Official Title: A Phase I, Open-Label Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Escalating Doses of DHES0815A in Patients With HER2-Positive Breast Cancer

NCT Number: NCT03451162

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PROTOCOL

TITLE:	**A PHASE I, OPEN-LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ESCALATING DOSES OF DHES0815A IN PATIENTS WITH HER2-POSITIVE BREAST CANCER**
PROTOCOL NUMBER:	GO39869
VERSION NUMBER:	2
EUDRACT NUMBER:	To be determined
IND NUMBER:	133077
TEST PRODUCT:	DHES0815A
MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	08-May-2019 17:42:38

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol GO39869 has been amended to limit the highest dose for patients enrolled in Cohorts 1–5 of this study to 2.4 mg/kg of DHES0815A every 3 weeks (Q3W) (see Section 3.1). [redacted]

In addition, this amendment provides updated stopping rules for safety for the expansion cohort (Section 6.1.2). The revised stopping rules employ a Bayesian posterior probability approach (Thall and Simon 1994) to evaluate toxicity in the expansion cohorts, including the rate of dose-limiting toxicity (DLT)-equivalent events that occur during Cycle 1 of study treatment. Events that are DLT-equivalent in the expansion cohort are defined by the same criteria used to identify DLT events in the dose-escalation cohorts (Section 3.1.1.1).

Additional clarifications have been made to the exclusion criteria (Section 4.1.2):

- The wash-out period for lapatinib has been qualified to be 14-days, given its short half-life.
- Examples of medical conditions for exclusion regarding evidence of significant uncontrolled concomitant disease [redacted] have been included:

  Patients with vascular leak syndrome or with a history of or who have active interstitial lung disease or pulmonary fibrosis or other clinically significant lung disease are not eligible for the study.

  Patients who have any malignancies other than breast cancer are excluded from the study with the exception of patients who have a history of localized malignancies and were treated with curative intent and whose disease is unlikely to recur are eligible for the study.

- The following qualification has been included in the exclusion criterion for clinically significant history of liver disease to reflect the lower safety risk for asymptomatic hepatitis B carriers:

  Patients who are asymptomatic hepatitis B virus (HBV) carriers based on serologic studies, with no history of clinically significant hepatitis, may be eligible if peripheral blood HBV viral load is undetectable by polymerase chain reaction (PCR). HBV carriers should receive prophylactic anti-viral therapy and be monitored for active HBV replication during trial participation per local standard of care.

Other minor revisions have been made to improve clarity and consistency:

- Names of countries in which study will be conducted have been removed from Section 3.1, as changes to this list may evolve with the ongoing needs of the study.
- It has been clarified that absolute counts are required for neutrophils and lymphocytes, but that percentages can be reported for other cell counts (Section 4.5.6.1 and Appendix 1, footnote "o").
- The number of ECGs required at screening has been aligned with language in Sections 4.1.2 and 4.5.7 (Appendix 1, footnote "k").
- Anti-drug antibody (ADA) and pharmacokinetic (PK) sample collection in footnotes "d" and "e" of Appendix 2 has been aligned with information provided in the table of Appendix 2.
- The Genentech Medical Monitor name and contact information has been updated (Protocol Cover Page, Protocol Amendment Acceptance Form, and Section 5.4.1).

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE I, OPEN-LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ESCALATING DOSES OF DHES0815A IN PATIENTS WITH HER2-POSITIVE BREAST CANCER**
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MEDICAL MONITOR:	[redacted], *M.D.*
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor and/or CRO.

PROTOCOL SYNOPSIS

TITLE: **A PHASE I, OPEN-LABEL STUDY EVALUATING THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ESCALATING DOSES OF DHES0815A IN PATIENTS WITH HER2-POSITIVE BREAST CANCER**

PROTOCOL NUMBER: GO39869

VERSION NUMBER: 2

EUDRACT NUMBER: To be determined

IND NUMBER: 133077

TEST PRODUCT: DHES0815A

PHASE: Phase I

INDICATION: HER2-Positive Breast Cancer

SPONSOR: Genentech, Inc.

Objectives and Endpoints

This study will evaluate the safety, pharmacokinetics, and activity of DHES0815A in patients with advanced and/or metastatic HER2-positive breast cancer (BC). Specific objectives and corresponding endpoints for the study are outlined in the table below.

Safety Objective (Primary Study Objective)	**Corresponding Endpoints**
• To evaluate the safety and tolerability of escalating doses of DHES0815A administered by IV infusion every 3 weeks to patients with advanced or metastatic HER2-positive BC including estimation of the MTD, determination of the RP2D, and characterization of DLTs	• Occurrence and severity of adverse events including DLTs, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results, including ECGs • Number of cycles received and dose intensity • LVEF as assessed by ECHO or MUGA scan
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the DHES0815A pharmacokinetics when administered by IV infusion	• Concentration of three key PK analytes of DHES0815A (i.e., DHES0815A Total Antibody, acPBD-MA, and unconjugated PBD-MA) at specified timepoints • PK parameters of DHES0815A Total Antibody, acPBD-MA, and unconjugated PBD-MA
Activity Objective	**Corresponding Endpoints**
• To make a preliminary assessment of the anti-tumor activity of DHES0815A	• Objective response, defined as a complete response or partial response on two consecutive occasions $\geq$ 4 weeks apart, as determined by the investigator according to RECIST v1.1

	• Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1
Immunogenicity Objective	**Corresponding Endpoints**
• To evaluate and characterize the immunogenic response to DHES0815A (by measuring anti-DHES0815A antibodies) administered by IV infusion, including the potential effects of ADAs on other outcome measures	• Incidence of ADA formation to DHES0815A (anti-DHES0815A antibodies) during the study relative to the prevalence of ADA at baseline • Relationship between ADA status and safety, PK, biomarkers, or preliminary efficacy endpoints
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To evaluate the potential relationships between selected covariates and exposure of DHES0815A • To evaluate the relationships between clinical parameters and exposure of DHES0815A	• Relationships between selected covariates and concentration or PK parameters of DHES0815A • Relationships between efficacy and/or safety and concentration or PK parameters of DHES0815A
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify and evaluate tissue- and blood-based biomarkers that are associated with response or resistance to DHES0815A, or that can increase the understanding of disease biology under DHES0815A treatment	[redacted]

acPBD-MA = antibody-conjugated PBD-MA; ADA = anti-drug antibody; BC = breast cancer; DLT = dose-limiting toxicity; ECHO = echocardiogram; [redacted]; LVEF = left ventricular ejection fraction; [redacted] MTD = maximum tolerated dose; MUGA = multiple-gated acquisition; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v4.0; PBD-MA = pyrrolo[2,1-c][1,4]benzodiazepine-monoamide; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RP2D = recommended Phase II dose; [redacted]

Study Design

Description of Study

This is a first-in-human, Phase I, open-label, multicenter, dose-escalation study using a 3+3 dose-escalation design to evaluate the safety, tolerability, and pharmacokinetics of DHES0815A as a single agent in patients with advanced and/or metastatic HER2-positive BC for whom established treatment has proven ineffective or intolerable or for whom established treatment is unavailable.

Approximately 24–30 patients may be enrolled in the dose-escalation cohort of the study to examine the safety, tolerability, and pharmacokinetics of increasing doses of DHES0815A administered by intravenous (IV) infusion on Day 1 of a 21-day cycle. Alternative DHES0815A dosing schedules may also be explored based on an ongoing review of the totality of the data.

The dose-expansion cohort of this Phase I study may include up to approximately 25 patients with HER2-positive BC at the dose and schedule proposed for future studies (the recommended Phase II dose [RP2D]). The decision on whether to open this expansion cohort will be based on an ongoing assessment of the totality of data obtained in this study.

The exact sample size for this trial will be determined by the number and size of the cohorts needed per the dose-escalation and cohort expansion rules. This number is estimated to be 55 patients, but the number of patients and cohorts may decrease or increase if fewer cohorts are required, patients need to be replaced, or additional cohorts are enrolled.

Patients in this study will be initially assessed for eligibility during the screening period (lasting ≤28 days). Following confirmation of eligibility, patients will receive DHES0815A by IV infusion on the first day of every cycle. A detailed pharmacokinetic (PK) evaluation will be performed during Cycle 1 and more limited PK assessments thereafter. Patients will be evaluated weekly by physical examination and by blood collections for routine hematologic and metabolic laboratory assessments for the first four cycles of DHES0815A treatment during dose escalation, the first two cycles during dose expansion, and less frequently thereafter. Cardiac ejection fraction (left ventricular ejection fraction [LVEF]) will be monitored by transthoracic echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) at baseline and in the last week (Days 15–21) of Cycles 1, 2, 4, and 6, and then after every four cycles thereafter. Ophthalmic examinations (best corrected visual acuity [BCVA] and anterior segment slit lamp examination with fluorescein) to monitor for visual and/or corneal changes will occur at baseline and during the last week (Days 15–21) of Cycles 2, 4, and 6, and every four cycles thereafter. Tumor assessment will occur at baseline and during the last week (Days 15–21) of every even-numbered cycle until Cycle 8 (i.e., at Cycles 2, 4, 6, and 8) and at every three cycles thereafter (i.e., at Cycles 11, 14, 17, etc.) until discontinuation or study termination.

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Patients deriving clinical benefit may be offered continued treatment with DHES0815A until disease progression or intolerable toxicity at the discretion of the investigator.

Disease status will be assessed using the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Tumor status will be categorized as a complete response (CR), partial response (PR), stable disease, or progressive disease (PD), per RECIST v1.1. Objective response should be confirmed by repeat physical examination or image-based evaluation ≥4 weeks after the initial documentation, per RECIST v1.1.

Blood samples will be collected for assessment of molecular and genetic biomarkers at baseline and end of study.

[redacted] *Patients enrolled in Cohorts 1–5 (0.6 mg/kg Q3W, 1.2 mg/kg Q3W, 2.4 mg/kg Q3W, 4.0 mg/kg Q3W, and 6.0 mg/kg Q3W, respectively) may not receive a dose higher than 2.4 mg/kg Q3W,* [redacted]

Number of Patients

A total of approximately 55 patients will be enrolled in the study. Approximately 24–30 patients will be enrolled in the dose-escalation stage. After dose escalation has been completed, up to approximately 25 patients may be enrolled in the expansion stage.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed written informed consent approved by the institution's independent Ethics Committee (EC) or Institutional Review Board (IRB).
- Age ≥18 years at time of signing Informed Consent Form
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life-expectancy ≥12 weeks at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease by RECIST v1.1 with at least one measurable target lesion

- Histologically or cytologically documented HER2-positive BC (see American Society of Clinical Oncology-College of American Pathologists 2013 HER2 testing guidelines). Based on review of the available data, enrollment into the expansion cohort may be restricted to patients with HER2-positive BC prospectively confirmed by central HER2 testing.
- Locally advanced or metastatic BC that has relapsed or is refractory to established therapies and for which there is no available established therapy or the therapy is contraindicated
- Availability of formalin-fixed, paraffin-embedded (FFPE) tumor specimen obtained at the time of the original diagnosis of HER2-positive BC and the most recent available metastatic biopsy (if applicable), accompanied by associated pathology reports, with adequate viable tumor tissue to establish HER2 status. Patients who only have available tumor tissue from one biopsy may still be eligible for participation in this Phase I study upon discussion with the Medical Monitor.
    - Tumor specimen may consist of
        - Either a tissue block (preferred) or at least [redacted] slides
            - Fewer than [redacted] slides may be acceptable upon discussion with the Medical Monitor
    - Cytologic or fine-needle aspiration samples are not acceptable.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to initiation of study treatment:
    - ANC $\geq$ 1500/μL without growth factor support within 28 days prior to Cycle 1, Day 1
    - Platelet count $\geq$ 100,000/μL without transfusion support or thrombopoeitin mimetic agents within 28 days prior to Cycle 1, Day 1
    - Hemoglobin $\geq$ 9.0 g/dL without transfusion or erythropoiesis stimulating agent support within 28 days prior to Cycle 1, Day 1
    - Total bilirubin $\leq 1.5 \times$ ULN
    - AST and ALT$\leq 1.5 \times$ ULN in the absence of liver metastases. In patients with documented liver metastases: AST and/or ALT $\leq 2.5 \times$ ULN
    - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 65 mL/min on the basis of either 24-hour urine collection or the Cockroft-Gault glomerular filtration rate estimation
    - INR $\leq$ 1.5 and PT/aPTT $\leq 1.5 \times$ ULN in the absence of anticoagulation therapy. If patients are on anticoagulation therapy, INR and PT/aPTT should be within the therapeutic range for the medical indication
- All acute, clinically significant treatment-related toxicity from prior therapy, except for alopecia and anorexia, resolved to Grade $\leq$ 1 prior to study entry
- For women of childbearing potential, a negative serum pregnancy test within 7 days prior to commencement of dosing. In patients whose BC produces hCG, documentation of an evaluation by an obstetrical specialist will be required to confirm that the patient is not pregnant within 7 days prior to starting DHES0815A dosing.
- A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). Women who are considered not to be of childbearing potential are not required to have a pregnancy test.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<$ 1% per year during the treatment period and for at least 8.5 months after the last dose of DHES0815A.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for 5.5 months after the last dose of DHES0815A. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 42 days after the last dose of DHES0815A to avoid exposing the embryo.

- <u>For dose-expansion cohorts only</u>: no more than two prior systemic chemotherapy-containing regimens in the advanced/metastatic setting (excluding trastuzumab emtansine, which is considered a targeted cytotoxic agent)

<u>Exclusion Criteria</u>

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment with chemotherapy, hormonal therapy (except hormone replacement therapy, oral contraceptives), immunotherapy, biologic therapy, radiation therapy (except palliative radiation to bony metastases), or herbal therapy as cancer therapy within 4 weeks prior to initiation of DHES0815A.

  A shorter interval may be acceptable for patients on oral endocrine therapy provided that any clinically relevant drug-related toxicity has completely resolved and prior approval is obtained from the Medical Monitor.

  For lapatinib, a 14-day washout is adequate on the condition that any related toxicities have resolved to Grade ≤1 or baseline prior to initiation of DHES0815A.

- Treatment with any other ADC compound containing a DNA-damaging agent (i.e., topoisomerase inhibitors, DNA alkylators), including but not limited to DS-8201a, SYD-982, and ADCT-502 at any time prior to initiation of DHES0815A

  Trastuzumab emtansine is not considered a DNA-damaging agent.

- History of exposure to the following cumulative doses of anthracycline as specified below:

  Doxorubicin > 500 mg/m^2

  Liposomal doxorubicin > 500 mg/m^2

  Epirubicin > 720 mg/m^2

  Mitoxantrone > 120 mg/m^2

  Idarubicin > 90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 of doxorubicin.

- History of severe allergic or anaphylactic reactions to monoclonal antibody therapies (or recombinant antibody–related fusion proteins)
- Pregnancy, lactation, or breastfeeding
- Major surgical procedure within 4 weeks prior to Day 1

- Evidence of a significant uncontrolled concomitant disease of the nervous system, pulmonary (including obstructive pulmonary disease and history of symptomatic bronchospasm), autoimmune, renal, hepatic, endocrine, or gastrointestinal disorders; or a serious non-healing wound or fracture

  Note: Patients with vascular leak syndrome or with a history of or who have active interstitial lung disease or pulmonary fibrosis or other clinically significant lung disease are not eligible for the study.

  Patients who have any malignancies other than breast cancer are excluded from the study. However, patients who have a history of localized malignancies and were treated with curative intent and whose disease is unlikely to recur in the opinion of the investigator (e.g., resected cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, etc.) are considered not to have another malignancy at time of study entry and are therefore eligible for the study.
- Known active bacterial, viral, fungal, mycobacterial, or other infection
- Clinically significant history of liver disease, including active viral or other hepatitis, current alcohol abuse, or cirrhosis

  Patients who are asymptomatic hepatitis B virus (HBV) carriers based on serologic studies, with no history of clinically significant hepatitis, may be eligible if peripheral blood HBV viral load is undetectable by PCR. HBV carriers should receive prophylactic anti-viral therapy and be monitored for active HBV replication during trial participation per local standard of care.
- Untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control).

