

The DLT-evaluable set will include all subjects enrolled in the study who received at least 1 dose of U3-1402, with the exception of those subjects for whom DLT evaluation could not be adequately conducted.

11.2.1.2. Safety Analysis Set

The safety analysis set will include all subjects enrolled in the study who received at least 1 dose of U3-1402.

11.2.1.3. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects enrolled in the study who received at least 1 dose of U3-1402 and had measurable serum concentrations of U3-1402, total anti-HER3 antibody or MAAA-1181a.

11.3. Study Population Data

Disposition and reasons for ending the treatment and discontinuing from the study will be summarized and listed for subjects in the enrolled analysis set.

Demographic and baseline characteristics such as age, sex, race, ethnicity, baseline ECOG PS, histology, cancer stage, best response to prior chemotherapy, lines of prior regimens, and prior treatment type will be summarized for the FAS, and safety analysis set. If 2 analysis sets within a part of the study are identical to each other, the table will be presented only once.

11.4. Statistical Analysis

11.4.1. Efficacy Analyses

Efficacy endpoints will include ORR (the sum of CR and PR rates); DCR (the sum of CR rate, PR rate, and SD rate), DOR, CBR, TTR, PFS, OS, and percent change in target lesion(s). Tumor responses will be assessed by an Investigator and an independent central imaging CRO according to RECIST 1.1.

The efficacy endpoints will be listed and summarized. For ORR and DCR and CBR, point estimates 2-sided 95% exact binomial confidence intervals will be provided. Time to event variables including PFS, OS, TTR, and DOR will be summarized descriptively using the Kaplan-Meier method. PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic PD or death due to any cause. Censoring rules for the PFS analysis will be specified in the SAP.

Descriptive statistics for the best percent change from baseline in the sum of diameters of measurable tumors will be provided. A waterfall plot of the best percent change in the sum of diameters for each subject will be presented.

11.4.2. Pharmacokinetic Analyses

PK analyses will be performed on the PK analysis set. Serum concentration-time data for U3-1402, total anti-HER3 antibody and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics by cohort at each point and in study period.

PK parameters of U3-1402, total anti-HER3 antibody and MAAA-1181a will be listed and summarized using descriptive statistics.

The comparison of the PK profile between each region (Japan and the US) will also be assessed.

Serum concentration data will be used to perform a population PK modeling. The influences of intrinsic or extrinsic factor will be assessed in the population PK analysis. If performed, results of population PK analyses will be reported separately (ie, not in the Clinical Study Report).

11.4.3. Pharmacodynamic Analyses

Not applicable.

11.4.4. Biomarker and Exploratory Analyses

Explorative analyses for biomarkers will be listed and summarized using descriptive statistics.

11.4.5. Safety Analyses

Safety endpoints will include TEAEs, SAEs, AESIs, clinical laboratory measurements, vital sign measurements, ECG recordings, physical examination findings, ECHO/MUGA findings, and ophthalmologic findings. In the Dose Escalation Part, the incidence of DLTs will also be evaluated.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the Dose Escalation Part, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized by cohort. Additional details regarding safety analyses will be described in the SAP.

11.4.5.1. Adverse Event Analyses

A TEAE is defined as an AE that emerges or worsens during the on-treatment period. The on-treatment period is defined as from the start date of study treatment (inclusive) to 47 days after the end date of study treatment (inclusive). SAEs starting or worsening after the on-treatment period, if reported as related to the study treatment, are also considered TEAEs. The AE summary will only include TEAEs.

The number and percentage of subjects reporting TEAEs will be tabulated by the worst NCI-CTCAE grade, System Organ Class (SOC), and preferred term.

Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to U3-1402.

A by-subject AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, preferred term, SOC, NCI-CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from U3-1402, will be listed.

11.4.5.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for selected clinical laboratory test results (hematology and chemistry) and changes from baseline by scheduled time of evaluation, including the EOT visit, maximum post-treatment value, and minimum post-treatment value.

Abnormal laboratory results will be graded according to NCI-CTCAE version 5.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment

value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

11.4.5.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation, including the EOT visit and the maximum and minimum post-treatment values.

11.4.5.4. Electrocardiogram Analyses

Descriptive statistics will be provided for ECG parameters and changes from baseline by scheduled time of evaluation, including the EOT visit and the maximum post-treatment value. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms).

The QT intervals will be corrected for heart rate by Fridericia's formula ($QTcF = QT/[RR]^{1/3}$).

Relationship between drug concentrations and QTcF may be analyzed. This analysis will be performed for subjects across all dose levels.

11.4.5.5. Exploratory Safety Analyses

Not Applicable.

11.4.5.6. Other Safety Analyses

All other safety variables (physical examination findings including ECOG PS, ECHO/MUGA findings, and ophthalmologic findings) will be listed.

11.5. Sample Size Determination

The Dose Escalation Part of this study consists of mCRM with EWOC design with at least 3 DLT-evaluable subjects per dose level. Sample size has been determined by practical considerations and no formal statistical assessment has been performed for the Dose Escalation Part.

A total of approximately 12 subjects will be enrolled between Dose Escalation and Dose Finding for each of the Q3W Dosing Cohorts evaluated in Dose Finding. For the alternative dosing cohorts evaluated in Dose Finding, a total of approximately 12 subjects will be enrolled into each cohort. RDE(s) will be determined based on the risk and benefit assessment.

For the Dose Expansion Part, there are 4 planned expansion cohorts (HER3-high, HR-positive [6.4 mg/kg], HER3-high, HR-positive [4.8 mg/kg], HER3-low, HR-positive [6.4 mg/kg] and HER3-high, TNBC [6.4 mg/kg]):

- Approximately 60 eligible subjects with HER3-high, HER2-negative, HR-positive disease will be randomized into 1 of 2 cohorts: 4.8 mg/kg or 6.4 mg/kg.

- Subjects with HER3-low, HER2-negative, HR-positive breast cancer will not be randomized. Approximately 20 eligible subjects in this setting will be enrolled into a HER3-low, HR-positive (6.4 mg/kg) cohort.
- Subjects with HER3-high, TNBC will not be randomized. Approximately 30 eligible subjects in this setting will be enrolled into an HER3-high, TNBC (6.4 mg/kg) cohort.

A total of approximately 110 subjects will be enrolled into the Dose Expansion Part.

In HER3-high, HR-positive cohorts of the Dose Expansion Part, if target ORR is more than 10% (null hypothesis: ORR ≤0.10, alternative hypothesis: ORR >0.10), then the probability of no response out of 30 subjects will be less than 5%. The probability that more than 6 responders out of 30 subjects (ORR >20%) are observed will be less than 5% under the null hypothesis with ORR ≤0.10 but more than 80% under alternative hypothesis with ORR = 0.30.

In the HER3-low, HR-positive cohort of the Dose Expansion Part, if target ORR is more than 10% (null hypothesis: ORR ≤0.10, alternative hypothesis: ORR >0.10), then the probability of no response out of 20 subjects will be less than 15%. The probability that more than 3 responders out of 20 subjects (ORR >15.0%) are observed will be less than 15% under the null hypothesis with ORR ≤0.10 but more than 75% under alternative hypothesis with ORR = 0.25.

In the HER3-high, TNBC cohort of the Dose Expansion Part, if target ORR is more than 20% (null hypothesis: ORR ≤0.20, alternative hypothesis: ORR >0.20), then the probability of no response out of 30 subjects will be less than 5%. The probability that more than 9 responders out of 30 subjects (ORR >30.0%) are observed will be less than 10% under the null hypothesis with ORR ≤0.20 but more than 80% under alternative hypothesis with ORR = 0.40.

The probability values for the sample size are derived based on binomial distribution using SAS® version 9.4.

11.6. Statistical Analysis Process

The clinical study will be analyzed by DS or its agent/CRO followed by this protocol, and SAP which will demonstrate all methodologies and displays/shells for statistical analyses.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC 27513).

11.7. Specification of Modified Continuous Reassessment Method with Escalation with Overdose Control

11.7.1. Bayesian Logistic Regression Model for Modified Continuous Reassessment Method

The dose-toxicity relationship for mCRM with EWOC principle will be described by following 2-parameter BLRM:

$\text{logit}(\pi(d)) = \log(\alpha) + \beta \log(d/d^*)$, $\alpha>0$, $\beta>0$

where $\text{logit}(\pi(d)) = \ln(\pi(d)/(1-\pi(d)))$, $\pi(d)$ is the probability of a DLT or the DLT rate at dose d. Doses are rescaled as d/d^* with the reference dose $d^* = 9.7$ mg/kg. As a consequence, $\log(\alpha)$ is equal to $\text{logit}(\pi(d^*))$ at dose d^*. Note that for a dose equal to zero, the probability of toxicity is zero.

11.7.2. Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally-informative bivariate normal prior for the model parameters $(\log(\alpha),\log(\beta))$ is obtained as follows[21]:

- Based on extrapolation of nonclinical toxicology studies in monkeys, the MTD is projected to be greater than 9.7 mg/kg in humans (the HNSTD of monkeys is 30 mg/kg and assuming humans and monkeys are equally sensitive, the MTD is projected to be greater than 9.7 mg/kg in humans). The median prior probabilities of DLT are set to be approximately 8.0% and 24.5% at 1.6 mg/kg (projected starting dose for dose escalation using mCRM) and at 9.7 mg/kg, respectively.
- For the remaining doses, the medians of probability of DLT are assumed linear in log-dose on the logit-scale.
- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals (obtained from minimally informative Beta distributions), the optimal parameters of the bivariate normal distribution can be obtained as follows:

Parameters	Means	Standard deviations	Correlation
$\log(\alpha)$, $\log(\beta)$	(-1.0981, -0.4913)	(2.0445, 0.8677)	-0.3317

11.7.3. Escalation with Overdose Control Principle

Dose recommendation for the next cohort will be based on summaries of the posterior probability of the DLT rate for provisional doses: 1.6, 3.2, 4.8, 6.4, and 8.0 mg/kg. After subjects of each cohort complete DLT evaluation during Cycle 1, the posterior distributions of the DLT rate are derived for all provisional dose levels based on the BLRM using the DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level will then be calculated: 0% ≤DLT rate ≤16% as the DLT rate interval for under-dosing, 16% <DLT rate ≤33% as the target DLT rate interval, 33% <DLT rate ≤60% as the DLT rate interval for excessive toxicity, and 60% <DLT rate ≤100% as the DLT rate interval for

unacceptable toxicity, and used for dose recommendation for the next cohort according to the EWOC principle. The above provisional doses are based on an initial estimate of the human MTD of 9.7 mg/kg using the HNSTD of monkeys in nonclinical toxicology studies (30 mg/kg). It is therefore conceivable that the posterior probability of DLT rate for dose recommendation may be generated using alternative provisional doses as long as the predicted exposure increments are no more than 100% (Section 3.1.3).

The EWOC principle requires that the mCRM recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval of 16% <DLT rate ≤33% among all doses fulfilling the overdose control constraint: there is less than 25% of probability for the DLT rate >33% (probability for excessive or unacceptable toxicity).

12. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

12.1. Monitoring and Inspections

The CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each site. The monitor is responsible for inspecting the CRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the CRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, GCP, and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study site may be selected for audit by representatives from the Sponsor. Audit of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings. In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

The Investigator or study staff will enter the data in the eCRF (see Section 17.6) in accordance with the CRF Completion Guidelines that are provided by the Sponsor.

eCRF completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. The eCRF will be completed, reviewed and signed off or e-signed by the Investigator after all queries have been satisfactorily resolved.

The Investigator e-signs according to the study data flow.

Any data recorded on the study CRF will be collected and included in the database according to Clinical Data Interchange Standards Consortium (CDISC) standards and subjected to the same procedures as other data.

12.3. Data Management

Each subject will be identified in the database by a unique Subject Number as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor or CRO. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the Electronic Data Capture (EDC) application. During this review, subject data will be checked for consistency, completeness, and any apparent discrepancies. To resolve any questions arising from the Clinical Data Management review process for eCRFs queries will be raised and resolved within the EDC application.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

SAEs in the clinical database will be reconciled with the safety database.

All medical and surgical history and Adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All prior cancer therapy and prior/concomitant medications entered into the database will be coded by using the latest version of World Health Organization Drug Dictionary.

12.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Signature List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, date and outcome of screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the Investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical

supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Trial Master File includes:

- Subject files containing completed CRFs, ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB/EC and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at site, accountability records, final reconciliation, and applicable correspondence.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Trial Master File will be retained by the Investigator until at least 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

No study document should be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

13. FINANCING AND INSURANCE

13.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with DS or a CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

Daiichi-Sankyo is committed to meeting the highest standards of publication and public disclosure of information arising from clinical trials sponsored by the company. We will comply with US, EU, and Japanese policies for public disclosure of the clinical trial protocol and clinical trial results, and for sharing of clinical trial data. We follow the principles set forward in "Good Publication Practice for Communicating Company-sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure that we are in compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be accepted, reviewed, and approved in writing by the Sponsor prior to submission.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312, as appropriate.
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 Mar 1997.
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 Nov 2014.
- Other applicable local regulations.

15.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique Subject Number as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. ICF for examination of tumor tissue will be prepared in a separate ICF. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that

have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) is provided in the Sponsor ICF template for the Investigator to prepare the documents to be used at his or her site.

For study site in the US, an additional consent is required for the HIPAA.

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to the study initiation. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the IRB and/ or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will insure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies, as required.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authority(ies) in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the Investigator becomes aware of.