  Patients with a history of treated CNS metastases are eligible, provided that all of the following criteria are met:
  - Presence of evaluable or measurable disease outside the CNS
  - Radiographically demonstrated stabilization or improvement upon completion of CNS-directed therapy and no evidence of interim progression between completion of CNS-directed therapy and the screening radiographic study.
  - Completion of radiotherapy ≥ 8 weeks prior to the screening radiographic study
  - Discontinuation of high-dose corticosteroids and anticonvulsants ≥ 4 weeks prior to the screening radiographic study (physiologic corticosteroid replacement is allowed)

- Cardiopulmonary dysfunction as defined by the following:
  - Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
  - Inadequate left ventricular ejection function at baseline, $< 50\%$ by either ECHO or MUGA
  - History of symptomatic congestive heart failure-Grade ≥ 3 per NCI CTCAE v4.0 or Class $\geq$ II New York Health Association
  - History of a decrease in LVEF to $< 40\%$ or symptomatic congestive heart failure with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of randomization
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Serious cardiac arrhythmia not controlled by adequate medication
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease, coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome

- QT interval corrected through use of Fridericia's formula (QTcF) $>$470 ms demonstrated by at least two ECGs $>$30 minutes apart
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up (42 days following last dose) is received from the last patient, whichever occurs later. The end of the study is expected to occur about 12 months after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 45 months.

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is DHES0815A with no comparator or placebo arm.

Test Product (Investigational Drug)

DHES0815A administration will be performed in a setting with emergency medical facilities and access to a critical care unit with staff who are trained to monitor for and respond to potentially serious reactions. The total dose of DHES0815A for each patient will depend on the dose assignment and the patient's weight on Day 1 of each cycle (or within 72 hours prior to Day 1 of that cycle). Patients may receive the initial (Cycle 1) dose of DHES0815A unless the patient's body weight has changed by $>$5% from baseline weight, in which case a new DHES0815A dose must be calculated. This new dose of DHES0815A may be given in subsequent cycles, unless the patient experiences another $>$5% change in body weight, in which case a new DHES0815A dose must be calculated. DHES0815A will be administered once every 21 days. Patients may continue to receive treatment with DHES0815A so long as they meet the criteria to do so or until they are required or choose to discontinue from study treatment as outlined in the protocol.

DHES0815A will be administered to patients by IV infusion using either a polyvinyl chloride (PVC) or polyolefin composed of polyethylene and polypropylene (PO-PE-PP) bag containing 0.9% NaCl and using an infusion set equipped with a 0.2-μm in-line filter. The final DHES0815A concentration will be determined by dose and patient weight.

Statistical Methods

Primary Analysis

The objective of the dose escalation is to determine the MTD/MAD and RP2D of DHES0815A.

If the safety and PK profile seen in the dose-escalation portion of the study is deemed to be favorable to justify further continuation of the study, expansion cohorts will be enrolled to further confirm safety and tolerability and to assess preliminary evidence of anti-tumor activity and exploratory pharmacodynamic markers of response.

The final analysis will be based on patient data collected through patient discontinuation or study discontinuation, whichever occurs first. All analyses will be based on the safety-evaluable population. All summaries will be presented according to the assigned dose level and cohort. In general, data will be summarized as warranted, and listings will be used in place of tables when the samples sizes are small. Continuous variables will be summarized using means, standard deviations, median, and ranges; categorical variables will be summarized using counts and percentages.

Determination of Sample Size

Approximately 24–30 patients will be enrolled in the dose-escalation stage. The exact number of patients to be enrolled in the study will depend upon the observed safety and pharmacokinetic/pharmacodynamic profile according to the dose-escalation rules.

At the RP2D, up to approximately 25 patients will be enrolled to further assess the safety, tolerability, and preliminary evidence of anti-tumor activity of DHES0815A.

This study is intended to obtain preliminary safety, PK, pharmacodynamic, and activity information in the safety-evaluable population. The sample sizes do not reflect any explicit power and type I error considerations.

Efficacy analyses will be performed on an ongoing basis in close collaboration with the study investigators for the expansion portion of the study to guide potential early stopping of enrollment in the event of lack of efficacy. Decisions to stop enrollment into the expansion cohort for futility will be made based on the totality of the available data, taking into account both safety and efficacy. Anti-tumor activity will be summarized by cohorts with an 80% CI. For example, in a cohort with 25 patients, if 10 of 25 patients have CR or PR, the objective response rate and its 80% CI will be summarized as 40% (27%–55%).

Continuous safety monitoring and interim analyses will be performed for the expansion portion of the study to guide potential early stopping of enrollment in the event of unacceptable toxicity. The first safety interim analysis will occur after approximately 6 patients complete 2 cycles in the expansion cohort or every 6 months, whichever occurs first.

A Bayesian posterior probability approach (Thall and Simon 1994) will be used to evaluate the toxicity in the expansion cohorts, including the rate of DLT-equivalent events that occur during Cycle 1 of study treatments. Events that are DLT-equivalent in the expansion cohort are defined by the same criteria used to identify DLT events in the dose-escalation cohorts. During continuous safety monitoring or in an interim analysis, if the number of observed DLT-equivalent events indicates that there is an approximately 80% chance that the true DLT rate is ≥ 25%, accrual to the cohort may be paused. The Medical Monitor and Safety Scientist will determine whether further enrollment in the cohort should be halted and may provide other recommendations as described in the protocol. The final decision will be based on the totality of the observed DLT-equivalent events, other safety events, as well as feedback from study investigators, Biostatistics, and Clinical Pharmacology. The protocol provides examples that cover scenarios with different true DLT-equivalent event rate assumptions. The examples show the number of observed DLT-equivalent events that might lead the Sponsor to stop enrollment and the corresponding operating characteristics using the posterior probability approach with a non-informative prior beta (1,1) and the stopping criteria stated above.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
acPBD-MA	antibody-conjugated pyrrolo[2,1-c][1,4]benzodiazepine-monoamide
ADA	anti-drug antibody
ADC	antibody–drug conjugate
BC	breast cancer
BCVA	best corrected visual acuity
CR	complete response
CT	computerized tomography
[redacted]	[redacted]
DAR	drug-to-antibody ratio
DDI	drug–drug interactions
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECD	extracellular domain
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
FFPE	formalin-fixed, paraffin-embedded
GLP	Good Laboratory Practice
HBV	*hepatitis B virus*
hCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HNSTD	highest non-severely toxic dose
ICH	International Council for Harmonisation
[redacted]	[redacted]
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
[redacted]	[redacted]
IxRS	interactive voice or web-based response system
LVEF	left ventricular ejection fraction
MAb	monoclonal antibody
MAD	maximum administered dose

Abbreviation	Definition
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
OS	overall survival
PBD-MA	pyrrolo[2,1-c][1,4]benzodiazepine monoamide
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PO-PE-PP	polyolefin composed of polyethylene and polypropylene
PR	partial response
PVC	poly-vinyl chloride
Q3W	every three weeks
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase II dose
ULN	upper limit of normal
[redacted]	[redacted]

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE BREAST CANCER

Breast cancer (BC) is the most common cancer among women in the world, with an estimated 1.68 million cases diagnosed globally per year and a mortality rate of approximately 520,000 deaths per year (Ferlay et al. 2015). While advances in early diagnosis and adjuvant therapy have led to a decrease in mortality rates from BC in developed countries, the prevalence of metastatic breast cancer (MBC) is still high and MBC is not considered curable, with the main goals of treatment being to improve patients' quality of life and prolong survival (Cardoso et al. 2014).

HER2, also known as erbB2/neu and p185HER2, represents a prominent target in BC with approximately 15%–20% of patients with primary invasive BC overexpressing the HER2 receptor (Reese and Slamon 1997; Owens et al. 2004; Wolff et al 2013). In the absence of HER2-targeted therapy, primary breast cancers that overexpress HER2 are associated with a poorer prognosis, including a greater risk of relapse and shortened survival compared with that of HER2-negative tumors (Slamon et al. 1987; Toikkanen et al. 1992; Andrulis et al. 1998; Pauletti et al. 2000; Rubin and Yarden 2001).

Until recently, for patients with HER2-positive MBC, the combination of trastuzumab and a taxane was widely accepted as the first-line treatment option of choice on the basis of the survival advantage demonstrated in two large pivotal trials (Studies H0648g [Slamon et al. 2001] and M77001 [Marty et al. 2005]). The regimen of pertuzumab, which binds HER2 at an epitope that is distinct from trastuzumab, in combination with trastuzumab and docetaxel, has shown clear superiority in terms of both progression-free survival (PFS) and overall survival (OS) with a generally similar safety profile (Study WO20698/TOC4129g [Baselga et al. 2012; Swain et al. 2015]) and is the new standard of care in many countries. The 5-year median OS of 56.5 months with the trastuzumab/pertuzumab/docetaxel regimen compared to 40.8 months with trastuzumab/docetaxel (Swain et al. 2015) suggests there may be therapeutic value to engagement of HER2 at multiple binding sites.

In patients with HER2-positive advanced BC previously treated with trastuzumab and a taxane, trastuzumab emtansine has significantly prolonged PFS and OS with a more favorable safety profile than lapatinib plus capecitabine (Study BO21977/TDM4370g, [Verma et al 2012]). Trastuzumab emtansine also improved PFS and OS compared with physicians' choice of treatment in patients who previously received trastuzumab, a taxane, and lapatinib (Study TDM4997g/BO25734 [Krop et al. 2014; Krop et al. 2017]). Trastuzumab emtansine is considered standard of care in many countries in the aforementioned patient population. However, the combination of trastuzumab emtansine with pertuzumab in patients with previously untreated MBC, while not inferior to trastuzumab and docetaxel or paclitaxel, failed to demonstrate superiority (Study TDM4788g/BO22589 [Perez et al. 2015]).

Although the treatment of MBC is palliative rather than curative in intent, improvement in survival is an important treatment goal. There is a significant need for new agents with novel mechanisms of action and acceptable toxicity that may be combined with established treatments to improve patient outcomes. Results to date suggest that engagement of HER2 at multiple epitopes may confer advantageous clinical benefit and that tumor-directed cytotoxic agents may yield a more optimal safety profile over systemic chemotherapy.

1.2 BACKGROUND ON DHES0815A

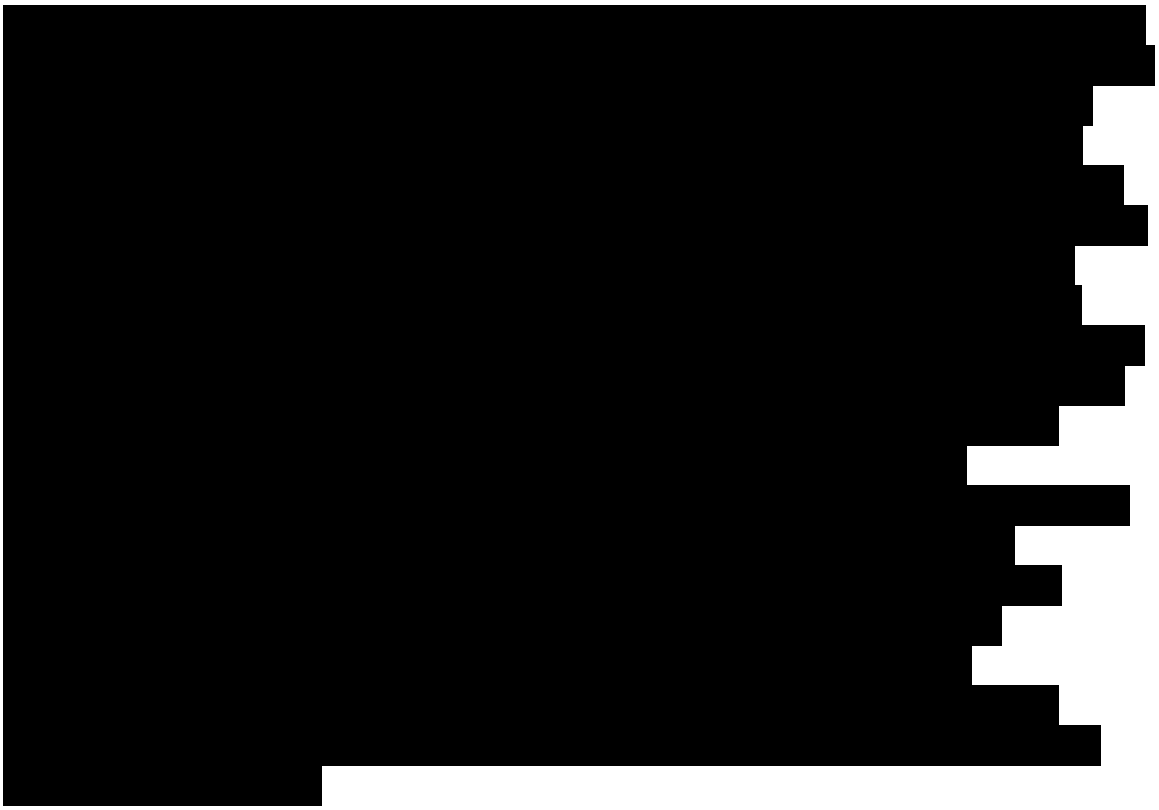
Amplification of HER2 occurs in approximately 20% of patients with BCs and, without targeted therapy, is associated with more aggressive disease and shortened survival (Slamon et al. 1987; Dawood et al. 2010). High expression of HER2 is also found in a subset of other solid tumors, including gastric and esophageal junction cancer (Bang et al. 2010; Yan et al. 2015). DHES0815A is a THIOMAB™ antibody–drug conjugate that consists of MHES0488A, a humanized Ig G1 anti-HER2 (also called ERBB2) monoclonal antibody (MAb) (murine clone 7C2), conjugated to the DNA alkylating agent, pyrrolo[2,1-c][1,4]benzodiazepine monoamide (PBD-MA) via a disulfide linker. The PBD class of naturally occurring anti-tumor agents binds to the minor groove of DNA (Antonow and Thurston 2011). Numerous other PBD dimer–containing antibody–drug conjugates (ADCs) are currently in clinical trials (Kung Sutherland et al. 2013; Rudin et al. 2017). The PBD payload on DHES0815A is a monoalkylator, in which one of the two PBD moieties containing an amide functionality is not involved in DNA alkylation, making it less potent than the corresponding bis-alkylator to potentially improve tolerability.

DHES0815A binds domain I of the HER2 extracellular domain (ECD) and has a distinct epitope from trastuzumab and pertuzumab, thereby enabling combination therapy with these agents. When bound to HER2, DHES0815A undergoes receptor-mediated internalization and is subsequently trafficked to lysosomes where it undergoes degradation. Following lysosomal degradation, the disulfide linkage is reduced, resulting in self-immolation of the linker and intracellular release of the active PBD-MA (Zhang et al. 2016). The released payload covalently binds to DNA in a sequence-selective manner leading to DNA alkylation but not cross-linking. This DNA alkylation ultimately results in cell death. DHES0815A was designed using THIOMAB antibody technology enabling the conjugation of two PBD-MA linker–drug molecules per antibody to engineered cysteine residues (Junutula et al. 2008). [redacted]. DHES0815A is being developed as a potential therapeutic for HER2-expressing cancers either as a single agent or in combination with existing treatments for HER2-positive BC.

Nonclinically, DHES0815A shows potent anti-tumor activity in murine xenograft models of HER2-positive breast and gastric cancer as a single agent and in combination, has acceptable pharmacokinetic (PK) properties, and has an acceptable safety profile that supports its clinical development in patients with HER2-positive cancers. Collectively, data from the nonclinical program with DHES0815A support DHES0815A entry into clinical trials and provide adequate safety factors to enable a starting dose of 0.6 mg/kg in humans. Refer to the DHES0815A Investigator's Brochure for details on nonclinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Metastatic HER2-positive BC remains an incurable disease with a median OS of less than 5 years reported for patients with previously untreated disease who received a combination of a taxane, pertuzumab, and trastuzumab (Swain et al. 2015). Therefore, novel treatments that can further improve patient outcomes are needed. DHES0815A is being developed for treatment of HER2-positive malignancies, including metastatic HER2-positive BC. In nonclinical models, DHES0815A demonstrated anti-tumor efficacy in HER2-positive models of breast and gastric cancer, including in models insensitive to trastuzumab emtansine.



This Phase I trial will enroll patients with locally advanced or metastatic HER2-positive BC to assess safety, tolerability, and pharmacokinetics and to make a preliminary assessment of anti-tumor activity of DHES0815A. Given the relatively poor prognosis

and limited treatment options for these patients, this population is considered appropriate for early-stage trials of novel therapeutic candidates, and the benefit–risk ratio of a clinical study of DHES0815A is considered acceptable.

Once preliminary DHES0815A safety data are available and a recommended Phase II dose (RP2D) has been determined for DHES0815A, a combination of DHES0815A with trastuzumab emtansine is planned to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of this combination treatment.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, pharmacokinetics, and activity of DHES0815A in patients with advanced and/or metastatic HER2-positive BC. Specific objectives and corresponding endpoints for the study are outlined below (see Table 1). In this protocol, "study treatment" refers to DHES0815A.

Table 1 Objectives and Corresponding Endpoints

Safety Objective (Primary Study Objective)	Corresponding Endpoints
• To evaluate the safety and tolerability of escalating doses of DHES0815A administered by IV infusion every 3 weeks to patients with advanced or metastatic HER2-positive BC including estimation of the MTD, determination of the RP2D, and characterization of DLTs	• Occurrence and severity of adverse events including DLTs, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results, including ECGs • Number of cycles received and dose intensity • LVEF as assessed by ECHO or MUGA scan
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the DHES0815A pharmacokinetics when administered by IV infusion	• Concentration of three key PK analytes of DHES0815A (i.e., DHES0815A Total Antibody, acPBD-MA, and unconjugated PBD-MA, see Section 6.5) at specified timepoints • PK parameters of DHES0815A Total Antibody, acPBD-MA, and unconjugated PBD-MA
Activity Objective	**Corresponding Endpoints**
• To make a preliminary assessment of the anti-tumor activity of DHES0815A	• Objective response, defined as a complete response or partial response on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1 • Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1

Immunogenicity Objective	Corresponding Endpoints
• To evaluate and characterize the immunogenic response to DHES0815A (by measuring anti-DHES0815A antibodies) administered by IV infusion, including the potential effects of ADAs on other outcome measures	• Incidence of ADA formation to DHES0815A (anti-DHES0815A antibodies) during the study relative to the prevalence of ADA at baseline • Relationship between ADA status and safety, PK, biomarkers, or preliminary efficacy endpoints
Exploratory Pharmacokinetic Objectives	**Corresponding Endpoints**
• To evaluate the potential relationships between selected covariates and exposure of DHES0815A • To evaluate the relationships between clinical parameters and exposure of DHES0815A	• Relationships between selected covariates and concentration or PK parameters of DHES0815A • Relationships between efficacy and/or safety and concentration or PK parameters of DHES0815A
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To identify and evaluate tissue- and blood-based biomarkers that are associated with response or resistance to DHES0815A, or that can increase the understanding of disease biology under DHES0815A treatment	[redacted]

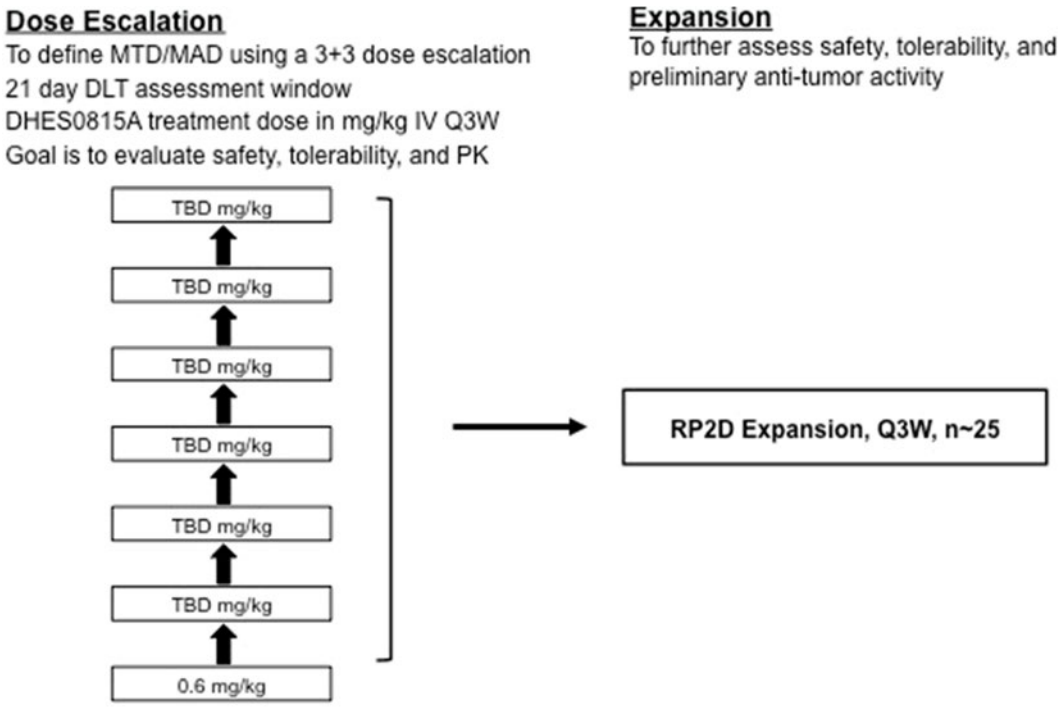
acPBD-MA=antibody-conjugated PBD-MA; ADA=anti-drug antibody; BC=breast cancer; DLT=dose-limiting toxicity; ECHO=echocardiogram; [redacted] LVEF=left ventricular ejection fraction; [redacted] MTD=maximum tolerated dose; MUGA=multiple-gated acquisition; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v4.0; PBD-MA=pyrrolo[2,1-c][1,4]benzodiazepine-monoamide; PK=pharmacokinetic; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, Version 1.1; RP2D=recommended Phase II dose; [redacted]

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a first-in-human, Phase I, open-label, multicenter, dose-escalation study using a 3+3 dose-escalation design to evaluate the safety, tolerability, and pharmacokinetics of DHES0815A as a single agent in patients with advanced and/or metastatic HER2-positive BC for whom established treatment has proven ineffective or intolerable or for whom established treatment is unavailable (see Figure 1).

Figure 1 Study Schema



DLT = dose-limiting toxicity; MAD = maximum administered dose; MTD = maximum tolerated dose; RP2D = recommended Phase II dose; TBD = to be determined; Q3W = every three weeks.

Notes: Dose escalation will begin at 0.6 mg/kg and may proceed with ≤ 100% dose increases until a safety signal has been observed, defined as a DLT in 1 patient or ≥ 2 patients with a ≥ Grade 2 DHES0815A-related major organ adverse event (unless present at baseline) in DLT window (Cycle 1: Study Days 1–21).

Dose escalation may proceed with ≤ 50% increases after safety signal has been observed.

Approximately 24–30 patients may be enrolled in the dose-escalation cohort of the study to examine the safety, tolerability, and pharmacokinetics of increasing doses of DHES0815A administered by IV infusion on Day 1 of a 21-day cycle. Alternative DHES0815A dosing schedules may also be explored based on an ongoing review of the totality of the data.

The dose-expansion cohort of this Phase I study may include up to approximately 25 patients with HER2-positive BC at the dose and schedule proposed for future studies (the RP2D). The decision on whether to open this expansion cohort will be based on an ongoing assessment of the totality of data obtained in this study.

The exact sample size for this trial will be determined by the number and size of the cohorts needed per the dose-escalation and cohort expansion rules. This number is estimated to be 55 patients, but the number of patients and cohorts may decrease or increase if fewer cohorts are required, patients need to be replaced, or additional cohorts are enrolled.

Patients in this study will be initially assessed for eligibility during the screening period (lasting ≤28 days). Following confirmation of eligibility, patients will receive DHES0815A by IV infusion on the first day of every cycle. A detailed PK evaluation will be performed during Cycle 1 and more limited PK assessments thereafter. Patients will be evaluated weekly by physical examination and by blood collections for routine hematologic and metabolic laboratory assessments for the first four cycles of DHES0815A treatment during dose escalation, the first two cycles during dose expansion, and less frequently thereafter. Cardiac ejection fraction (left ventricular ejection fraction [LVEF]) will be monitored by transthoracic echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA) at baseline and in the last week (Days 15–21) of Cycles 1, 2, 4, and 6, and then after every four cycles thereafter. Ophthalmic examinations (best corrected visual acuity [BCVA] and anterior segment slit lamp examination with fluorescein) to monitor for visual and/or corneal changes will occur at baseline and during the last week (Days 15–21) of Cycles 2, 4, and 6, and every four cycles thereafter. Tumor assessment will occur at baseline and during the last week (Days 15–21) of every even-numbered cycle until Cycle 8 (i.e., at Cycles 2, 4, 6, and 8) and at every three cycles thereafter (i.e., at Cycles 11, 14, 17, etc.) until discontinuation or study termination.

Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Patients deriving clinical benefit may be offered continued treatment with DHES0815A until disease progression or intolerable toxicity at the discretion of the investigator (see Section 3.1.1.4).

Disease status will be assessed using the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009; see Appendix 3). Tumor status will be categorized as a complete response (CR), partial response (PR), stable disease, or progressive disease (PD), per RECIST v1.1. Objective response should be confirmed by repeat physical examination or image-based evaluation ≥4 weeks after the initial documentation, per RECIST v1.1 (see Appendix 3).

Blood samples will be collected for assessment of molecular and genetic biomarkers at baseline and end of study.

A detailed schedule of activities is provided in Appendix 1 and Appendix 2.

[redacted]. *Patients enrolled in Cohorts 1–5 (0.6 mg/kg Q3W, 1.2 mg/kg Q3W, 2.4 mg/kg Q3W, 4.0 mg/kg Q3W, and 6.0 mg/kg Q3W, respectively) may not receive a dose higher than 2.4 mg/kg Q3W,* [redacted]

3.1.1 Dose-Escalation Stage

Approximately 24–30 patients will be enrolled in the dose-escalation stage. Cohorts of 3–6 patients each will be treated at escalating doses of DHES0815A in accordance with the dose-escalation rules described below. The starting dose of DHES0815A is based on nonclinical safety assessments and will be no higher than 0.6 mg/kg IV Q3W (see Section 3.3.2 for more details). For added safety during dose escalation, treatment will be staggered such that the first patient treated at each dose level will receive his or her first infusion at least 1 day prior to subsequent patients in that cohort. In addition, cohorts may be expanded even in the absence of dose-limiting toxicities (DLTs) in order to evaluate non-DLT adverse events further or to collect additional safety or PK data. Intrapatient dose escalation as per Section 3.1.1.3 will be allowed.

Patients will be closely monitored for adverse events during the DLT assessment window, defined as Days 1–21 of Cycle 1. Adverse events identified as DLTs, as defined in Section 3.1.1.1, will be reported to the Sponsor within 24 hours (see Section 5.3.1).

Patients who discontinue from the study prior to completing the DLT assessment window for reasons other than a DLT will be considered non-evaluable for dose-escalation decisions and maximum tolerated dose (MTD) assessments and will be replaced by an additional patient at that same dose level. Patients who receive supportive care during the DLT assessment window that confounds the evaluation of DLTs may be replaced at the discretion of the Medical Monitor.

3.1.1.1 Definition of Dose-Limiting Toxicity

For dose-escalation purposes, any one of the following events will be considered a DLT if it occurs during the DLT assessment window, unless clearly attributed to another identified etiology by the investigator (e.g., cancer progression):

- $\geq$15% decrease from baseline in LVEF or $\geq$10% decrease to less than a 50% LVEF
- Grade $\geq$3 non-hematologic toxicity with the following exceptions:
  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade $\leq$1 with standard-of-care therapy in $\leq$7 days
  - Grade 3 fatigue that resolves to Grade $\leq$2 in $\leq$7 days
  - Grade 3 elevation of serum hepatic transaminase (ALT or AST) without an increase in direct bilirubin $>$ 2$\times$ upper limit of normal (ULN) or clinical jaundice and lasting $<$7 days
  - Grade 3 laboratory abnormalities that are asymptomatic and considered by the investigator not to be clinically significant
- Grade $\geq$4 neutropenia (ANC $<$500 cells/μL) lasting $>$7 days
- Grade $\geq$3 febrile neutropenia
- Grade $\geq$4 anemia

- Grade ≥ 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Any increase in hepatic transaminase (ALT or AST) $> 3 \times$ baseline in combination with either an increase in direct bilirubin $> 2 \times$ ULN or clinical jaundice, in the absence of cholestasis or other contributory factors (e.g., worsening of metastatic disease, concomitant exposure to known hepatotoxic agent, or documented infectious etiology).

  This is suggestive of potential drug-induced liver injury (according to Hy's Law) and will be considered a DLT.

3.1.1.2 Starting Dose, Dose-Escalation Rules, and Determination of the Maximum Tolerated Dose

The starting dose of DHES0815A is 0.6 mg/kg administered by IV infusion Q3W to patients in the first cohort. The dose may be increased by up to 100% of the preceding dose level for each successive cohort until a safety signal (defined as a DLT in 1 patient or study drug–related Grade ≥ 2 major organ adverse events (unless present at baseline) in at least 2 patients during the DLT assessment window in a given cohort) is observed. Once a safety signal has been observed in a given cohort, the dose may be increased by up to 50% of the preceding dose level for each successive cohort. Intrapatient dose escalation may be allowed for some patients (see Section 3.1.1.3).

Dose escalation of DHES0815A will occur in accordance with the rules listed below.

- A minimum of 3 patients will initially be enrolled in each cohort.
- If none of the first 3 DLT-evaluable patients experiences a DLT, enrollment of the next cohort at the next highest dose level may proceed.
- If 1 of the first 3 DLT-evaluable patients experiences a DLT, the cohort will be expanded to 6 patients. If there are no further DLTs in the first 6 DLT-evaluable patients, enrollment of the next cohort at the next highest dose level may proceed.
- If 2 or more DLT-evaluable patients in a cohort experience a DLT, the MTD will have been exceeded and dose escalation will stop. An additional 3 patients will be evaluated for DLTs at the preceding dose level, unless 6 patients have already been evaluated at that level. However, if the dose level at which the MTD is exceeded is $\geq 15\%$ higher than the preceding dose level, 6 patients may be evaluated at an intermediate dose level.
- If the MTD is exceeded at any dose level, the highest dose at which fewer than 2 of 6 DLT-evaluable patients (i.e., $< 33\%$) experience a DLT will be declared the MTD.
- If the MTD is not exceeded at any dose level, the highest dose administered in this study will be declared the maximum administered dose (MAD).
- As long as the MTD has not been exceeded, additional patients may be enrolled at a given dose level in a given arm to explore factors influencing adverse events or to accumulate additional safety data.

Relevant demographic, adverse event, laboratory, dose administration, and PK (if available) data will be reviewed prior to dose-escalation decisions, which will be made by the Sponsor Medical Monitor in consultation with the Principal Investigators and a committee composed of the following Sponsor representatives: Medical Monitor and clinical safety scientist, with consultation from the statistician, clinical pharmacologist, and clinical trial leader. On the basis of a review of real-time safety data and available preliminary PK data, dose escalation may be halted or modified by the Sponsor as deemed appropriate.

3.1.1.3 Intrapatient Dose Escalation

To minimize the exposure of patients to suboptimal doses and to maximize the collection of information at relevant doses, patients may progressively escalate from their current dose of DHES0815A to the highest dose level tolerated by completed cohorts. Patients will need to complete at least three cycles at their originally assigned DHES0815A dose level, as well as at each of the subsequent dose levels, prior to any further dose escalation.

Once the MTD is declared and the RP2D is determined, patients who remain in the study and continue to tolerate the study drug may escalate their dose to the RP2D level or the dose level below the RP2D under their current dosing schedule. The RP2D will be at or below the MTD (or MAD) and determined by the totality of data, including DLTs, safety, activity, and PK data (see Section 3.1.1.2).

All intrapatient dose-escalation decisions will be made by the Sponsor in consultation with the participating investigators and will include assessment of safety data within the treatment cohorts, as well as the totality of the safety data.

For patients in Cohorts 1–5, please also refer to Section 3.1.

3.1.1.4 Continuation of DHES0815A (Cycles ≥2)

Patients without a DLT during the DLT assessment window will be eligible to receive additional infusions of DHES0815A at the same dose level at which they were enrolled or at an increased dose as detailed in Section 3.1.1.3 (the day of infusion being Day 1 of each cycle), provided that they meet the following criteria for acceptable toxicity and ongoing clinical benefit:

- Acceptable toxicity: All adverse events experienced with prior infusions that were not attributed to constitutional symptoms of the patient's cancer or intercurrent illness must have decreased to Grade 1 or baseline grade on or before the day of the next infusion.