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the Investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

15.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, IRBs/ECs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB/EC. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

15.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Daiichi Sankyo or the CRO. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

Changes made by protocol amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A protocol amendment may be implemented after it has been approved by the IRB/EC and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

15.8. Study Termination

Refer to Section 3.1.6.

15.9. Data and Safety Monitoring Board

Not applicable.

15.10. Address List

Address list will be addressed in Supplement 3.

16. REFERENCES

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17. APPENDICES

17.1. Blood Collection Volume by Category and Total

Table 17.1: Blood Collection in Dose Escalation Part

Time Point	Test Item	Frequency[a]	Collection Volume
Screening examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (HER3ECD, cTnI)	1	8 mL
	ADA	-	-
Cycle 1	Laboratory test	4	(Collected in each site)
	Pharmacokinetics	9 (10[b])	45 mL (50 mL[b])
	Biomarker (HER3ECD, cTnI)	1	4 mL
	ADA	2	8 mL
Cycle 2	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	4 (5[b])	20 mL (25 mL[b])
	Biomarker (HER3ECD, cTnI)	1	4 mL
	ADA	1	4 mL
Cycle 3	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	9 (10[b])	45 mL (50 mL[b])
	Biomarker (HER3ECD, cTnI)	1	4 mL
	ADA	-	-
Cycle 4 and subsequent cycles	Laboratory test	1	(Collected in each site)
	Pharmacokinetics (Only Cycle 4, 6, and 8)	1	5 mL
	Biomarker (HER3ECD, cTnI)	1	4 mL
	ADA (Every 2 cycles from Cycle 4 to EOT)	1	4 mL
End of Treatment	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (HER3ECD, cTnI)	1	4 mL
	ADA	1	4 mL
Follow-up examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (HER3ECD, cTnI)	-	-
	ADA[c]	1	4 mL

ADA = anti-drug antibody; cTnI = cardiac troponin I; F/U = follow-up; HER3ECD = human epidermal growth factor receptor 3 extracellular domain.

[a] Blood collection in subjects with adverse events should be continued until resolution of the events (even after the scheduled observation period).

[b] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.

[c] For subjects with positive ADA at F/U visit, additional serum ADA samples (4 mL) may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

Table 17.2: Blood Collection in Dose Finding (Q3W Dosing Schedule) and Dose Expansion Parts

Time Point	Test Item	Frequency[a]	Collection Volume
Screening examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	1	4 mL
	Biomarker (HER3ECD)	1[d]	4 mL[d]
	ADA	-	-
Cycle 1	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	9 (10[b])	45 mL (50 mL[b])
	Biomarker (cTnI)	1	4 mL
	Biomarker (HER3ECD, cfDNA, cfRNA)[e]	1[e]	24 mL[e]
	ADA	2	8 mL
Cycle 2	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	2 (3[e,f])	10 mL (15 mL[e,f])
	Biomarker (cTnI)	1	4 mL
	ADA	1	4 mL
	Biomarker (HER3ECD, cfDNA, cfRNA)[e,f]	1[e,f]	24 mL[e,f]
Cycle 3	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	7 (8[b])	35 mL (40 mL[b])
	Biomarker (cTnI)	1	4 mL
	ADA	-	-
Cycle 4	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	1	5 mL
	Biomarker (cTnI)	1	4 mL
	ADA	1	4 mL
Cycle 5	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	5	25 mL
	Biomarker (cTnI)	1	4 mL
Cycle 6 and subsequent cycles	Laboratory test	1	(Collected in each site)
	Pharmacokinetics (Only Cycles 6 and 8)	1	5 mL
	Biomarker (cTnI)	1	4 mL
	ADA (Every 2 cycles from Cycle 6 to EOT)	1	4 mL
End of Treatment	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	1	4 mL
	Biomarker (HER3ECD, cfDNA, cfRNA)[e]	1[e]	24 mL[e]
	ADA	1	4 mL
Follow-up examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	-	-
	ADA[c]	1	4 mL

ADA = anti-drug antibody; cTnI = cardiac troponin I; F/U = follow-up; HER3ECD = human epidermal growth factor receptor 3 extracellular domain.

[a] Blood collection in subjects with adverse events should be continued until resolution of the events (even after the scheduled observation period).
[b] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.
[c] For subjects with positive ADA at F/U visit, additional serum ADA samples (4 mL) may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
[d] Dose Finding Part only.
[e] Dose Expansion Part only.
[f] ± 4 hours from time of optional biopsy, if obtained.

Table 17.3: Blood Collection in Dose Finding Part (Q2W Dosing Schedule)

Time Point	Test Item	Frequency[a]	Collection Volume
Screening examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	1	4 mL
	Biomarker (HER3ECD)	1	4 mL
	ADA	-	-
Cycle 1	Laboratory test	2	(Collected in each site)
	Pharmacokinetics	7 (8[b])	35 mL (40 mL[b])
	Biomarker (cTnI)	1	4 mL
	ADA	2	8 mL
Cycle 2	Laboratory test	2	(Collected in each site)
	Pharmacokinetics	2	10 mL
	Biomarker (cTnI)	1	4 mL
	ADA	1	4 mL
Cycle 3	Laboratory test	2	(Collected in each site)
	Pharmacokinetics	7 (8[b])	35 mL (40 mL[b])
	Biomarker (cTnI)	1	4 mL
	ADA	-	-
Cycle 4 and subsequent cycles	Laboratory test	3[d] 1[e]	(Collected in each site)
	Pharmacokinetics	7 (8[b])[d] 1[g] 5[f]	35 mL (40 mL[b])[d] 5 mL[g] 25 mL[f]
	Biomarker (cTnI)	1	4 mL
	ADA (Every 2 cycles from Cycle 4 to EOT)	1	4 mL
End of Treatment	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	1	4 mL
	ADA	1	4 mL
Follow-up examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	-	-
	ADA[c]	1	4 mL

ADA = anti-drug antibody; cTnI = cardiac troponin I; F/U = follow-up; HER3ECD = human epidermal growth factor receptor 3 extracellular domain

[a] Blood collection in subjects with adverse events should be continued until resolution of the events (even after the scheduled observation period).

[b] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.

[c] For subjects with positive ADA at F/U visit, additional serum ADA samples (4 mL) may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

[d] In Cycle 4.

[e] In Cycle 5 and subsequent cycles.

[f] In Cycle 6.

[g] In Cycles 5 and 8.

Table 17.4: Blood Collection in Dose Finding Part (Q3W Dosing Schedule with Up-titration)

Time Point	Test Item	Frequency[a]	Collection Volume
Screening examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	1	4 mL
	Biomarker (HER3ECD)	1	4 mL
	ADA	-	-
Cycle 1	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	7 (8[b])	35 mL (40 mL[b])
	Biomarker (cTnI)	1	4 mL
	ADA	2	8 mL
Cycle 2	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	7 (8[b])	35 mL (40 mL[b])
	Biomarker (cTnI)	1	4 mL
	ADA	1	4 mL
Cycle 3	Laboratory test	3	(Collected in each site)
	Pharmacokinetics	7 (8[b])	35 mL (40 mL[b])
	Biomarker (cTnI)	1	4 mL
	ADA	-	-
Cycle 4 and subsequent cycles	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	1[e] 5[d]	5 mL[e] 25 mL[d]
	Biomarker (cTnI)	1	4 mL
	ADA (Every 2 cycles from Cycle 4 to EOT)	1	4 mL
End of Treatment	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	1	4 mL
	ADA	1	4 mL
Follow-up examination	Laboratory test	1	(Collected in each site)
	Pharmacokinetics	-	-
	Biomarker (cTnI)	-	-
	ADA[c]	1	4 mL

ADA = anti-drug antibody; cTnI = cardiac troponin I; F/U = follow-up; HER3ECD = human epidermal growth factor receptor 3 extracellular domain.

[a] Blood collection in subjects with adverse events should be continued until resolution of the events (even after the scheduled observation period).

[b] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.

[c] For subjects with positive ADA at F/U visit, additional serum ADA samples (4 mL) may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

[d] Only in Cycle 5.

[e] In Cycle 4, 6, and 8.

17.2. Additional Information (for Japanese Study Sites Only)

17.2.1. GCP compliance

With regard to related regulations in Section 15.1 (for Japanese study sites only): This study will be conducted in compliance with the standards stipulated in Article 14-3 and Article 80-2 of the Pharmaceutical Affairs Law and by the "Ordinance Regarding Good Clinical Practice" (MHLW Ordinance No. 28, dated 27 Mar 1997) (referred to below as the "GCP Ordinance"). In compliance with the ethical principles of the Declaration of Helsinki, the human rights, welfare, and safety of the subjects will be the first considerations in the conducting of this study.

17.2.2. Study Period

During 01 Nov 2016 to 31 Dec 2023.

17.2.3. Payment for Participation, Compensation for Study-Related Injuries, and Insurance

17.2.3.1. Payment for Participation

If the subjects receive payment, the money will be paid to the subjects by the study site(s). That money will be taken from the fees paid by the Sponsor to each study site and will be paid in accordance with each study site's regulations.

17.2.3.2. Compensation and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury. Reimbursement, indemnity and insurance shall be addressed in Supplement 5.

17.3. Eastern Cooperative Oncology Group Performance Status Scale

GRADE	DESCRIPTION
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, eg, light house work, 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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

17.4. Response Evaluation Criteria in Solid Tumors, Version 1.1

Tumor response will be assessed in accordance with the RECIST v1.1, described below. The details will be described in the Independent Review Charter developed by the imaging CRO selected by the Sponsor.

17.4.1. Measurability of Tumor at Baseline

17.4.1.1. Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

17.4.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥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 in F/U, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

17.4.1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

17.4.1.1.3. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment.

17.4.1.1.3.1. Bone Lesions

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

17.4.1.1.3.2. Cystic Lesions

- 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 noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

17.4.1.1.3.3. Lesions with Prior Local Treatment

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion.

17.4.1.2. Specifications by Methods of Measurements

17.4.1.2.1. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 28 days of the first dose of study drug administration.

17.4.1.2.2. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during F/U. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

17.4.2. Tumor Response Evaluation

17.4.2.1. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

Only subjects with measurable disease at baseline should be included in the study.

17.4.2.2. Baseline Documentation of "Target" and "Non-target" Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (representative of all involved organs) should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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 as noted above, 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.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

17.4.2.3. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

17.4.2.3.1. Evaluation of Target Lesions

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

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

PD: At least a 20% increase in the sum of 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.

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.

17.4.2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement

should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: it is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

17.4.2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing non-target lesions.

17.4.2.3.4. Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows:

When the subject also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease: The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in

non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in 'volume' [which is equivalent to a 20% increase diameter in a measurable lesion]). If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

17.4.2.3.5. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a F/U study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and F/U evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

17.4.2.4. Evaluation of Best Overall Response

Best response in this study is defined as the best response across all time points (eg, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of SD). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, 6 weeks (± 7 days). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

17.4.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.5 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, Table 17.6 is to be used.

Table 17.5: Overall Response: Subjects with Target (± Non-target) Disease

Time Point Response: Subjects with Target (± Non-target) Disease			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 17.6: Overall Response: Subjects with Non-target Disease Only

Time Point Response: Subjects with Non-target Disease Only		
Non-target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = inevaluable; PD = progressive disease.

17.4.2.4.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is performed at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at F/U only

2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

17.4.2.4.3. Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject is known.

Best response determination in this study where confirmation of CR or PR IS NOT required: Best response in this study is defined as the best response across all time points (eg, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, 6 weeks (± 1 week). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments.

17.4.2.4.4. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

17.4.2.5. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted every 6 weeks in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to F/U. Scan dates should not be adjusted or rescheduled due to dose delay of any type.

Baseline tumor assessments must be performed within 28 days of the first dose of study drug administration.

All efforts should be made to ensure consistency between the baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation must include CT or MRI scanning of the brain, chest, abdomen, and pelvis at screening period. Any additional suspected sites of disease should also be imaged.

Every effort should be made to use the same assessment modality for all assessments for each subject. However, if there is no brain metastasis at the time of screening, CT or MRI should only be done when symptoms associated with brain metastasis occur during study period. If no clinical symptoms are observed, brain CT or MRI is not mandatory during study period. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and non-target sites are evaluated at each time point of tumor assessment.

17.5. New York Heart Association Functional Classification

Class	Functional Capacity
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: https://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp (Updated: Apr 23, 2014)

17.6. Electronic Data Capture System

The EDC system used for completing eCRF in this study is shown below.

Name of EDC system	**Medidata Rave®**
EDC system developer	Medidata Solutions Inc.
Entry method	Web-based data entry
Input terminal	Desktop/laptop computer at the study site
Incompatible operating systems	None
Recommended browsers	The Medidata Rave® supports any browser which is HTML 5 and CSS2 compliant. Browsers must have JavaScript enabled.
Screen Resolution	The minimum screen resolution required to properly display Medidata Rave applications is 1024 × 764.
Connection Speed	128kbps is the minimum connection speed recommended for using Medidata Rave.
Other	Adobe Flash Player: ver. 10 or above is required.

17.7. Supplement List

Supplements are printed separately from protocol, and their versions are independent from study protocol. Some supplement will be applied to specific study sites or specific country. Supplement 3, 4 and 5 is only submitted for Japanese site's IRB.