  Exceptions on the basis of ongoing clinical benefit may be allowed after a careful assessment and discussion of benefit versus risk with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation

from the study but must be approved by the Medical Monitor. Dose modifications are described in Section 5.1.2.1.

- Ongoing clinical benefit: Patients must demonstrate improvement/stabilization in tumor burden, according to the RECIST v1.1 (Appendix 3) or demonstrate clinical signs or symptoms of benefit, as judged by the investigator, independent of RECIST.

  All tumors assessed at screening must be documented and re-assessed at each subsequent tumor evaluation (see Appendix 1 for tumor assessment schedule). For each patient, the same imaging modality should be used throughout the study.

For patients in Cohorts 1–5, please also refer to Section 3.1.

Women of childbearing potential will need to undergo a urine pregnancy test prior to each DHES0815A cycle (patients whose breast tumor produces human chorionic gonadotropin [hCG] and were confirmed not be pregnant prior to enrollment should be monitored with serum pregnancy tests rather than urine pregnancy tests prior to each cycle of study treatment). If a urine pregnancy test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Patients who are pregnant must permanently discontinue study treatment.

DHES0815A administration will be discontinued in patients who experience a DLT during the DLT assessment window (Days 1–21 of the first cycle) if this toxicity does not return to baseline grade within 14 days. Patients who experience a DLT during the first cycle (Days 1–21) and whose toxicity returns to baseline within 14 days may be restarted at a dose level tolerated by the prior cohort following discussion with the Medical Monitor. A treatment delay beyond 14 days may be acceptable upon discussion with the Medical Monitor (see Section 5.1.2.1).

3.1.2 Expansion Stage

After dose escalation has been completed, up to approximately 25 patients may be enrolled in the expansion stage. Patients may be treated at or below the MTD or MAD to obtain additional safety, tolerability, and PK data, as well as preliminary evidence of anti-tumor activity.

If the frequency of Grade 3 or 4 toxicities or other unacceptable toxicities at the initial expansion-stage dose level suggest that the MTD has been exceeded, accrual at that dose level of DHES0815A will be halted. Consideration will then be given to enrolling patients in an expansion cohort at a lower dose level.

Patients in the dose-expansion cohort will be eligible to receive DHES0815A treatment after Cycle 1 provided that they meet the same criteria for acceptable toxicity and ongoing clinical benefit as outlined for the dose-escalation cohorts in Section 3.1.1.4.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up (42 days following last dose) is received from the last patient, whichever occurs later. The end of the study is expected to occur about 12 months after the last patient is enrolled. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 45 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Patients with HER2-positive MBC can derive significant clinical benefit from HER2-directed therapies. Despite advances in treatment options for patients with HER2-positive MBC that include trastuzumab, pertuzumab, trastuzumab emtansine, lapatinib, and chemotherapy, HER2-positive MBC remains an incurable disease. Nearly all patients with HER2-positive MBC will eventually suffer disease progression and die from their disease (Verma et al. 2012; Swain et al. 2015). Given the relatively poor prognosis for patients with HER2-positive MBC and limited treatment options, this patient population is considered appropriate for early-stage trials of novel therapeutic candidates. DHES0815A is a novel ADC designed to target HER2-positive tumor cells, providing a rationale for studying this investigational agent in patients with HER2-positive BC.

3.3.2 Rationale for Starting Dose and Schedule of DHES0815A

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[redacted]

Refer to the DHES0815A Investigator's Brochure for additional details of the nonclinical studies described above.

3.3.3 Rationale for Evaluating Patients in the Dose-Expansion Cohort

It is expected that the small number of patients in each cohort during the dose-escalation stage will limit the extent to which the relationships between dose, drug exposure, and adverse events related to DHES0815A can be evaluated. Therefore, a total of approximately 25 patients with HER2-positive advanced and/or metastatic breast cancer may be enrolled at the proposed RP2D to further characterize the pharmacokinetics of DHES0815A, collect additional safety data, and assess for evidence of anti-tumor activity.

3.3.4 Rationale for Pharmacokinetic Sampling Schedule

The PK sampling schedule that follows the DHES0815A administration is designed to capture DHES0815A exposure data at a sufficient number of timepoints to provide a detailed profile of the concentration–time curve for DHES0815A total antibody (all drug-to-antibody ratios [DARs] including fully conjugated, partially deconjugated, and fully deconjugated anti-HER2 antibody), antibody-conjugated PBD-MA (acPBD-MA), and unconjugated PBD-MA.

DHES0815A is designed to be structurally stable in circulation. However, it is possible that catabolism could occur, resulting in—for example—deconjugation of the cytotoxic drug and changes in the overall DAR. Exploratory structural data (e.g., changes in DAR distribution) may provide additional insight on the safety and efficacy of DHES0815A.

3.3.5 Rationale for Biomarker Assessments

HER2 status is routinely assessed on tumor tissue using approved assays [redacted] in patients with BC to assess whether they may benefit from currently approved HER2-directed therapies. The possible relationship between HER2 expression and DHES0815A anti-tumor activity will be explored in this Phase I trial. HER2 expression in available tumor tissue will be

analyzed [redacted].

3.3.6 Rationale for Collecting Blood Samples to Identify [redacted]

[redacted]

3.3.7 Rationale for Collection of Pre-treatment Paraffin-Embedded Tumor Samples for Tumor Marker Assessment and Optional Tumor Tissue Biopsy on Progression

Paraffin-embedded tumor samples (either blocks [preferred] or at least [redacted] slides) will be required from all patients for the central laboratory evaluation of HER2 expression and other biomarker assessments (see Section 4.5.6.2). Tumor tissue obtained at the time of the original diagnosis of HER2-positive BC and the most recent available metastatic biopsy (if applicable) should be submitted. Patients who only have available tumor tissue from one timepoint may still be eligible for participation in this Phase I study upon discussion with the Medical Monitor.

For patients who consent, an additional optional biopsy may be collected per investigator discretion, preferably at the time of radiographic progression. Biopsies should be minimally invasive, defined as requiring only local anesthesia, and in general, exclude brain, lungs, or any internal organs that may subject patients to significant risk as referenced in Section 4.5.6.2.

The tumor tissues will be evaluated for HER2 and other biomarkers that are potentially relevant to study disease evolution, impact of prior treatments, and DHES0815A anti-tumor activity. Associations between biomarkers with outcomes measures will be explored. Tissue may be analyzed using molecular assays including, but not limited to, [redacted], immunofluorescence, [redacted].

Central review of HER2 status in patient tumor samples will be performed on an ongoing basis [redacted]. Based on a review of the data, enrollment into the expansion cohort may be restricted to patients with centrally confirmed HER2-positive MBC.

3.3.8 Rationale for Collection of Anti-Drug Antibody Samples

As with any recombinant antibody, DHES0815A may elicit an immune response and patients may develop antibodies against DHES0815A. Anti-drug antibody (ADA) response and potential correlation of response to relevant clinical safety endpoints will therefore be assessed for all treated patients. This could include ADA to the antibody, linker, drug, or epitopes involving multiple ADC components. Although ADAs directed against DHES0815A are not expected to result in significant clinical sequelae, patients will be monitored for any potential immune response to DHES0815A in the Phase I clinical trial. Validated screening and confirmatory assays will be employed to detect ADAs at multiple timepoints before, during, and after treatment with DHES0815A (see analysis Section 5.1.1.11). Serum samples will be collected from all patients prior to their first dose of DHES0815A and at several additional timepoints (see Appendix 1 and Appendix 2).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 55 patients with HER2-positive advanced and/or metastatic BC will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed written informed consent approved by the institution's independent Ethics Committee (EC) or Institutional Review Board (IRB).
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life-expectancy $\geq$ 12 weeks at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Measurable disease by RECIST v1.1 with at least one measurable target lesion
- Histologically or cytologically documented HER2-positive BC (see Wolff et al. 2013 for American Society of Clinical Oncology-College of American Pathologists 2013 HER2 testing guidelines). Based on review of the available data, enrollment into the expansion cohort may be restricted to patients with HER2-positive BC prospectively confirmed by central HER2 testing.
- Locally advanced or metastatic BC that has relapsed or is refractory to established therapies and for which there is no available established therapy or the therapy is contraindicated

- Availability of formalin-fixed, paraffin-embedded (FFPE) tumor specimen obtained at the time of the original diagnosis of HER2-positive BC and the most recent available metastatic biopsy (if applicable), accompanied by associated pathology reports, with adequate viable tumor tissue to establish HER2 status. Patients who only have available tumor tissue from one biopsy may still be eligible for participation in this Phase I study upon discussion with the Medical Monitor.
    - Tumor specimen may consist of
        - Either a tissue block (preferred) or at least [redacted] slides
            - Fewer than [redacted] slides may be acceptable upon discussion with the Medical Monitor
    - Cytologic or fine-needle aspiration samples are not acceptable.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 2 weeks prior to initiation of study treatment:
    - ANC $\geq$ 1500/μL without growth factor support within 28 days prior to Cycle 1, Day 1
    - Platelet count $\geq$ 100,000/μL without transfusion support or thrombopoeitin mimetic agents within 28 days prior to Cycle 1, Day 1
    - Hemoglobin $\geq$ 9.0 g/dL without transfusion or erythropoiesis stimulating agent support within 28 days prior to Cycle 1, Day 1
    - Total bilirubin $\leq$ 1.5 $\times$ ULN
    - AST and ALT $\leq$ 1.5 $\times$ ULN in the absence of liver metastases. In patients with documented liver metastases: AST and/or ALT $\leq$ 2.5 $\times$ ULN
    - Serum creatinine $\leq$ 1.5 $\times$ ULN or creatinine clearance $\geq$ 65 mL/min on the basis of either 24-hour urine collection or the Cockroft-Gault glomerular filtration rate estimation
    - INR $\leq$ 1.5 and PT/aPTT $\leq$ 1.5 $\times$ ULN in the absence of anticoagulation therapy. If patients are on anticoagulation therapy, INR and PT/aPTT should be within the therapeutic range for the medical indication
- All acute, clinically significant treatment-related toxicity from prior therapy, except for alopecia and anorexia, resolved to Grade $\leq$ 1 prior to study entry
- For women of childbearing potential, a negative serum pregnancy test within 7 days prior to commencement of dosing. In patients whose BC produces hCG, documentation of an evaluation by an obstetrical specialist will be required to confirm that the patient is not pregnant within 7 days prior to starting DHES0815A dosing.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical

sterilization (removal of ovaries and/or uterus). Women who are considered not to be of childbearing potential are not required to have a pregnancy test.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 8.5 months after the last dose of DHES0815A.

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, and established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for 5.5 months after the last dose of DHES0815A. Men must refrain from donating sperm during this same period.

  With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 42 days after the last dose of DHES0815A to avoid exposing the embryo.

- <u>For dose-expansion cohorts only</u>: no more than two prior systemic chemotherapy-containing regimens in the advanced/metastatic setting (excluding trastuzumab emtansine, which is considered a targeted cytotoxic agent)

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment with chemotherapy, hormonal therapy (except hormone replacement therapy, oral contraceptives), immunotherapy, biologic therapy, radiation therapy (except palliative radiation to bony metastases), or herbal therapy as cancer therapy within 4 weeks prior to initiation of DHES0815A.

  A shorter interval may be acceptable for patients on oral endocrine therapy provided that any clinically relevant drug-related toxicity has completely resolved and prior approval is obtained from the Medical Monitor.

  For lapatinib, a 14-day washout is adequate on the condition that any related toxicities have resolved to Grade ≤1 or baseline prior to initiation of DHES0815A.

- Treatment with any other ADC compound containing a DNA-damaging agent (i.e., topoisomerase inhibitors, DNA alkylators), including but not limited to DS-8201a, SYD-982, and ADCT-502 at any time prior to initiation of DHES0815A

  Trastuzumab emtansine is not considered a DNA-damaging agent.

- History of exposure to the following cumulative doses of anthracycline as specified below:

  Doxorubicin > 500 mg/m^2

  Liposomal doxorubicin > 500 mg/m^2

  Epirubicin > 720 mg/m^2

  Mitoxantrone > 120 mg/m^2

  Idarubicin > 90 mg/m^2

  If another anthracycline or more than one anthracycline has been used, then the cumulative dose must not exceed the equivalent of 500 mg/m^2 of doxorubicin.

- History of severe allergic or anaphylactic reactions to monoclonal antibody therapies (or recombinant antibody–related fusion proteins)
- Pregnancy, lactation, or breastfeeding
- Major surgical procedure within 4 weeks prior to Day 1
- Evidence of a significant uncontrolled concomitant disease of the nervous system, pulmonary (including obstructive pulmonary disease and history of symptomatic bronchospasm), autoimmune, renal, hepatic, endocrine, or gastrointestinal disorders; or a serious non-healing wound or fracture

  Note: Patients with vascular leak syndrome or with a history of or who have active interstitial lung disease or pulmonary fibrosis or other clinically significant lung disease are not eligible for the study.

  Patients who have any malignancies other than breast cancer are excluded from the study. However, patients who have a history of localized malignancies and were treated with curative intent and whose disease is unlikely to recur in the opinion of the investigator (e.g., resected cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, etc.) are considered not to have another malignancy at time of study entry and are therefore eligible for the study.

- Known active bacterial, viral, fungal, mycobacterial, or other infection
- Clinically significant history of liver disease, including active viral or other hepatitis, current alcohol abuse, or cirrhosis

  Patients who are asymptomatic hepatitis B virus (HBV) carriers based on serologic studies, with no history of clinically significant hepatitis, may be eligible if peripheral blood HBV viral load is undetectable by PCR. HBV carriers should receive prophylactic anti-viral therapy and be monitored for active HBV replication during trial participation per local standard of care.

- Untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control).

  Patients with a history of treated CNS metastases are eligible, provided that all of the following criteria are met:

  - Presence of evaluable or measurable disease outside the CNS
  - Radiographically demonstrated stabilization or improvement upon completion of CNS-directed therapy and no evidence of interim progression between completion of CNS-directed therapy and the screening radiographic study.
  - Completion of radiotherapy ≥ 8 weeks prior to the screening radiographic study
  - Discontinuation of high-dose corticosteroids and anticonvulsants ≥ 4 weeks prior to the screening radiographic study (physiologic corticosteroid replacement is allowed)

- Cardiopulmonary dysfunction as defined by the following:
  - Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg)
  - Inadequate left ventricular ejection function at baseline, $< 50\%$ by either ECHO or MUGA
  - History of symptomatic congestive heart failure-Grade ≥ 3 per NCI CTCAE v4.0 or Class $\geq$ II New York Health Association (see Appendix 5)
  - History of a decrease in LVEF to $< 40\%$ or symptomatic congestive heart failure with prior trastuzumab treatment
  - Myocardial infarction or unstable angina within 6 months of randomization
  - Current dyspnea at rest due to complications of advanced malignancy, or other disease requiring continuous oxygen therapy
  - Serious cardiac arrhythmia not controlled by adequate medication
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease, coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- QT interval corrected through use of Fridericia's formula (QTcF) > 470 ms demonstrated by at least two ECGs > 30 minutes apart
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

4.2 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study. Patients will be assigned to dose levels in the order in which they are enrolled and in accordance with the DLT review and dose-escalation and expansion plan.

After signed informed consent has been obtained and preliminary eligibility has been established for a patient, the study site will submit documentation supporting eligibility to the Sponsor and obtain the Sponsor's approval to enroll the patient. Once the Sponsor reviews and approves the patient for enrollment, the Sponsor will provide the dose group assignment. No pre-planned protocol deviations or waivers will be allowed.

During the dose-escalation stage of the study, when the last patient in a cohort has completed the 21-day DLT assessment window, a dose-escalation meeting will be held to review whether DLTs were observed in any patients in that cohort, as well as to review available cumulative safety data for the current and prior cohorts. Dose-escalation decisions will be made and communicated to the sites in writing prior to the opening of the next cohort.

Treatment assignment will be conducted using an interactive voice or web-based response system (IxRS). After written informed consent has been obtained, all patients will receive a screening number, which will be assigned by the IxRS. Following completion of the screening period and after all patient eligibility requirements are confirmed, the Sponsor will provide the dose group assignment and patients will be assigned an identification number by the IxRS.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is DHES0815A.