Supplements are listed as follow:

- Supplement 1: Serious Adverse Event Report (SAVER) form
- Supplement 2: EIU Reporting Form
- Supplement 3: Address list
- Supplement 4: The list of Study Centers and Investigators (for Japanese Study Center Only)
- Supplement 5: Compensation and Insurance (for Japanese Study Center Only)
- Supplement 6: Targeted Questionnaire

17.8. Schedule of Events

Table 17.7: Schedule of Events (Dose Escalation Part)

	SCR	Cycle 1							Cycle 2					Cycle 3							Cycle 4 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI						BI	EOI				BI	EOI						BI	EOI		
					± 1d	± 1d	± 1d	(+ 2d)			± 2d	± 2d	(± 2d)				± 1d	± 2d	± 2d	(± 2d)				
Informed consent	X																							
Confirmation of the HER3 status[d]	X																							
I/E Criteria	X																							
Administration of U3-1402		X							X					X							X			
Demographic information	X																							
Height	X																							
Pregnancy test	X[e]																						X	
Physical examination, weight	X[g]	X[f]							X[f]					X[f]							X[f]		X	X
ECOG PS	X[e]	X[f]							X[f]					X[f]							X[f]		X	X
Vital sign	X[e]	X[f]	X	X	X	X	X		X[f]	X	X	X		X[f]	X			X	X		X[f]		X	X
SpO_2		X[f]							X[f]					X[f]							X[f]		X	

Table 17.7: Schedule of Events (Dose Escalation Part) (Continued)

	SCR	Cycle 1							Cycle 2					Cycle 3							Cycle 4 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI						BI	EOI				BI	EOI						BI	EOI		
					± 1d	± 1d	± 1d	(+ 2d)			± 2d	± 2d	(± 2d)				± 1d	± 2d	± 2d	(± 2d)				
Ophthalmo-logic assessments	X[g]								X[h]												X[h,i]		X	
ECHO or MUGA (LVEF)	X[g]								X[f]					X[f]							X[f]		X	
12-lead ECG in triplicate[j]	X[g]	X[k]	X[l,m]	X[n]	X			X	X[k]					X[k]	X[l,m]	X[p]	X			X	X[u]		X	
Laboratory tests	X[e]	X[f]		X		X	X		X[f]		X	X		X[f]				X	X		X[f]		X	X
PK[x]		X[k,o]	X[l,m,o]	X[n,o]	X[o]	X	X	X[o]	X[k,o]	X[l]	X	X	X	X[k,o]	X[l,m,o]	X[o,p]	X[o]	X	X	X[o]	X[k,o,q]			
PK Sampling for CQ/HCQ Administration		If CQ or HCQ is administered for COVID-19, and if subject provides consent, additional PK blood samples should be collected at the following visits: ● Prior to the first CQ or HCQ dose (Day 1) ● Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) ● Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) ● The day of U3-1402 resumption, after the CQ/HCQ washout period*, (within 8h BI of U3-1402). * A washout period of more than 14 days is required before restarting U3-1402.																					
ADA		X[k]				X			X[k]												X[k,r]		X	X[s]
HER3ECD (blood)	X[e]																							
cTnI (blood)	X[e,w]		X[v]							X[v]					X[v]							X[v]	X[w]	
COVID-19Sample[x]																					X[x]		X[x]	
Tumor assessment	X[d,g]	X[t] Every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1, and thereafter every 12 weeks (± 7 days)																					X	
Concomitant medications		X																						
AEs	X																							

F/U = follow-up, BI = before infusion, EOI = end of infusion, EOT = end of treatment; .ADA = anti-drug antibody; AEs = adverse events; COVID-19 = coronavirus disease 2019; CQ/HCQ = chloroquine/hydroxychloroquine; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; h = hour; HER3 = human epidermal growth factor receptor 3; HER3ECD = human epidermal growth factor receptor 3 extracellular domain; ICF = informed consent form; MUGA = multiple gated acquisition scan; PK = pharmacokinetic; PS = performance status; LVEF = left ventricular ejection fraction; SCR = screening; SpO_2 = oxygen saturation of peripheral artery.

[a] The date Investigator decides the discontinuation of the study treatment (+ 7 days).
[b] 28 days (− 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first.
[c] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.
[d] Obtain a separate signed and dated ICF for examination of the tumor (confirmation of HER3 status and existence of a measurable lesion by RECIST version1.1).
[e] Latest data within 7 days prior to enrollment.
[f] Latest data within 3 days prior to infusion.
[g] Latest data within 28 days prior to enrollment.
[h] Latest data within 7 days prior to infusion.
[i] Every 4 cycles from Cycle 5 to EOT (eg, Cycle 5, 9, 13...).
[j] ECGs will be taken in close succession, a few minutes apart, after being in a supine/semi-recumbent position for 5 minutes.
[k] Within 8 hours BI.
[l] Within 30 minutes after EOI
[m] 2, 4, 7 hours (± 15 minutes) after start of infusion.
[n] 24 hours (± 2 hours) after the start of Day 1 infusion.
[o] Blood collection will be performed within 15 minutes after the end of ECG measurement.
[p] 24 hours (- 2 to + 4 hours) after the start of Day 1 infusion.
[q] Every 2 cycles from Cycle 4 to 8 (ie, Cycle 4, 6, 8).
[r] Every 2 cycles from Cycle 4 to EOT (eg, Cycle 4, 6, 8, 10...).
[s] For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
[t] Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1 and should continue until progressive disease or until a new anticancer therapy is started, whichever occurs first.
[u] Within 8 hours BI for Cycle 4 only; then within 3 days prior to infusion for Cycle 5 and subsequent cycles.
[v] Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety. In addition, obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory.
[w] Obtain a blood sample for cTnT (alternatively cTnI) for on-site safety. In addition, obtain a blood sample for cTnI testing by central laboratory.
[x] If subject provides consent, obtain a serum sample prior to study drug infusion on Cycle 5, Day 1 and every 4 cycles thereafter, and at EOT. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Appendix 17.9.