4.3.1 Study Treatment Formulation, Packaging, and Handling

DHES0815A will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. DHES0815A vials must be refrigerated at 2°C–8°C (36°F–46°F) until use. DHES0815A should not be used beyond the expiration date provided by the manufacturer. Vial contents should not be frozen or shaken and should be protected from light during storage. Vials are intended for single use only; therefore, any remaining solution should be discarded. For additional information on the formulation and handling of DHES0815A, see the pharmacy manual.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of DHES0815A should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events

associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.2.

DHES0815A administration will be performed in a setting with emergency medical facilities and access to a critical care unit with staff who are trained to monitor for and respond to potentially serious reactions. The total dose of DHES0815A for each patient will depend on the dose assignment and the patient's weight on Day 1 of each cycle (or within 72 hours prior to Day 1 of that cycle). Patients may receive the initial (Cycle 1) dose of DHES0815A unless the patient's body weight has changed by $>5\%$ from baseline weight, in which case a new DHES0815A dose must be calculated. This new dose of DHES0815A may be given in subsequent cycles, unless the patient experiences another $>5\%$ change in body weight, in which case a new DHES0815A dose must be calculated. DHES0815A will be administered once every 21 days. Patients meeting the criteria outlined in Section 3.1.1.4 may continue to receive treatment with DHES0815A until they meet criteria for study treatment discontinuation (see Section 4.6.1), discontinue the study (see Section 4.6.2), or the Sponsor terminates the study.

DHES0815A will be administered to patients by IV infusion using either a polyvinyl chloride (PVC) or polyolefin composed of polyethylene and polypropylene (PO-PE-PP) bag containing 0.9% NaCl and using an infusion set equipped with a 0.2-μm in-line filter. The final DHES0815A concentration will be determined by dose and patient weight. Compatibility testing has shown that DHES0815A is stable and does not adsorb to the IV bags or IV administration sets when diluted in 0.9% NaCl solution in PVC or PO-PE-PP bags at expected concentrations. For additional information on the dose solution preparation and handling of DHES0815A, see the pharmacy manual and the DHES0815A Investigator's Brochure.

The initial infusion (i.e., Cycle 1) should be administered over 90 (± 10) minutes. The DHES0815A infusion may be slowed or interrupted for patients experiencing infusion-related adverse events (see Table 3 in Section 5.1.2.3 for management guidelines for infusion-related adverse events). If no infusion-related reactions (IRRs) are observed for Cycle 1, the time for subsequent infusions (Cycle 2 and beyond) may be reduced to 30 (± 10) minutes. Patients will be observed for 2 hours for fever, chills, rigors, hypotension, nausea, or other infusion-related adverse events following the first two infusions of DHES0815A at Cycle 1 and Cycle 2. Patients who experience infusion-related adverse events following any given infusion should be observed for 2 hours following the next subsequent infusion. In the absence of infusion-related adverse events, infusions of DHES0815A subsequent to Cycle 2 may be administered over 30 (± 10) minutes followed by a 30-minute observation period after the infusion.

DHES0815A infusions will be administered per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Infusions of DHES0815A

	Cycle 1	Cycle 2	Cycle 3 and Beyond
Infusion time	90 minutes	30 minutes	30 minutes
Observation time	2 hours	2 hours	30 minutes

Notes:

Infusion and observation times assume that no infusion-related adverse events occurred during the prior infusion. If no infusion-related adverse event occurred during the first infusion, the infusion time for Cycle 2 can be shortened to 30 minutes, but the observation time should remain at 2 hours. If no infusion-related adverse events have occurred after the first two cycles, both the infusion time and the observation time can be shortened to 30 minutes.

If a patient experiences an infusion-related reaction, refer to Section 5.1.1.10 for details on management.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (DHES0815A) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to DHES0815A

The Sponsor (Genentech, a member of the Roche Group) will offer continued access to Genentech IMP (DHES0815A) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Genentech IMP (DHES0815A) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Genentech IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Genentech IMP (DHES0815A) after completing the study if any of the following conditions are met:

- The Genentech IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for advanced and/or metastatic HER2-positive BC
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for advanced and/or metastatic HER2-positive BC
- Provision of the Genentech IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives, hormone-replacement therapy, or other maintenance therapy
- Hematopoietic growth factors such as erythropoietin, granulocyte colony-stimulating factor (filgrastim, pegfilgrastim), and granulocyte-macrophage colony-stimulating factor (sargramostim) as clinically indicated and when used in accordance with instructions provided in the package inserts.

  Any use of these agents during the DLT assessment window must be discussed with the Medical Monitor.
- Bisphosphonates and denosumab for prevention of skeletal-related events as clinically indicated and when used in accordance with instructions provided in the package inserts
- Biologic agents (other than those listed above and not intended for the treatment of cancer) as clinically indicated and when used in accordance with instructions provided in the package inserts

In general, investigators should manage a patient’s care with supportive therapies as clinically indicated, per local standard practice.

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

DHES0815A consists of a human monoclonal IgG1 antibody, a cleavable disulfide-linker, and PBD-MA. There is a low risk of PK drug–drug interactions (DDI) between the MAb component and small molecules due to different metabolic pathways that each undergo. In vitro data also suggest there is low risk of DDI specifically with the released payload from DHES0815A, unconjugated PBD-MA. PBD-MA was found to be a weak competitive inhibitor of CYP2C8 and CYP3A4/5 and a time-dependent inhibitor for CYP3A4/5 as well as CYP2B6 at concentrations much higher than expected to be reached given the projected administered clinical doses of DHES0815A. Given that the expected liver concentration of the PBD-MA will likely be low at the administered clinical dose, the DDI potential for the unconjugated PBD-MA as a perpetrator is likely low. In human and animal liver microsomes the unconjugated PBD-MA was extensively metabolized by oxidation pathways, which are catalyzed mainly by CYP3A4/5 as well as CYP2J2 (minor). However, in vivo contribution of CYP3A to the total clearance of unconjugated PBD-MA following administration of DHES0815A is not known at this time. Therefore, the DDI potential for unconjugated PBD-MA is unclear as a victim and the use of strong CYP3A inhibitors should be avoided in patients who are administered DHES0815A. Patients should be closely monitored for adverse reactions if taking strong CYP3A inhibitors cannot be avoided; these include, but are not limited to, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, or voriconazole. Investigators may also consult the Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers web site for a non-exhaustive list of CYP3A:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy for progressive disease except for cases where localized radiotherapy is indicated and approval of the Medical Monitor is obtained
- Immunotherapy for the treatment of cancer
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents for the treatment of cancer
- Herbal therapy
- Any therapies intended specifically for the treatment of advanced cancer, whether approved by regulatory authorities or investigational

Patients who require the use of any of these agents will be discontinued from DHES0815A treatment. Questions about whether specific medications are prohibited therapy during this Phase I study should be discussed with the Medical Monitor.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Collection of any non–safety-related data or patient samples may be terminated by the Sponsor at any time if further collection of such data or samples is also not related to the study's primary objective(s). The decision to discontinue any data collection will be communicated to sites (IRBs and ECs) by means of a memorandum and will not require a protocol amendment.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to screening visit will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination will be done at screening and should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatologic, musculoskeletal, respiratory, genitourinary, gastrointestinal, and neurologic systems.

Weight will be measured at each cycle within 72 hours prior to administration of study drug. Height will be measured during the screening period only.

Targeted physical examinations should be limited to systems of primary relevance (i.e., cardiovascular, respiratory, skin, and any system that might be associated with tumor assessment) and systems associated with symptoms.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, heart rate, systolic and diastolic blood pressures while the patient is in a seated position, pulse oximetry, and temperature.

On Day 1 of Cycle 1 and on Day 1 of Cycle 2 and on any day of infusion where a 2-hour post-infusion observation period is warranted (see Section 4.3.2), vital signs will be assessed prior to infusion, every 15 (± 5) minutes during infusion, at the end of infusion (± 5 minutes), and every 30 (± 10) minutes after the infusion for 2 hours. For all other days of infusion where a 30-minute post-infusion observation period is allowed (see Section 4.3.2), vital signs will be assessed prior to infusion, every 15 (± 5) minutes during infusion, at the end of infusion (± 5 minutes), and at 30 (± 10) minutes after infusion. Oxygen saturation via pulse oximetry will be monitored at a minimum every 15 (± 5) minutes during infusion from pretreatment to the end of the observation period. Additional monitoring should be performed if clinically indicated. Vital signs will be monitored at the timepoints specified in Appendix 1.

4.5.5 Tumor and Response Evaluations

All measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response will be assessed using RECIST v1.1 (see Appendix 3). Assessments should include an evaluation of all sites of disease.

Computed tomography (CT) scans should include the chest, abdomen, and pelvis; CT scans of the neck should be included if clinically indicated. Magnetic resonance imaging (MRI) scan may be used instead of CT scans in patients for whom CT scans are contraindicated or in circumstances in which MRI is the preferred imaging modality.

The same method of assessment and the same technique should be used at baseline and for all on-study assessments.

If at any time during the treatment phase there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled tumor assessment should be performed.

Objective responses using RECIST v1.1 should be confirmed by repeat assessments performed ≥4 weeks after initial documentation of response.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Local Laboratory Analyses

Local laboratory (i.e., non-central laboratory) assessments may be performed up to 72 hours preceding DHES0815A administration unless otherwise specified. Pre-infusion laboratory samples should be drawn within 0–4 hours before the start of infusion. Post-infusion laboratory samples should be drawn within 0–30 minutes after the end of infusion, unless otherwise specified. Results from predose assessments must be reviewed by the investigator and the review documented prior to DHES0815A administration.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: complete blood count, including hemoglobin, hematocrit, platelet count, RBC count, WBC count, and absolute differential count *for* neutrophils *and* lymphocytes*; percentage or absolute count is acceptable for all other cell types (e.g., eosinophils, monocytes, basophils, bands, and other cells)*
- Serum chemistry panel: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, LDH, ALT, AST, and ALP.
- Coagulation: INR, aPTT, PT
- Pregnancy test: serum and urine pregnancy tests
- Urinalysis, including macroscopic analysis (specific gravity, protein, pH, glucose, ketones, blood, bilirubin, leukocyte esterase, urobilinogen, and nitrite) and, if any abnormalities, microscopic analysis (RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast).

4.5.6.2 Central Laboratory Analyses

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Archival Tumor Tissue

  Patients will provide the following tumor tissue samples:

  1. Tumor tissue sample collected at time of initial diagnosis
  2. The most recent available metastatic tumor biopsy tissue

     Archival tissue will be used for determination of HER2 status and for exploratory biomarker research.

  Availability of a representative FFPE tumor specimen in a paraffin block (preferred) or at least [redacted] sections with an associated pathology report must be confirmed prior to study enrollment. If less than [redacted] slides are available, the patient may still be eligible for the study after Medical Monitor approval has been obtained.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

  In the event that enrollment into the expansion cohort of the study is restricted to patients with HER2-positive tumors as prospectively assessed [redacted] (see Section 3.3.7), tumor samples will need to be submitted and assessed for HER2 expression prior to the first dose of DHES0815A.

- Optional Tumor Biopsy

  An additional optional minimally invasive biopsy may be collected per investigator discretion, preferably at the time of radiographic progression. The suitability and timing of biopsy collection for individual patients will be based on discussion with and the approval of the Sponsor's Medical Monitor. Patients who agree to undergo these additional biopsies will be asked to sign an optional Informed Consent Form.

- Blood for Biomarker Analysis

  [redacted]

4.5.6.3 Sponsor or Designee for Analysis

The following samples will be sent to the Sponsor or a designee for analysis:

- Blood samples for PK analysis of DHES0815A: serum DHES0815A total antibody (all DAR species, including DAR 0 and DAR ≥ 1), plasma acPBD-MA, and unconjugated PBD-MA concentrations with the use of validated methods.
- Plasma samples for assessment of DHES0815A catabolism
- A baseline serum sample (Cycle 1, Day 1 only) may be used, depending upon review of DHES0815A PK/ADA data, to measure HER2 ECD, pertuzumab, trastuzumab, and/or trastuzumab emtansine levels in order to better understand potential drug interferences or impact on pharmacokinetics.
- Serum samples for ADA

  A validated antibody-bridging ELISA will be used to screen for and confirm the presence of anti-DHES0815A antibodies in patient samples as well as to characterize domain specificity and titer of ADA in positive samples.

At the discretion of the Sponsor, these samples may also be used for exploratory analyses related to DHES0815A, if considered necessary.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Samples collected for PK and immunogenicity (ADA) analysis may be needed for additional method development, validation, biomarker assays, and characterization. These samples, if not used up, will be destroyed within 15 years after the final clinical study report has been completed.
- Blood samples collected for [redacted] will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- Blood and tumor tissue samples collected for biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site upon request.

When a patient withdraws from the study, samples collected prior to the date of withdrawal will still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, any data collected prior to patient request for destruction of samples will still be used for analysis.

Data arising from sample analysis, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

[redacted] The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.7 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1). ECGs acquired on different days should be as closely time-matched as feasible. Three interpretable ECG recordings (e.g., without artifacts) must be obtained at each timepoint (±5 minutes). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Single ECG recordings may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at a central location. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is >500 ms and/or 60 ms longer than the baseline value, another triplicate ECG must be recorded, ideally within the next 5 minutes, and triplicate ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.8 Cardiac Assessments with Echocardiography or MUGA

ECHO is the preferred method of assessment of LVEF, although MUGA scan is also accepted. All efforts should be made to use the same method and the same facilities throughout the entire study for each patient and to have the same assessor for each.

LVEF is to be assessed at screening, during the last week (Days 15–21) of Cycles 1, 2, 4, and 6, and then every four cycles thereafter, or as clinically indicated. Please refer to Appendix 1 for the schedule of cardiac assessments.

4.5.9 Ocular Assessments with BCVA and Anterior Slitlamp Examination

Ophthalmic examinations will include assessment of BCVA and an anterior segment slit lamp examination with fluorescein. Ophthalmic examinations must be conducted during the screening period, during the last week (Days 15–21) of even-numbered cycles until Cycle 6 (i.e., at Cycles 2, 4, and 6) and every four cycles thereafter (i.e., at Cycles 10, 14, 18, etc.), at the study discontinuation visit (unless the most recent ophthalmic examination has occurred within the past 4 weeks) and at unscheduled time points if clinically indicated.

[redacted]

[redacted]

[redacted]

[redacted]

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to DHES0815A or HER2-positive BC:

- Blood plasma samples collected at baseline and disease progression
- Tumor tissue samples from biopsies performed at the investigator's discretion during the study at time of progression, if deemed clinically feasible, for exploratory research on biomarkers

  Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred.
- Leftover serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for testing, which may include, but are not limited to, analysis of germline or somatic mutations via [redacted], whole exome sequencing, [redacted], or other genomic and molecular analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. [redacted] and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies.

The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO39869

does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study GO39869.

4.5.11.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Pregnancy
- Use of an anti-cancer therapy other than DHES0815A
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to RECIST v1.1 unless a patient continues to demonstrate signs and symptoms of clinical benefit from DHES0815A treatment that is independent of RECIST v1.1, as judged by the investigator and upon discussion with the Medical Monitor (see Appendix 3)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced unless enrolled in the dose-escalation cohorts and they discontinue prior to completion of the 21-day DLT window.

Patients will return to the clinic for a treatment discontinuation visit within 42 days after the last dose of study drug (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from Study

Patients will return to the clinic for a study discontinuation visit at treatment discontinuation.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

DHES0815A is not approved, and clinical development is ongoing. This is the first study in which DHES0815A will be administered to humans. The safety plan for patients in this study is based on nonclinical experience with DHES0815A, clinical experience with HER2-targeting molecules (i.e., trastuzumab, pertuzumab, and trastuzumab emtansine), and published clinical data of rovalpituzumab tesirine (DLL3-targeting ADC linked to a

PBD dimer; Rudin et al. 2017) and SJG-136 (PBD dimer; Hochhauser et al. 2009). The anticipated important potential safety risks for DHES0815A are outlined below. Please refer to the DHES0815A Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Potential Risks Associated with DHES0815A

5.1.1.1 Left Ventricular Dysfunction

Patients treated with DHES0815A may be at risk of developing left ventricular dysfunction. Significant cardiac events, including LVEF of $<40\%$, have been observed with HER2-targeting molecules (i.e., trastuzumab, pertuzumab, and trastuzumab emtansine).

Patients must meet specified LVEF requirements to be included in this study (see Section 4.1.2).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO (or MUGA) scans as described in Section 4.5.8 and the schedule of activities (see Appendix 1).

Guidelines for management of patients who develop left ventricular dysfunction are provided in Table 3.