Table 17.8: Schedule of Events (Dose Finding [Q3W Dosing Cohorts] and Dose Expansion Parts)

	SCR	Cycle 1							Cycle 2					Cycle 3					Cycle 4 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)[c]	Day 1		Day 3	Day 8	Day 15	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI						BI	EOI				BI	EOI				BI	EOI		
					± 1d	± 1d	± 1d	(+ 2d)			+ 1d	± 2d	± 2d			± 2d	± 2d	(± 2d)				
Informed consent	X																					
Confirmation of the HER3 status[d]	X																					
Tumor biopsy	X[e,r]										X[s,t]										X[x]	
I/E Criteria	X																					
Administration of U3-1402		X							X					X					X			
Demographic information	X																					
Height	X																					
Pregnancy test	X[f]																				X	
Physical examination, weight	X[h]	X[g]							X[g]					X[g]					X[g]		X	X
ECOG PS	X[f]	X[g]							X[g]					X[g]					X[g]		X	X
Vital sign	X[f]	X[g]	X	X	X	X	X		X[g]	X		X	X	X[g]	X	X	X		X[g]		X	X
SpO_2		X[g]							X[g]					X[g]					X[g]		X	

Table 17.8: Schedule of Events (Dose Finding [Q3W Dosing Cohorts] and Dose Expansion Parts) (Continued)

	SCR	Cycle 1							Cycle 2					Cycle 3					Cycle 4 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)[c]	Day 1		Day 3	Day 8	Day 15	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI		± 1d	± 1d	± 1d	(+ 2d)	BI	EOI	+ 1d	± 2d	± 2d	BI	EOI	± 2d	± 2d	(± 2d)	BI	EOI		
Ophthalmologic assessments	X[h]								X[i]										X[i,j]		X	
ECHO or MUGA (LVEF)	X[h]								X[g]					X[g]					X[g]		X	
12-lead ECG in triplicate[k]	X[h]	X[l]	X[m,v]			X			X[l]					X[l]	X[m,v]	X			X[g]		X	
Laboratory tests	X[f]	X[g]				X	X		X[g]			X	X	X[g]		X	X		X[g]		X	X
PK		X[l,y]	X[m,n,y]	X	X	X[y]	X	X	X[l]	X[m]	X[t,z]			X[l,y]	X[m,n,y]	X[y]	X	X	X[l,o]	X[bb]		
PK Sampling for CQ/HCQ Administration		If CQ or HCQ is administered for COVID-19, and if subject provides consent, additional PK blood samples should be collected at the following visits: ● Prior to the first CQ or HCQ dose (Day 1) ● Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) ● Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) ● The day of U3-1402 resumption, after the CQ/HCQ washout period*, (within 8h BI of U3-1402). * A washout period of more than 14 days is required before restarting U3-1402.																			
ADA		X[l]				X			X[l]										X[l,p]		X	X[q]
cfDNA, cfRNA		X[l,t]									X[t,z]										X[t]	
HER3ECD (blood)	X[f,w]	X[l,t]									X[t,z]										X[t]	
cTnI (blood)	X[f,cc]		X[aa]							X[aa]					X[aa]					X[aa]	X[cc]	
COVID-19 Sample [dd]																			X[dd]		X[dd]	
Tumor assessment	X[d,h]	X[u] Every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1, and thereafter every 12 weeks (± 7 days)																			X	
Concomitant medications		X																				
AEs	X																					

COVID-19 = coronavirus disease 2019; CQ/HCQ = chloroquine/hydroxychloroquine; SCR =screening; F/U = follow-up; BI = before infusion; EOI = end of infusion; EOT = end of treatment; ADA = anti-drug antibody; AEs = adverse events; cfDNA = cell-free DNA; cdRNA = cell-free RNA; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ECG = electrocardiogram; ECOG = Eastern

Cooperative Oncology Group; HER3 = human epidermal growth factor receptor 3; h = hour; HER3ECD = human epidermal growth factor receptor 3 extracellular domain; ICF = informed consent form; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition scan; PK = pharmacokinetic; PS = performance status.

[a] The date Investigator decides to discontinue study drug (+ 7 days).
[b] 28 days (− 7 days) after the last dose of study drug or before starting new anticancer treatment, whichever comes first.
[c] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.
[d] Obtain a separate signed and dated ICF for examination of the tumor.
[e] Perform a fresh tumor biopsy for subjects with HER3-positive tumor tissue that was assayed using an archived tumor tissue sample. This is **mandatory** in Dose Expansion Part and **optional** in Dose Finding Part.
[f] Latest data within 7 days prior to enrollment.
[g] Latest data within 3 days of infusion.
[h] Latest data within 28 days prior to enrollment.
[i] Latest data within 7 days of infusion.
[j] Every 4 cycles from Cycle 5 to EOT (eg, Cycle 5, 9, 13...).
[k] ECGs will be taken in close succession, a few minutes apart, after being in a supine/semi-recumbent position for 5 minutes.
[l] Within 8 hours BI.
[m] Within 30 minutes after EOI.
[n] 2, 4, 7 hours (± 15 minutes) after the start of infusion.
[o] Only in Cycle 4, Day 1; Cycle 5, Day1; Cycle 6, Day 1; and Cycle 8, Day 1.
[p] Every 2 cycles from Cycle 4 to EOT (eg, Cycle 4, 6, 8, 10...).
[q] For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
[r] Mandatory in Dose Expansion Part.
[s] [Optional] In Dose Expansion Part only, approximately 48 to 72 hours after EOI on Cycle 2, Day 1. Additionally, blood samples for HER3ECD, cfDNA, cfRNA and PK should be collected ±4 hours from the time of this optional biopsy, if obtained. Consent for this biopsy should be documented in the tissue consent portion of the ICF. Tumor tissue from this biopsy may be obtained from primary tumor or metastatic site.
[t] In Dose Expansion Part only.
[u] Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1 and should continue until progressive disease or until a new anticancer therapy is started, whichever occurs first.
[v] 4 hours (± 15 minutes) after start of infusion.
[w] Dose Finding Part only
[x] [Optional] In Dose Expansion Part only.
[y] Blood collection will be performed within 15 minutes after the end of ECG measurement.
[z] ± 4 hours from the time of the optional on-study tumor biopsy, if obtained.
[aa] Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety. Obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory.
[bb] [Cycle 5, Day 1 only] Blood for PK should be collected within 30 minutes after EOI and 2, 4, and 7 hours (± 15 minutes) after the start of infusion.
[cc] Obtain a blood sample for cTnT (alternatively cTnI) for on-site safety. In addition, obtain a blood sample for cTnI testing by central laboratory.
[dd] If subject provides consent, obtain a serum sample prior to study drug infusion on Cycle 5, Day 1 and every 4 cycles thereafter, and at EOT. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Appendix 17.9.

Table 17.9: Schedule of Events (Dose Finding Part [Q2W Dosing Cohorts])

	SCR	Cycle 1					Cycle 2			Cycle 3					Cycle 4					Cycle 5 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 4	Day 8	(Day 15)[c]	Day 1		Day 8	Day 1		Day 4	Day 8	(Day 15)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI				BI	EOI		BI	EOI				BI	EOI				BI	EOI		
				± 1d	± 1d	(+ 2d)			± 2d			± 1d	± 2d	(± 2d)			± 2d	± 2d	(± 2d)				
Informed consent	X																						
Confirmation of the HER3 status[d]	X																						
Tumor biopsy	X[e]																						
I/E Criteria	X																						
Administration of U3-1402		X					X			X					X					X			
Demographic information	X																						
Height	X																						
Pregnancy test	X[f]																					X	
Physical examination, weight	X[h]	X[g]					X[g]			X[g]					X[g]					X[g]		X	X
ECOG PS	X[f]	X[g]					X[g]			X[g]					X[g]					X[g]		X	X
Vital sign	X[f]	X[g]	X	X	X		X[g]	X	X	X[g]	X		X		X[g]	X	X	X		X[g]		X	X
SpO_2		X[g]					X[g]			X[g]					X[g]					X[g]		X	
Ophthalm-ologic assessments	X[h]						X[i]													X[i,j]		X	