5.1.1.2 Dermatologic Toxicity

Skin disorders, including hyperpigmentation, erythema, and rash may occur in patients treated with DHES0815A. In nonclinical studies, hyperpigmentation has been observed in cynomolgus monkeys and did not reverse during the recovery period. HER2-targeting molecules can cause skin disorders, including erythema, rash, and pruritus. Skin disorders have also been observed with rovalpituzumab tesirine, including Grade ≥ 3 events of rash, erythema, and photosensitivity (Rudin et al 2017).

Patients should be monitored closely for skin toxicity. Patients are advised to prevent exposure to UV light and apply sunscreen to exposed areas of the skin when outside in the sun. If skin toxicity occurs, patients should be evaluated by a dermatologist, and a proper dermatologic diagnosis should be established and recorded on the eCRF. For Grade ≥ 2 dermatologic events, photographs of the affected area should be obtained if possible and submitted to the sponsor to document the type and course of the skin toxicity. The photographs will be taken in such a manner as not to create any risk of

identifying the patient; photographs will be thoroughly de-identified at the sites prior to providing them to the Sponsor.

5.1.1.3 Hematological Toxicity

In nonclinical studies, mild decreases in lymphocytes, eosinophils, and reticulocytes have been observed in cynomolgus monkeys. In addition, minimal lymphoid depletion was noted in spleen and lymph nodes. Thrombocytopenia has been reported in patients in clinical trials of trastuzumab emtansine and cases of severe bleeding events, some with a fatal outcome, have been observed (Kadcyla® U.S. Package Insert). Declines in other hematopoietic lineages were less frequent with the use of trastuzumab emtansine than that observed for platelets. Thrombocytopenia also occurred in 12% of patients treated with rovalpituzumab tesirine (including two Grade 4 and one fatal event; Rudin et al. 2017).

Hematologic laboratory parameters will be monitored as described in Section 4.5.6 and the schedule of activities (see Appendix 1). Guidelines for management of DHES0815A in patients who develop hematologic toxicity are provided in Table 3.

5.1.1.4 Nephrotoxicity

No renal findings or changes in urinalysis were observed in GLP toxicology studies with DHES0815A in cynomolgus monkeys. However, tubular degeneration had been seen in nonclinical studies at higher doses of DHES0815A than were tested in the GLP toxicology studies.

Patients with a baseline serum creatinine level higher than $1.5 \times$ ULN or creatinine clearance $<$65 mL/min will be excluded from this study. To address potential renal toxicity, BUN and creatinine will be measured frequently and urinalysis will be done at each cycle.

5.1.1.5 Hepatic Toxicity

No pathological liver findings and no changes in liver function tests were observed in GLP toxicology studies in cynomolgus monkeys. Hepatic toxicity (including liver failure and death) and nodular regenerative hyperplasia of the liver are identified risks for trastuzumab emtansine and elevated transaminases (Grades 2–4) were observed with both SJG-136 (Hochhauser et al. 2009) and rovalpituzumab tesirine (Rudin et al. 2017).

Patients must meet specified hepatic laboratory test requirements to be included in this study (see Section 4.1.2). Hepatic laboratory parameters will be monitored as described in Section 3.1.1.1 and the schedule of activities (see Appendix 1).

5.1.1.6 Ocular Toxicity

In GLP toxicology studies in cynomolgus monkeys, corneal pigmentation was observed after administration of DHES0815A. Ocular toxicity is therefore a potential risk for patients treated with DHES0815A and may present with impaired vision.

Ophthalmic examinations will include assessment of BCVA and an anterior segment slitlamp examination with fluorescein. Ophthalmic examinations must be conducted during the screening period, during the last week (Days 15–21) of even-numbered cycles until Cycle 6 (i.e., at Cycles 2, 4, and 6) and every four cycles thereafter (i.e., at Cycles 10, 14, 18, etc.), and at the study discontinuation visit (unless the most recent ophthalmic examination has occurred within the past 4 weeks). Patients who experience ocular symptoms, including but not limited, to eye pain, dry eyes, blurred vision, or a decline in visual acuity, will be required to undergo an ophthalmic examination at an unscheduled visit as soon as practical. Such visits should include the same assessments as those described above, along with any additional assessments deemed clinically indicated per standard of care.

If no study drug–related ophthalmic adverse events Grade $\geq$2 are reported during dose escalation, ophthalmic examinations may not be required for patients enrolled in the expansion cohort.

5.1.1.7 Pulmonary Toxicity

In GLP toxicology studies in cynomolgus monkeys, an increase in alveolar macrophages was observed after the administration of DHES0815A. Mild alveolar degeneration and fibroplasia was observed in nonclinical studies when cynomolgus monkeys received DHES0815A at dose levels higher than those given in the GLP toxicology studies. Cases of interstitial lung disease, including pneumonitis, some leading to acute respiratory distress syndrome or death, have been reported in patients receiving HER2-targeting drugs (i.e., trastuzumab, pertuzumab, trastuzumab emtansine). Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at risk of pulmonary events. Therefore, patients with clinically significant pulmonary symptoms or disease will be excluded from this study (see Section 4.1.2). Patients who develop new respiratory symptoms or imaging findings suggestive of pulmonary toxicity should be evaluated by a pulmonologist.

5.1.1.8 Vascular Leak Syndrome

GLP studies in cynomolgus monkeys receiving DHES0815A did not reveal indications for vascular leak, edema, or serosal effusion. In clinical trials with SJG-136 (Hochhauser et al. 2009) and rovalpituzumab tesirine (Rudin et al. 2017), vascular leak syndrome, serosal effusions, and edema were observed.

Patients treated with DHES0815A will be closely monitored for clinical signs and symptoms indicating vascular leak. As part of scheduled tumor assessment, CT or MRI imaging of chest and abdomen will be performed that may also be assessed for evidence of internal effusions.

5.1.1.9 Gastrointestinal Toxicity

Gastrointestinal toxicity (watery diarrhea, mucosal atrophy in small and large intestine and stomach) was observed in nonclinical studies when cynomolgus monkeys received DHES0815A at dose levels higher than those given in the GLP toxicity study.

Patients will be closely monitored for clinical signs of gastrointestinal toxicity, and supportive treatment will be initiated at the investigator's discretion.

5.1.1.10 Infusion-Related Reactions, Hypersensitivity, Anaphylaxis

Some MAbs may be associated with the development of allergic or anaphylactic reactions to either the active protein or excipients. True allergic/anaphylactic reactions are rare with the first dose of a product, because they require prior sensitization. Patients with true allergic/anaphylactic reactions should not receive further doses of the product.

MAbs may also be associated with reactions that are clinically indistinguishable from true allergic/anaphylactic reactions but that are mediated through direct release of cytokines or other pro-inflammatory mediators. Such reactions are often termed IRRs. IRRs typically occur with the first infusion of a MAb product and are generally less frequent and/or less severe with subsequent infusions. They can often be managed by slowing the infusion rate and/or pretreatment with various medications.

Despite the different pathophysiology of IRRs (reactions involving cytokine release) and hypersensitivity (allergic) reactions, the clinical manifestations are the same and include flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia. Allergic/anaphylactic reactions and IRRs typically begin during or within several hours after completing the infusion. The onset of symptoms may be rapid, and some reactions may be life threatening.

Patients with a history of allergic/anaphylactic reactions to MAbs, including trastuzumab, pertuzumab, or trastuzumab emtansine, will be excluded from this study (see Section 4.1.2).

Administration of DHES0815A will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients should be closely monitored for IRRs during and after each infusion of DHES0815A, as described in Section 4.3.2.

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in Table 3. Please see Appendix 6 for guidance on anaphylaxis precautions.

5.1.1.11 Immunogenicity

As with any recombinant antibody, DHES0815A may elicit an immune response and patients may develop antibodies against DHES0815A. ADA response and potential

correlation of response to relevant clinical safety endpoints will therefore be assessed for all treated patients. Validated screening and confirmatory assays with appropriate sensitivity and therapeutic tolerance will be employed to detect ADAs at multiple timepoints before, during, and after treatment with DHES0815A. Serum samples will be collected from all patients prior to their first dose of DHES0815A and at several additional timepoints (see Appendix 2).

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose and Schedule Modifications

The dose of DHES0815A can be reduced by one dose level up to two times for management of drug-related toxicities. If further dose reduction is indicated after two dose reductions, the patient must discontinue DHES0815A. Dose increases after prior dose reduction for drug-related toxicities will not be permitted.

DHES0815A treatment may be temporarily suspended in patients who experience toxicity considered to be related to study drug. Dose delays for >14 days because of toxicity have to be discussed with and approved by the Medical Monitor; otherwise, the patient should be discontinued from DHES0815A. DHES0815A treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.2.2 Management Guidelines for Patients Who Experience Adverse Events

Guidelines for managing DHES0815A-related toxicities other than the ones specified in Table 3 are as follows:

- For Grade ≥ 3 adverse events: DHES0815A treatment should be withheld for Grade ≥ 3 DHES0815A-related toxicities that have not recovered to Grade ≤ 1 or baseline prior to planned dosing. The next scheduled dose may be delayed by up to14 days. Longer dose interruptions are only allowed upon discussion with the Medical Monitor. If improvement to Grade ≤ 1 or baseline does not occur within 14 days (or a longer interval approved by the Medical Monitor), DHES0815A treatment should be discontinued. If the DHES0815A-related toxicity improves to Grade ≤ 1 or baseline, DHES0815A may be restarted at a reduced dose.

  The DHES0815A dose in subsequent cycles should be reduced to either the next lowest dose level tested in dose escalation for patients in the dose escalation cohort, or by approximately 25%–50% (upon discussion with the Medical Monitor) for patients in the expansion cohort. No more than two dose reductions are permitted on study.

- For Grade 2 adverse events: DHES0815A treatment should be withheld for Grade 2 DHES0815A-related toxicities that have not recovered to Grade 1 or baseline prior to planned dosing. The next scheduled dose may be delayed by 14 days. Longer dose interruptions may be allowed upon discussion with the Medical Monitor. If improvement to Grade ≤ 1 or baseline does not occur within

14 days (or a longer interval approved by the Medical Monitor), DHES0815A treatment should be discontinued. If the DHES0815A-related toxicity improves to Grade ≤1 or baseline, DHES0815A may be restarted at the current dose.

5.1.2.3 Management Guidelines for Patients Who Experience Specific Adverse Events

Guidelines for management of specific adverse events (hematologic toxicity and IRRs/hypersensitivity) are outlined in Table 3. Additional guidelines are provided in Figure 2 (left ventricular dysfunction) and below for increases in QT interval and ocular toxicities.

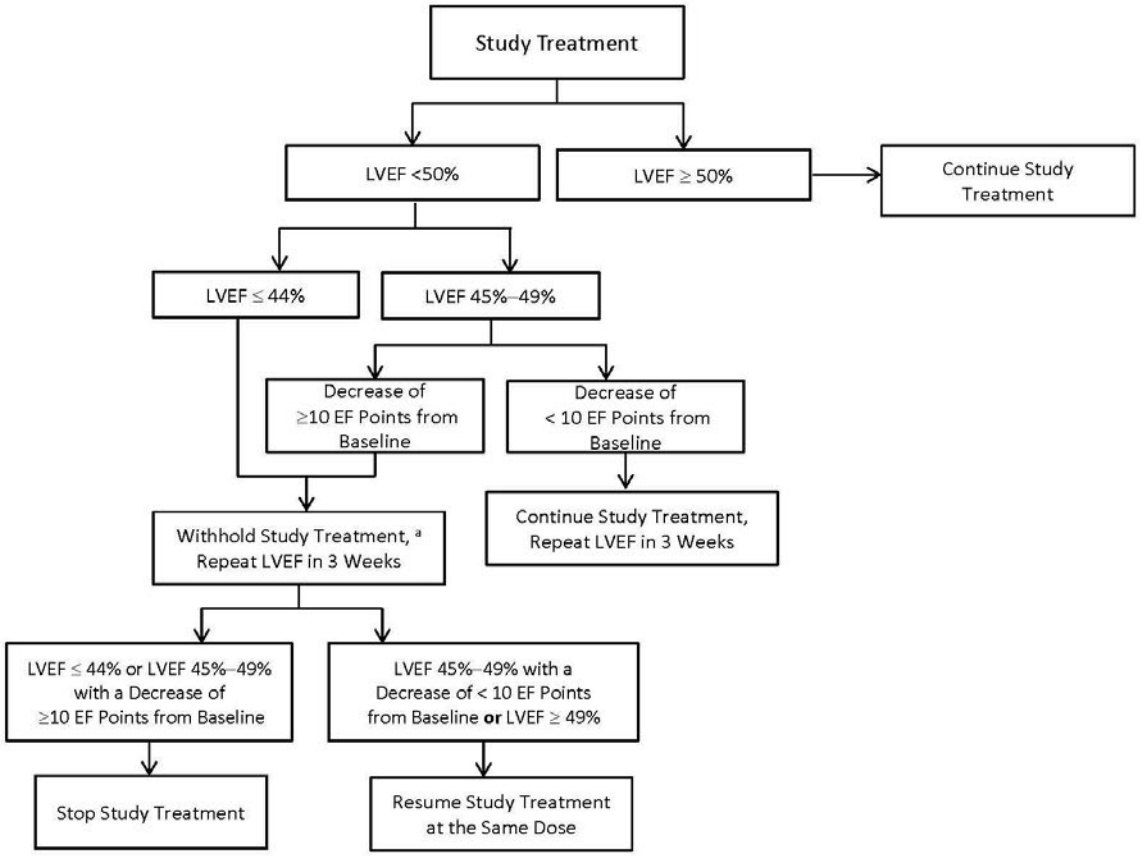
Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Hematologic toxicity as manifested in any one of the below laboratory abnormalities: • Absolute neutrophils < 1500/mm^3 • Hemoglobin < 8 g/dL • Platelets < 100,000/mm^3	• Withhold all study treatment up to 14 days; longer dose interruption may be allowed upon discussion with the Medical Monitor. • Give supportive treatment as clinically indicated per local practice. • Resume DHES0815A treatment if ANC ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 8 g/dL. • If hematologic toxicity leading to dose hold recurs in consecutive cycles, resume DHES0815A treatment at a reduced dose if ANC ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, and hemoglobin ≥ 8 g/dL. • If hematologic toxicity leading to dose hold occurs in two consecutive cycles at the reduced dose, discontinue DHES0815A.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Infusion-related reaction or hypersensitivity Grades 1–2	Reduce DHES0815A infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate or according to local standard of care, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Patient may continue DHES0815A infusion (in same cycle and subsequent cycles) at the same dose level but at a decreased infusion rate at the investigator's discretion. • Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine, acetaminophen/paracetamol or corticosteroids) may be given at the investigator's discretion for subsequent infusions. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue DHES0815A permanently.
Infusion-related reaction or hypersensitivity Grade 3	Stop DHES0815A infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Note: If Grade 3 symptoms included wheezing, hypoxia, generalized urticaria, angioedema or other signs and symptoms indicating anaphylactic reaction, discontinue DHES0815A permanently. For other Grade 3 events, patients may continue DHES0815A (in same cycle and subsequent cycles) at the same dose level but reduced infusion rate at the investigator's discretion. • Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine, acetaminophen/paracetamol or corticosteroids) should be given for subsequent infusions. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue DHES0815A permanently.
Infusion-related reaction or hypersensitivity Grade 4	Stop DHES0815A infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Discontinue DHES0815A.

Figure 2 Left Ventricular Dysfunction Management Guidelines



EF = ejection fraction; LVEF = left ventricular ejection fraction.

[a] Patient may continue study treatment after up to a maximum of two study drug holds for reduction in LVEF. DHES0815A should be permanently discontinued if a third dose hold would be required per algorithm above.

Management of Increases in QT Interval

Study drug should be discontinued in patients who develop any of the following, unless there is a clear alternative cause for the changes:

- Sustained (at least two ECG measurements > 30 minutes apart) QTcF that is > 500 ms and > 60 ms longer than the baseline value
- Sustained absolute QTcF that is > 515 ms
- An episode of torsades de pointes or a new ECG finding of clinical concern

Of note, if there is a new intraventricular conduction block, the increase in QRS complex duration should be subtracted from the QTcF change, because this represents an increase in QTcF unrelated to alterations in repolarization. Also of note, it is not uncommon to record arrhythmias such as non-sustained ventricular tachycardia, supraventricular tachycardia, pauses, or atrial fibrillation in healthy volunteers receiving placebo during periods of extended ECG monitoring. Therefore, it is critical that expert cardiology advice be sought to confirm any ECG changes and to ascertain the likelihood

of a drug-induced arrhythmia versus the background occurrence of this arrhythmia. In such a situation, saving all available ECG data is highly suggested.

Management of patients with sustained QTcF prolongation should include close monitoring, with ECGs repeated at least hourly until two successive ECGs show resolution of the findings, correction of any electrolyte abnormalities, and possible discontinuation of other concomitant medications that are known to prolong the QT interval. Consultation with a cardiologist or electrophysiologist is recommended to help in the management of such patients.

In rare circumstances, it may be acceptable to resume study drug at a lower dose, provided that any ECG abnormalities have resolved and the patient is appropriately monitored. Clinical judgment should be applied.

Management of Ocular Toxicities

At the first occurrence of asymptomatic ocular findings on ophthalmologic examination that are considered related to DHES0815A, the patient may be re-treated with DHES0815A as per study schedule (i.e., dose hold or dose reduction not required) but needs to undergo ophthalmic examinations before each additional dose to reassess the ocular finding.

- If the ocular finding does not worsen and does remain asymptomatic in four consecutive cycles, the patient may continue dosing and resume the standard ophthalmic examination schedule (even-numbered cycles until Cycle 6, and every four cycles thereafter as described in Section 4.5.9).

- If the ocular finding worsens or if the patient develops ocular symptoms, study drug must be held until resolution or clear improvement. Re-treatment may be initiated upon discussion with the Medical Monitor.

At the first occurrence of symptomatic ocular findings considered related to study drug, DHES0815A must be held until resolution of visual symptoms and resolution or clear improvement of the ocular finding on ophthalmologic exam. The patient should undergo ophthalmic examinations at least every 3 weeks, or more often as clinically indicated for reassessment.

- Once visual symptoms resolve and ocular findings resolve or improve, re-treatment may be initiated upon discussion with the Medical Monitor.

In the case of first re-occurrence of asymptomatic or symptomatic ocular findings considered related to study drug, DHES0815A must be held until resolution of visual symptoms and resolution or clear improvement of the ocular finding. The patient should undergo ophthalmic examinations at least every 3 weeks, or more often as clinically indicated for reassessment.

Once visual symptoms resolve and ocular finding resolve or improve, re-treatment may be initiated upon discussion with the Medical Monitor at a reduced dose of DHES0815A.

If asymptomatic or symptomatic ocular findings re-occur for a second time, DHES0815A must be permanently discontinued.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10 for worsening of BC
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- All DLTs
- Cases of potential drug-induced liver injury that include any increase in hepatic transaminase (ALT or AST) $>3\times$ baseline in combination with either an increase in direct bilirubin $>2\times$ ULN or clinical jaundice, in the absence of cholestasis or other contributory factors (consistent with Hy's Law; Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Dose-Limiting Toxicities (Immediately Reportable to the Sponsor)

During the DLT assessment window, adverse events identified as DLTs, as defined in Section 3.1.1.1, are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 or reporting instructions).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 42 days after the last dose of study drug or until the patient is lost to follow-up, withdraws consent, initiates another anti-cancer therapy, or until study discontinuation/termination, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

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

Note: Based on the most recent version of NCI CTCAE (v 4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study

- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during study drug administration or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than IRRs, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver

failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

Another exception is symptomatic ocular events. In such cases, the symptoms reported by the patient and any abnormal findings observed on ophthalmologic examination should be recorded separately on the Adverse Event eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious"

to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia" and a decreased neutrophil count of 500/mm^3 should be recorded as "neutropenia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Sections 5.2.2 and 5.2.3).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of BC.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of

reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of breast cancer, "breast cancer progression" should be recorded on the Adverse Event eCRF and the details (e.g., clinical course, clinical findings, cause of death as per the death certificate) should be recorded in the Serious Adverse Event detail field.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease (e.g., new lesion, increase in target- or non-target-lesions) should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer (e.g. tumor pain or failure to thrive that require in-patient care)

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of DHES0815A are available.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- DLTs during the DLT assessment window (defined in Section 5.2.4; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Genentech Medical Monitor contact information:

Medical Monitor: [redacted], *M.D.*

Telephone No.: [redacted] (mobile)

Alternate Telephone No.: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest and Dose-Limiting Toxicities

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event) by faxing the form using the fax number provided to investigators.

Serious adverse events should be reported by fax to PPD.

North America
Telephone No.: 1 800 201 8725
Fax No.: 1 888 488 9697

EMEA and Asia Pacific
Telephone No.: 44 1223 374 240
Fax No.: 44 1223 374 102

Once the electronic data capture (EDC) system is available, all information will need to be entered and submitted via the EDC system.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 42 days after the last dose of study drug or until the patient is lost to follow-up, withdraws consent, initiates another anti-cancer therapy, or study discontinuation/termination, whichever occurs first. DLTs will be reported during the DLT assessment window. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event) by faxing the form using the fax number provided to investigators in Section 5.4.2.1. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 8.5 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy) by faxing the form using the fax number provided to investigators in Section 5.4.2.1. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 5.5 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy) by faxing the form using the fax number provided to investigators in Section 5.4.2.1. Attempts should be made to

collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events that are considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as

42 days after the last dose of study drug or until the patient is lost to follow-up, withdraws consent, initiates another anti-cancer therapy, or study discontinuation/termination, whichever occurs first) if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, by faxing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the DHES0815A Investigator's Brochure as a reference document.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The objective of the dose escalation is to determine the MTD/MAD and RP2D of DHES0815A.

If the safety and PK profile seen in the dose-escalation portion of the study is deemed to be favorable to justify further continuation of the study, expansion cohorts will be enrolled to further confirm safety and tolerability and to assess preliminary evidence of anti-tumor activity and exploratory pharmacodynamic markers of response.

The final analysis will be based on patient data collected through patient discontinuation or study discontinuation, whichever occurs first. All analyses will be based on the safety-evaluable population. All summaries will be presented according to the assigned dose level and cohort. In general, data will be summarized as warranted, and listings will be used in place of tables when the samples sizes are small. Continuous variables will be summarized using means, standard deviations, median, and ranges; categorical variables will be summarized using counts and percentages.

6.1 DETERMINATION OF SAMPLE SIZE

6.1.1 Dose Escalation

Approximately 24–30 patients will be enrolled in the dose-escalation stage. The exact number of patients to be enrolled in the study will depend upon the observed safety and pharmacokinetic/pharmacodynamic profile according to the dose-escalation rules (Section 3.1.1.2).

The operating characteristics of the dose-escalation stage of this study are shown in Table 6, which provides the probability of escalation to the next higher dose for each underlying true DLT rate. For example, for a toxicity that occurs in 5% of patients, there is a >95% probability of escalating. Conversely, for a common toxicity that occurs with a rate of 70%, the probability of escalating is <5%.

Table 6 Probability of Escalation to the Next Dose

True underlying DLT rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating the dose	97%	91%	71%	49%	31%	17%	8%	3%	1%	0.10%

DLT = dose-limiting toxicity.

Table 7 shows the probability of failing to observe toxicity in a sample size of 3 patients given various true underlying toxicity rates. For example, with 3 patients, the probability of failing to observe toxicity occurring at least 60% of the time is less than 7%.

Table 7 Probability of Failing to Observe Toxicity

True underlying DLT rate	5%	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of failing to observe toxicity (n = 3)	86%	73%	51%	34%	22%	13%	6.40%	2.70%	0.80%	0.01%

DLT = dose-limiting toxicity.

6.1.2 Dose Expansion

At the RP2D, up to approximately 25 patients will be enrolled to further assess the safety, tolerability, and preliminary evidence of anti-tumor activity of DHES0815A.

This study is intended to obtain preliminary safety, PK, pharmacodynamic, and activity information in the safety-evaluable population. The sample sizes do not reflect any explicit power and type I error considerations.

Efficacy analyses will be performed on an ongoing basis in close collaboration with the study investigators for the expansion portion of the study to guide potential early stopping of enrollment in the event of lack of efficacy. Decisions to stop enrollment into the expansion cohort for futility will be made based on the totality of the available data, taking into account both safety and efficacy. Anti-tumor activity will be summarized by cohorts with an 80% CI. For example, in a cohort with 25 patients, if 10 of 25 patients have CR or PR, the objective response rate and its 80% CI will be summarized as 40% (27%–55%).

Continuous safety monitoring and interim analyses will be performed for the expansion portion of the study to guide potential early stopping of enrollment in the event of unacceptable toxicity. The first safety interim analysis will occur after approximately 6 patients complete 2 cycles in the expansion cohort or every 6 months, whichever occurs first.

A Bayesian posterior probability approach (Thall and Simon 1994) will be used to evaluate the toxicity in the expansion cohorts, including the rate of DLT-equivalent events that occur during Cycle 1 of study treatments. Events that are DLT-equivalent in the expansion cohort are defined by the same criteria used to identify DLT events in the dose-escalation cohorts (Section 3.1.1.1). During continuous safety monitoring or in an interim analysis, if the number of observed DLT-equivalent events indicates that there is an approximately 80% chance that the true DLT rate is ≥ 25%, accrual to the cohort may be paused. The Medical Monitor and Safety Scientist will determine whether further enrollment in the cohort should be halted and may provide other recommendations as described in Section 3.1.1. The final decision will be based on the totality of the observed DLT-equivalent events, other safety events, as well as feedback from study investigators, Biostatistics, and Clinical Pharmacology. Table 8 provides examples that cover scenarios with different true DLT-equivalent event rate assumptions. The examples show the number of observed DLT-equivalent events that might lead the Sponsor to stop enrollment and the corresponding operating characteristics using the posterior probability approach with a non-informative prior beta (1,1) and the stopping criteria stated above.

Table 8 Examples of Early Stopping Rules Based on DLT-Equivalent Event Rate in an Expansion Cohort

Number of patients	*Number of events to recommend stopping enrollment*	*Probability of early stopping for DLT*		
		If true DLT rate = 40%	*If true DLT rate = 30%*	*If true DLT rate = 20%*
6	*≥ 3*	*46%*	*26%*	*10%*
12	*≥ 5*	*56%*	*28%*	*7%*
18	*≥ 6*	*79%*	*47%*	*13%*

DLT = dose-limiting toxicity (equivalent events).

Note: Recommend stopping enrollment if there is an approximately 80% chance that the true DLT rate is ≥ 25%.

6.2 SUMMARIES OF CONDUCT OF STUDY

Summaries of study conduct will include all enrolled patients in the study. The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for discontinuations and premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including, but not limited, to age, race/ethnicity, weight, type of malignancy, duration of malignancy, site of metastatic disease, baseline ECOG Performance Status, number of prior cancer regimens) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by dose level.

6.4 SAFETY ANALYSES

For safety analyses, the analysis population will include all enrolled patients who receive at least one dose of study medication.

Study treatment discontinuation and reasons for patient discontinuations from the study will be described and summarized. Study drug administration data will be listed and any dose modifications will be flagged.

6.4.1 Adverse Events

All adverse events occurring on or after treatment on Day 1 will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v4.0 toxicity grade.

All adverse events reported during the adverse event reporting period will be considered as treatment-emergent adverse events. Incidence rates will be summarized with frequency and percentage by mapped term, with all patients treated as the denominator, unless otherwise specified. In addition, adverse event incidence rates will also be summarized by severity and relationship to study drug. Treatment-related adverse events are those judged by the Investigator to be at least possibly related to the study drug.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, and DHES0815A exposure. All patients who receive study treatment on Cycle 1, Day 1 will be included in the analyses.

Adverse event data will be listed by patient number and study day. Serious adverse events, including deaths, will be listed separately and will be summarized.

Relevant laboratory and vital sign (pulse rate, blood pressure, and temperature) data will be displayed by time, with NCI CTCAE v4.0 Grades 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by NCI CTCAE v4.0.

Safety data will be accumulated up to the end of the patient's treatment period.

6.4.2 Clinical Laboratory Results

Normal ranges will be used to identify values that are outside the normal ranges, and abnormal laboratory results will be graded according to the NCI CTCAE v4.0.

A shift summary of baseline grade by maximum postbaseline NCI CTCAE grade will be presented, as appropriate. For each laboratory parameter, the baseline laboratory value will be defined as the last laboratory value collected on or prior to the date of the first dose of study drug.

Patients who develop toxicities of Grade ≥ 3 will be summarized. Laboratory test results not having NCI CTCAE grade will also be summarized. Parameters that have criteria available for both low and high values (e.g., hypocalcaemia vs. hypocalcemia) will be summarized for both criteria. Patients will only be counted once for each criterion.

6.5 PHARMACOKINETIC ANALYSES

The pharmacokinetics of DHES0815A will be characterized by measuring DHES0815A total antibody (all DARs including fully conjugated, partially deconjugated, and fully deconjugated anti-HER2 antibody) by ELISA, acPBD-MA by immunoaffinity LC-MS/MS, and unconjugated PBD-MA by LC-MS/MS. Two additional exploratory plasma PK samples (see Appendix 2) will be collected for catabolite and stability/biotransformation analyses. A baseline serum sample (Cycle 1, Day 1 only) may be used, depending upon review of DHES0815A PK/ADA data, to measure HER2 ECD, pertuzumab, trastuzumab, and/or trastuzumab emtansine levels in order to better

understand potential drug interferences or impact on pharmacokinetics. Individual and mean concentration of DHES0815A versus time data will be tabulated and plotted by dose level. The following PK parameters will be derived when appropriate as data allow:

- Total exposure (area under the concentration–time curve)
- Maximum observed serum concentration
- Minimum observed serum concentration
- Clearance
- Volume of distribution at steady state

Compartmental, non-compartmental, and/or population methods may be considered. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, coefficient of variation, median, minimum, and maximum). Other parameters, such as accumulation ratio, terminal half-life, and dose proportionality, may also be calculated.

Additional PK analyses will be conducted as appropriate.

6.6 ACTIVITY ANALYSES

Objective response will be summarized by dose level and cohort. Objective response is defined as a CR or PR, as determined by investigator assessment according to RECIST v1.1 and confirmed by repeat assessment $\geq$4 weeks after initial documentation. Patients with missing baseline or no response assessments will be classified as non-responders.

Among patients with an objective overall response, duration of response (DOR) will be defined as the time from the initial CR or PR to the time of disease progression or death, whichever occurs first. If a patient has not experienced disease progression or death, DOR will be censored at the day of the last tumor assessment showing no disease progression.

6.7 IMMUNOGENICITY ANALYSES

Patients are considered to have treatment-induced ADA responses if they are ADA negative at baseline and develop an ADA response following DHES0815A administration. Patients are considered to have treatment-enhanced ADA if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 4-fold greater than baseline titer (i.e., $\geq$ 0.60 titer units) following study drug administration. ADA incidence will be determined from the patients with treatment-induced and treatment-enhanced ADA.

Patients are considered to be negative for ADAs if they are ADA negative at all timepoints. Patients are considered to be treatment unaffected if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 4-fold

greater than the titer of the baseline sample. ADA prevalence will be determined from all patients with ADA-positive responses at baseline.

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The relationship between ADA status and safety, efficacy, PK, activity, and biomarker endpoints will be analyzed and reported via descriptive statistics, as data allow.

6.8 BIOMARKER ANALYSES

Potential exploratory biomarkers and changes will be listed by dose, schedule, and response status. Additional biomarker analyses with PK, efficacy, and safety data may be conducted as appropriate.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of

time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring. A contract research organization will be responsible for the overall study management.

Approximately 55 patients will be enrolled in this study at global sites. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving

an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Activities

Assessment / Day:	Screening	Cycles 1–4 [a]			Cycles 5–8 [a]			Cycles > 8 [a]		Study Discontinuation Visit [c]	Safety Follow-Up [d]
	−28 to −1	1 [b] (±1)	8 (±1)	15 (±1)	1 [b] (±1)	8 (±1)	15 (±1)	1 [b] (±1)	15 (±1)		
Informed consent	x										
Confirm eligibility criteria	x										
Medical history and demographics [e]	x										
Complete physical examination [f]	x										
Limited physical examination [g]		x	x	x	x	x		x		x	
Height (at screening only) and weight	x	x			x			x		x	
Vital signs [h]	x	x	x	x	x	x		x		x	
ECOG Performance Status	x	x	x	x	x	x		x		x	
Adverse events [i]		x [j]	x	x	x [j]	x		x [j]		x	x
Concomitant medications	x	x	x	x	x	x		x		x	
12-Lead ECG [k]	x	x								x	
Ophthalmic examination [l]	x			x [l]			x [l]		x [l]	x	
Tumor assessment—CT/MRI [m]	x			x			x		x	x	
PK sampling [n]		x	x	x						x	
Serum ADA [n]		x								x	
Hematology [o]	x	x	x	x	x	x		x		x	
Serum chemistry [p]	x	x	x	x	x	x		x		x	
ECHO/MUGA scan [q]	x			x [q]			x [q]		x [q]	x	
Coagulation (aPTT, PT, and INR)	x	As clinically indicated									

Appendix 1
Schedule of Activities (cont.)