Table 17.9: Schedule of Events (Dose Finding Part [Q2W Dosing Cohorts]) (Continued)

	SCR	Cycle 1					Cycle 2			Cycle 3					Cycle 4					Cycle 5 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 4	Day 8	(Day 15)[c]	Day 1		Day 8	Day 1		Day 4	Day 8	(Day 15)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI				BI	EOI		BI	EOI				BI	EOI				BI	EOI		
				± 1d	± 1d	(+ 2d)			± 2d			± 1d	± 2d	(± 2d)			± 2d	± 2d	(± 2d)				
ECHO or MUGA (LVEF)	X[h]						X[g]			X[g]					X[g]					X[g]		X	
12-lead ECG in triplicate[k]	X[h]	X[l]					X[l]			X[l]					X[g]					X[g]		X	
Laboratory tests	X[f]	X[g]			X		X[g]		X	X[g]			X		X[g]		X	X		X[g]		X	X
PK[v]		X[l]	X[m,n]	X	X	X	X[l]	X[m]		X[l]	X[m,n]	X	X	X	X[l]	X[m,n]	X	X	X	X[l,o]	X[m,u]		
PK Sampling for CQ/HCQ Administration		If CQ or HCQ is administered for COVID-19, and if subject provides consent, additional PK blood samples should be collected at the following visits: ● Prior to the first CQ or HCQ dose (Day 1) ● Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) ● Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) ● The day of U3-1402 resumption, after the CQ/HCQ washout period*, (within 8h BI of U3-1402). * A washout period of more than 14 days is required before restarting U3-1402.																				
ADA		X[l]			X		X[l]								X[l]					X[l,p)]		X	X[q]
HER3ECD (blood)	X[f]																						
cTnI (blood)	X[f,s]		X[t]					X[t]			X[t]					X[t]						X[t]	X[s]	
COVID-19 Sample[v]																				X[v]		X[v]	
Tumor assessment	X[d,h]	X[r] Every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1, and thereafter every 12 weeks (± 7 days)																				X	
Concomitant medications		X																					
AEs	X																						

CQ/HCQ = chloroquine/hydroxychloroquine; SCR = screening; F/U = follow-up; BI = before infusion; EOI = end of infusion; EOT = end of treatment; ADA = anti-drug antibody; AEs = adverse events; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HER3 = human epidermal growth factor receptor 3; HER3ECD = human epidermal growth factor receptor 3 extracellular domain; ICF = informed consent form; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition scan; PK = pharmacokinetic; PS = performance status; RECIST = Response Evaluation Criteria in Solid Tumors; SpO_2 = oxygen saturation of peripheral artery.

[a] The date Investigator decides to discontinue study drug (+ 7 days).
[b] 28 days (− 7 days) after the last dose of study drug or before starting new anticancer treatment, whichever comes first.
[c] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.
[d] Obtain a separate signed and dated ICF for examination of the tumor (confirmation of HER3 status and existence of a measurable lesion by RECIST version 1.1).
[e] [Optional] Perform a tumor biopsy for subjects with an archived sample for confirmation of the HER3 status in a fresh tumor tissue.
[f] Latest data within 7 days prior to enrollment.
[g] Latest data within 3 days prior to infusion.
[h] Latest data within 28 days prior to enrollment.
[i] Latest data within 7 days prior to infusion.
[j] Every 4 cycles from Cycle 5 to EOT (eg, Cycle 5, 9, 13...).
[k] ECGs will be taken in close succession, a few minutes apart, after being in a supine/semi-recumbent position for 5 minutes.
[l] Within 8 hours BI.
[m] Within 30 minutes after EOI.
[n] 2, 4, 7 hours (± 15 minutes) after the start of administration.
[o] Only in Cycle 5, Day1; Cycle 6, Day 1; and Cycle 8, Day 1.
[p] Every 2 cycles from Cycle 6 to EOT (eg, Cycle 6, 8, 10...).
[q] For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
[r] Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1 and should continue until progressive disease or until a new anticancer therapy is started, whichever occurs first.
[s] Obtain a blood sample for cTnT (alternatively cTnI) for on-site safety. In addition, obtain a blood sample for cTnI testing by central laboratory.
[t] Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety. Obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory.
[u] [Cycle 6, Day 1 only] Blood for PK should be collected 2, 4, 7 hours (± 15 minutes) after the start of infusion.
[v] If subject provides consent, obtain a serum sample prior to study drug infusion on Cycle 5, Day 1 and every 4 cycles thereafter, and at EOT. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Appendix 17.9.

Table 17.10: Schedule of Events (Dose Finding Part [Q3W with Up-titration Cohorts])

	SCR	Cycle 1					Cycle 2					Cycle 3					Cycle 4 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 8	Day 15	(Day 22)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI				BI	EOI				BI	EOI				BI	EOI		
				± 1d	± 1d	(+ 2d)			± 2d	± 2d	(± 2d)			± 2d	± 2d	(± 2d)				
Informed consent	X																			
Confirmation of the HER3 status[d]	X																			
Tumor biopsy	X[e]																			
I/E Criteria	X																			
Administration of U3-1402		X					X					X					X			
Demographic information	X																			
Height	X																			
Pregnancy test	X[f]																		X	
Physical examination, weight	X[h]	X[g]					X[g]					X[g]					X[g]		X	X
ECOG PS	X[f]	X[g]					X[g]					X[g]					X[g]		X	X
Vital sign	X[f]	X[g]	X	X	X		X[g]	X	X	X		X[g]	X	X	X		X[g]		X	X
SpO_2		X[g]					X[g]					X[g]					X[g]		X	
Ophthalm-ologic assessments	X[h]						X[i]										X[i,j]		X	

Table 17.10: Schedule of Events (Dose Finding Part [Q3W with Up-titration Cohorts]) (Continued)