Day: Assessment	Screening	Cycles 1–4 [a]			Cycles 5–8 [a]			Cycles > 8 [a]		Study Discontinuation Visit [c]	Safety Follow-Up [d]
	–28 to –1	1 [b] (±1)	8 (±1)	15 (±1)	1 [b] (±1)	8 (±1)	15 (±1)	1 [b] (±1)	15 (±1)		
Serum/urine pregnancy test [r]	x	x			x			x		x	
Urinalysis [s]	x	x			x			x		x	
Tumor tissue [t]	x										
Optional on-progression tumor tissue [u]										x	
Blood for biomarkers testing [v]	x	x								x	
[redacted]											
DHES0815A infusion [x]		x			x			x			

ADA = anti-drug antibody; BCVA = best corrected visual acuity; CT = computed tomography; DLT = dose-limiting toxicity; EC = Ethics Committee; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; hCG = human chorionic gonadotropin; IRB = Institutional Review Board; LVEF = left ventricular ejection fraction; MUGA= multiple-gated acquisition; MRI = magnetic resonance imaging; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; [redacted]

Notes: Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Screening tests and evaluations will be performed within 28 days prior to the first dose of any study drug, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used; such tests do not need to be repeated for screening. Assessments scheduled on a day of study drug administration should be performed prior to study drug dosing, unless otherwise specified.

[a] For patients in the dose-escalation cohort, the following assessments will take place weekly during the first four cycles of DHES0815A administration: limited physical examination, vital signs, ECOG Performance Status, hematology labs, and serum chemistry labs. Patients in the dose-expansion cohort will undergo those same assessments on a weekly basis for only the first two cycles of DHES0815A administration; starting with Cycle 3, these patients will be evaluated according to the schedule of assessments outlined for Cycles 5–8 until they reach Cycle 8.

[b] Laboratory assessments may be performed up to 72 hours preceding DHES0815A administration unless otherwise specified. Results from predose assessments must be reviewed and the review documented prior to DHES0815A administration.

[c] Perform within 42 days after the last infusion of DHES0815A or before starting a new treatment regimen, whichever is earlier. The visit at which response assessment shows progressive disease may be used as the study treatment discontinuation visit.

Appendix 1
Schedule of Activities (cont.)

[d] Patients who have not withdrawn consent or been lost to follow-up will be contacted 42 days after the last dose of study drug for information on adverse events and initiation of any subsequent anti-cancer therapies.

[e] Medical history includes all clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications used by the patient within 7 days preceding the screening visit (including prescription drugs, over-the-counter drugs, and herbal/homeopathic remedies and therapies). Demographic data includes age, sex, and self-reported race/ethnicity.

[f] Complete physical examination should include evaluation of head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[g] Limited physical examination should include systems of primary relevance (i.e., cardiovascular, respiratory, and any system that might be associated with tumor assessment) and systems associated with symptoms. Patients should be evaluated weekly by limited physical examination through Cycle 4, on Day 1 and Day 8 Cycles 5–8, and at least on Day 1 of each Cycle beyond Cycle 8.

[h] Vital signs include measurement of respiratory rate, heart rate, systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, and temperature. On Day 1 of Cycle 1 and on Day 1 of Cycle 2, and on the day of infusion where a 2-hour post-infusion observation period is warranted (Section 4.3.2), vital signs will be assessed prior to infusion, every 15 (± 5) minutes during infusion, at the end of infusion (± 5 minutes), and every 30 (± 10) minutes after the infusion for 2 hours. For all other days of infusion where a 30-minute post-infusion observation period is allowed, vital signs will be assessed prior to infusion, every 15 (± 5) minutes during infusion, at the end of infusion (± 5 minutes), and at 30 (± 10) minutes after infusion. Oxygen saturation via pulse oximetry will be monitored at a minimum every 15 (± 5) minutes during infusion from pre-treatment to the end of the observation period.

[i] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 42 days after the last dose of study drug or until the patient is lost to follow-up, withdraws consent, initiates another anti-cancer therapy, or study discontinuation/termination, whichever occurs first. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[j] Patients will be monitored for any untoward effects for 2 hours following completion of the first DHES0815A infusion on Day 1 of Cycle 1 and Day 1 of Cycle 2. If infusion-related events occur, manage as per Table 3 in Section 5.1.2.3. Patients who experience infusion-related adverse events following any given infusion should be observed for 2 hours following the subsequent infusion. In the absence of infusion-related adverse events after Cycle 2, subsequent infusions of DHES0815A may be followed by a 30-minute observation period (see Section 4.3.2).

Appendix 1
Schedule of Activities (cont.)

[k] *Except at screening, d*igitized, triplicate, 12-lead ECGs will be obtained at the following timepoints: on Cycle 1, Day 1 at 30 (±15) minutes before infusion and 30 (± 15) minutes after infusion; on Cycle 2, Day 1 at 30 (±15) minutes before infusion and 30 (± 15) minutes after infusion; on Cycle 4, Day 1 at 30 (±15) minutes before infusion and 30 (± 15) minutes after infusion; at end of treatment. Obtain post-screening ECGs as close as possible to scheduled serum and plasma PK samples (see Appendix 2). *For screening, to determine eligibility, two ECGs collected >30 minutes apart (Section 4.1.2) are required to assess QT interval through use of Fridericia's formula (QTcF).*

[l] Ophthalmic examinations should include assessment of BCVA and an anterior segment slit lamp examination with fluorescein. Ophthalmic examinations must be conducted during the screening period, during the last week (Days 15–21) of even-numbered cycles until Cycle 6 (i.e., at Cycles 2, 4, and 6) and every four cycles thereafter (i.e., at Cycles 10, 14, 18, etc.), and at the study discontinuation visit (unless the most recent ophthalmic examination has occurred within the past 4 weeks). Sites will provide the sponsor with ophthalmic examination clinic notes. Patients who experience ocular symptoms, including but not limited to eye pain, dry eyes, blurred vision, or a decline in visual acuity, will be required to undergo an ophthalmic examination at an unscheduled visit as soon as practical. Such visits should include the same assessments as those described above, along with any additional assessments deemed clinically indicated per standard of care. If no study drug–related ophthalmic adverse events Grade ≥2 are reported during dose escalation, ophthalmic examinations may not be required for patients enrolled into the expansion cohort.

[m] Tumor assessments should be performed at screening, during the last week (Days 15–21) of every even-numbered cycle until Cycle 8 (i.e., at Cycles 2, 4, 6, and 8) and every three cycles thereafter (i.e., at Cycles 11, 14, 17, etc.) until treatment discontinuation, and at study discontinuation visit (unless last prior tumor assessment was performed ≤4 weeks). Response should be assessed on the basis of physical examinations and image-based evaluations, using RECIST v1.1. CT scans should include the chest, abdomen, and pelvis; CT scans of the neck should be included if clinically indicated. MRI may be used instead of CT scans in patients for whom CT scans are contraindicated or in circumstances in which MRI is the preferred imaging modality. The same method of assessment and the same technique should be used at baseline and for all on-study assessments.

[n] Please see Appendix 2 for a complete list of PK and ADA blood draws.

[o] Hematology consists of complete blood count, including hemoglobin, hematocrit, platelet count, RBC count, WBC count, and absolute differential count *for* neutrophils *and* lymphocytes*; percentage or absolute count is acceptable for all other cell types (e.g., eosinophils, monocytes, basophils, bands, and other cells).*

[p] Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, LDH, ALT, AST, and ALP.

[q] ECHO or MUGA scans to monitor LVEF should be conducted during screening, at the end of the DLT window (i.e., end of Cycle 1), during the last week (Days 15–21) of even-numbered cycles until Cycle 6 (i.e., at Cycles 2, 4, and 6), every four cycles thereafter (i.e., at Cycles 10, 14, 18, etc.), and at the study discontinuation visit (unless no study drug has been given since the last ECHO or MUGA scan). Other assessments should be conducted if clinically indicated.

Appendix 1
Schedule of Activities (cont.)

[r] For women of childbearing potential, a serum pregnancy test must be performed within 7 days prior to Day 1. Urine pregnancy tests will be performed on the first day of every cycle during the study. If a urine pregnancy test result is positive, patient dosing will be postponed until the result is confirmed by a serum pregnancy test. Patients who become pregnant while on study must permanently discontinue study treatment as outlined in Section 4.6.1. Patients of childbearing potential whose tumors produce hCG and were confirmed not be pregnant prior to enrollment should be monitored with serum pregnancy tests rather than urine pregnancy tests prior to each cycle of study treatment.

[s] Urinalysis includes macroscopic analysis (specific gravity, protein, pH, glucose, ketones, blood, bilirubin, leukocyte esterase, urobilinogen, and nitrite) and, if any abnormalities, microscopic analysis (RBCs, WBCs, epithelial cells, casts, crystals, bacteria, and yeast). A urine pregnancy test will be performed on the first day of every cycle in women of childbearing potential (see Section 4.5.6.1).

[t] Patients will provide two types of tissue: 1) archival tumor samples collected at the time of initial diagnosis that were used to determine HER2 status and 2) metastatic tumor tissue obtained between the time of the last dose of the most recent prior anti-cancer therapy and enrollment into this study. Archival specimen must be a representative formalin-fixed, paraffin-embedded tumor specimen, accompanied by an associated pathology report, with adequate viable tumor tissue. The tumor specimen may consist of a tissue block (preferred) or at least [redacted], [redacted] slides. Cytologic or fine-needle aspiration samples are not acceptable.

[u] For patients who have signed the optional Informed Consent Form, on-progression tumor tissue biopsies may be collected during the study or at the study discontinuation visit.

[v] Blood samples for biomarker testing will be collected at screening, prior to DHES0815A administration on Cycle 1, Day1, and at the end-of-treatment visit.

[redacted]

[x] The infusion on Cycle 1, Day 1 will be administered over at least 90 (±10) minutes. In the absence of infusion-related adverse events, subsequent infusions of DHES0815A may be administered over 30 (±10) minutes. The DHES0815A infusion may be slowed or interrupted for patients experiencing infusion-related adverse events (Section 5.3.5.1).

Appendix 2 Schedule of Pharmacokinetic and Immunogenicity Samples

Study Visit	Timepoint	DHES0815A PK [a,b,c]	Anti-DHES0815A Antibody (ADA) [d]
Cycle 1, Day 1	Pre-infusion	x [e]	x
	30 minutes (±15 minutes) post-EOI	x	
	4 hours (±15 minutes) post-EOI	x	
Cycle 1, Day 2	24 hours (±2 hours) post-EOI	x	
Cycle 1, Day 3	48 hours (±2 hours) post-EOI	x	
Cycle 1, Day 8	7 days (±1 day) post-EOI	x	
Cycle 1, Day11	10 days (±1 day) post-EOI	x	
Cycle 1, Day 15	14 days (±1 day) post-EOI	x	
Cycle 1, Day 17	16 days (±1 day) post-EOI	x	
Cycles 2–4, Day 1	Pre-infusion	x	x
	30 minutes (±15 minutes) post-EOI	x	
Cycles 2–4, Day 8	7 days (±1 day) post-EOI	x	
Cycles 2–4, Day 15	14 days (±1 day) post-EOI	x	
Study treatment discontinuation visit	Within 42 days after last infusion	x	x

acPBD-MA=antibody-conjugated PBD-MA; ADA=anti-drug antibody; ECD=extracellular domain; EOI=end of infusion; NA=not applicable; PBD-MA=pyrrolo[2,1-c][1,4]benzodiazepine-monoamide; PK=pharmacokinetic; QTcF=QT interval corrected through use of Fridericia's formula.

Note: Samples will be submitted to a central laboratory. *Pre-infusion laboratory samples should be drawn within 4 hours before the start of infusion.*

[a] For PK sample collection instructions, please refer to the laboratory manual. In the event that a serious adverse event or a dose-limiting toxicity occurs at a time when a PK sample is not scheduled, every effort should be made to collect a PK sample as an unscheduled event.

[b] Clinical plans include measurement of the following analytes for PK assessment of DHES0815A: DHES0815A total antibody (serum, SER-PK), acPBD-MA (plasma, PL-PK1), and unconjugated PBD-MA (plasma, PL-PK2). Two additional exploratory PK samples (plasma, PL-PK-EXP1, PL-PK-EXP2) will be collected for catabolite and stability/biotransformation analyses.

[c] If an increase in QTcF is observed in an ECG measurement as described in Section 4.5.7 and a PK sample is not scheduled at that timepoint, then an unscheduled DHES0815A PK sample should be obtained.

[d] Serum samples for assessment of anti-DHES0815A antibodies (ADA) will be drawn at baseline (prior to dosing on Day1, Cycle 1), before dosing on Day 1 of Cycles 2–4, at study completion/early *discontinuation* visit.

[e] *In addition to PK samples specified in footnote "b," a* baseline serum sample (Cycle 1, Day 1 only) may be used, depending upon review of DHES0815A PK/ADA data, to measure HER2 ECD, pertuzumab, trastuzumab, and/or trastuzumab emtansine levels to better understand potential drug interferences or impact on pharmacokinetics.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity. [2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

a) Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, 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.

b) Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) 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, peritoneal spread, and abdominal

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c) Special Considerations Regarding Lesion Measurability

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

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring 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.

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 non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Target Lesions: Specifications by Methods of Measurements

a) 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 4 weeks before the beginning of the treatment.

b) 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 the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

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.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality

and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

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. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that 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 two dimensions in the plane in which the image is

obtained (for CT 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 that is reported as being 20 mm $\times$ 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 $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 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 of 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 of diameters will be used as a 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 Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

a) Evaluation of Target Lesions

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

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.

- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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

b) 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 < 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 complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that 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 CRF, as follows:

- 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 and BML (below measurable limit) should be ticked. (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 and BML should also be ticked).

<u>To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.</u>

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 maximum longest diameter for the coalesced lesion.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

c) 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. Although some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- Complete response (CR): Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease (PD): Unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d) Special Notes on Assessment of Progression of Non-Target Disease

When the Patient 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 in a magnitude that, even in the 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 one or more non-target lesions is usually not sufficient to qualify 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 Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have 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 patients 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, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that

point. Although 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.

e) 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, that is, 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 patient's baseline lesions show partial or complete response. 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 during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up 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.

Evaluation of Response

a) Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Table 1: Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

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 = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2: Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b) Missing Assessments and Not-Evaluable Designation

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

with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess” except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Table 3: Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c) 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 patients with CR may not have a total sum of "zero" on the CRF.

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Patients 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 patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

For equivocal findings of progression (e.g., 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.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 4 ECOG 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, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.

Appendix 5 New York Heart Association Classification

Class	Description
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present event at rest. If any physical activity is undertaken, discomfort is increased.

Excerpted from Oxford Textbook of Medicine. Vol 2, p. 2228. Oxford Press 1997.

Appendix 6 Recommended Anaphylaxis Management

The following equipment is needed in the event of a suspected anaphylactic reaction during study drug infusion:

Appropriate monitors (electrocardiogram, blood pressure, pulse oximetry)

Oxygen and masks for oxygen delivery

- Airway management devices per standard of care
- Epinephrine for intravenous, intramuscular, and/or endotracheal administration in accordance with institutional guidelines
- Salbutamol (or albuterol or equivalent)
- Antihistamines (H1 and H2 blockers)
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

The following are the recommended procedures to follow in the event of a suspected anaphylactic reaction during study drug infusion:

Stop the study drug infusion.

Call for additional assistance!

Maintain an adequate airway.

- Provide oxygen.
- Ensure that appropriate monitoring is in place, with continuous electrocardiogram and pulse oximetry monitoring, if possible.
- Administer epinephrine first, followed by antihistamines, albuterol, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.