	SCR	Cycle 1					Cycle 2					Cycle 3					Cycle 4 and subsequent cycles		EOT[a]	F/U[b]
		Day 1		Day 8	Day 15	(Day 22)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1		Day 8	Day 15	(Day 22)[c]	Day 1			
		BI	EOI				BI	EOI				BI	EOI				BI	EOI		
				± 1d	± 1d	(+ 2d)			± 2d	± 2d	(± 2d)			± 2d	± 2d	(± 2d)				
ECHO or MUGA (LVEF)	X[h]						X[g]					X[g]					X[g]		X	
12-lead ECG in triplicate[k]	X[h]	X[l]					X[l]					X[l]					X[g]		X	
Laboratory tests	X[f]	X[g]		X	X		X[g]		X	X		X[g]		X	X		X[g]		X	X
PK		X[l]	X[m,n]	X	X	X	X[l]	X[m,n]	X	X	X	X[l]	X[m,n]	X	X	X	X[l,o]	X[s,u]		
PK Sampling for CQ/HCQ Administration		If CQ or HCQ is administered for COVID-19, and if subject provides consent, additional PK blood samples should be collected at the following visits: ● Prior to the first CQ or HCQ dose (Day 1) ● Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) ● Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) ● The day of U3-1402 resumption, after the CQ/HCQ washout period*, (within 8h BI of U3-1402). * A washout period of more than 14 days is required before restarting U3-1402.																	
ADA		X[l]		X			X[l]										X[l,p]		X	X[q]
HER3ECD (blood)	X[f]																			
cTnI (blood)	X[f,v]		X[t]					X[t]					X[t]					X[t]	X[v]	
COVID-19 Sample[w]																	X[w]		X[w]	
Tumor assessment	X[d,h]	X[r] Every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1, and thereafter every 12 weeks (± 7 days)																	X	
Concomitant medications		X																		
AEs		X																		

COVID-19 = coronavirus disease 2019; CQ/HCQ = chloroquine/hydroxychloroquine; SCR = screening; F/U = follow-up; BI = before infusion; EOI = end of infusion; EOT = end of treatment; ADA = anti-drug antibody; AEs = adverse events; cTnI = cardiac troponin I; cTnT = cardiac troponin T; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HER3 = human epidermal

growth factor receptor 3; HER3ECD = human epidermal growth factor receptor 3 extracellular domain; LVEF = left ventricular ejection fraction; MUGA = multiple gated acquisition scan; PK = pharmacokinetic; PS = performance status.

[a] The date Investigator decides to discontinue study drug (+ 7 days).
[b] 28 days (− 7 days) after the last dose of study drug or before starting new anticancer treatment, whichever comes first.
[c] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle.
[d] Obtain a separate signed and dated ICF for examination of the tumor (Confirmation of HER3 status and existence of a measurable lesion by RECIST version 1.1).
[e] [Optional] Perform a tumor biopsy for subjects with an archived sample for confirmation of the HER3 status in a fresh tumor tissue.
[f] Latest data within 7 days prior to enrollment.
[g] Latest data within 3 days of infusion.
[h] Latest data within 28 days prior to start of enrollment.
[i] Latest data within 7 days of infusion.
[j] Every 4 cycles from Cycle 5 to EOT (eg, Cycle 5, 9, 13...).
[k] ECGs will be taken in close succession, a few minutes apart, after being in a supine/semi-recumbent position for 5 minutes.
[l] Within 8 hours BI.
[m] Within 30 minutes after EOI.
[n] 2, 4, 7 hours (± 15 minutes) after the start of infusion.
[o] On Cycle 4, 5, 6, and 8.
[p] Every 2 cycles from Cycle 4 to EOT (eg, Cycle 4, 6, 8, 10...).
[q] For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
[r] Tumor assessments should not be delayed by dose interruptions; they are timed relative to Cycle 1, Day 1 and should continue until progressive disease or until a new anticancer therapy is started, whichever occurs first.
[s] [Cycle 5, Day 1 only] Blood for PK should be collected 2, 4, and 7 hours (± 15 minutes) after the start of infusion.
[t] Obtain a blood sample for cTnT (alternatively cTnI) 3 hours (± 1 hour) after the end of infusion of U3-1402 for on-site safety. Obtain a blood sample 3 hours (± 1 hour) after the end of infusion of U3-1402 for cTnI testing by central laboratory.
[u] [Cycle 5, Day 1 only] Within 30 minutes after EOI.
[v] Obtain a blood sample for cTnT (alternatively cTnI) for on-site safety. In addition, obtain a blood sample for cTnI testing by central laboratory.
[w] If subject provides consent, obtain a serum sample prior to study drug infusion on Cycle 5, Day 1 and every 4 cycles thereafter, and at EOT. For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Appendix 17.9.

17.9. Instructions Related to Coronavirus Disease 2019 (COVID-19)

Due to the potential impact of coronavirus disease 2019 (COVID-19, due to severe acute respiratory syndrome coronavirus 2 [SARS CoV-2]), on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with U3-1402. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 5.0 general grading criteria to evaluate COVID-19.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

Dose Modification Criteria for Suspected or Confirmed COVID-19

If COVID-19 infection is suspected, interrupt U3-1402 and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Table 5.2.
- If COVID-19 is confirmed or is still suspected after evaluation follow dose modification as outlined in Table 17.11 below and manage COVID-19 per local guidance until recovery of COVID-19. COVID-19 recovery is defined as no signs/symptoms of COVID-19, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

Table 17.11: COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	**Schedule Modification for U3-1402**
Grade 1	Resume study drug at the same dose[a]
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved[a] Reduce by 1 dose level if chest CT findings are nearly resolved
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved Discontinue study drug if chest CT findings are **not** completely resolved
Grade 4	Discontinue study drug

COVID-19 = coronavirus 2019; CT = computed tomography

[a] Closely monitor signs/symptoms after resuming U3-1402, initially with a phone call every 3 days for the first week, and then with a weekly phone call thereafter, for a total of 6 weeks.

In addition to the recommendations outlined in Table 17.11, Investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 5.2).

Prior and Concomitant Medications - Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment.
  - If treatment is absolutely required for COVID-19, U3-1402 must be interrupted.
  - If administered, then a washout period of more than 14 days is required before resumption of U3-1402.

PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected from each subject who provides consent, if chloroquine or hydroxychloroquine is administered for COVID-19 infection, at the time points specified in the Schedule of Events (Appendix 17.8).

The chloroquine or hydroxychloroquine administration time and the exact time of blood sample collection for PK analysis must be recorded on the eCRF.

COVID-19 Assessment(s)

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, but the real-time RT-PCR test is not available at the site, the participant must not have any signs or symptoms of COVID-19 infection for at least 2 weeks and nearly or completely resolved chest CT findings.

Serum samples will be used for COVID-19 testing from each subject who provides consent. Samples will be collected prior to the study drug infusion, at the time points specified in the Schedule of Events (Section 17.8), shipped to a central laboratory, and stored there until the tests become available.

If subjects consent, the remaining serum samples will also be stored for future analysis.

Sample collection, preparation, handling, storage, and shipping instructions are provided in the Study Laboratory Manual.

Statistical Analysis - Assessment of the Impact of COVID-19

If deemed appropriate, analyses will be performed to explore the impact of COVID-19 on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of COVID-19 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the statistical analysis plan.

Signature Page for VV-CLIN-103538
U31402-A-J101_Global Amendment Protocol Version 9.0

Approval with eSign	PPD Clinical Development/Science 29-Nov-2022 18:37:34 GMT+0000

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