CLINICAL STUDY PROTOCOL

A PHASE 2, MULTICENTER, OPEN-LABEL STUDY OF DS-8201A, AN ANTI-HER2-ANTIBODY DRUG CONJUGATE (ADC) FOR HER2-POSITIVE, UNRESECTABLE AND/OR METASTATIC BREAST CANCER SUBJECTS PREVIOUSLY TREATED WITH T-DM1

DS8201-A-U201

IND/EudraCT NUMBERS: 127,553/2016-004986-18

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DAIICHI SANKYO

CRITICAL STUDY CONTACT LIST

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INVESTIGATOR AGREEMENT

A Phase 2, Multicenter, Open-Label Study of DS-8201a, an Anti-HER2-Antibody Drug Conjugate (ADC) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1

Sponsor Approval:

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

[redacted]	[redacted]
Print Name	**Signature**
Global Clinical Lead	26 Apr 2019
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

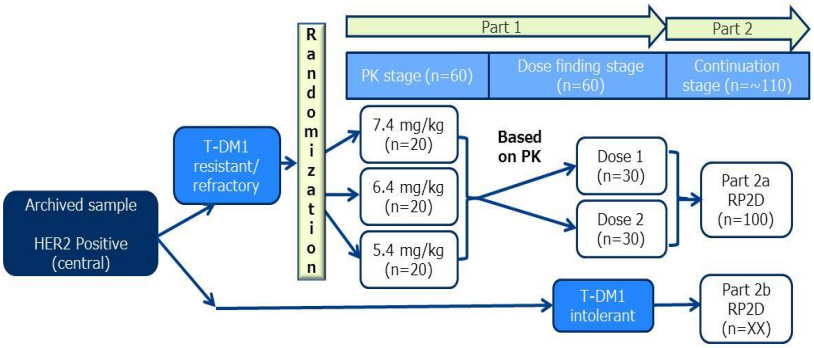
Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

SUMMARY OF CHANGES

DESCRIPTION OF EACH CHANGE AND RATIONALE	
Table 5.2 Section 9.3.1.2	Clarified that interstitial lung disease (ILD) biomarkers (i.e., KL-6, SP-D) will not be used for diagnosis or monitoring of drug-induced ILD.
Table 5.2 Section 9.3.1.2 Table 6.2 (footnote)	Specified that blood samples will be collected at the time of ILD event, if feasible, for PK and future exploratory analysis of biomarkers.
Table 5.2 Section 9.3.1.2 Table 6.2 (footnote)	Amended ILD monitoring plan to include that pulmonary function tests (PFTs) and pulse oximetry should be conducted, and arterial blood gas (ABG) exams should be conducted as clinically indicated, when evaluating potential ILD events.
Table 5.2	Reworded ILD dose modification language so it was clear that study drug should be interrupted for any ILD event regardless of CTCAE grade, and should be permanently discontinued in subjects demonstrating Grade 2, 3, or 4 toxicity.
Table 5.2 Section 9.3.1.2	Added statement to clarify that ILD events regardless of severity or seriousness will be followed until resolution even after drug discontinuation.

PROTOCOL SYNOPSIS

EudraCT:	2016-004986-18
IND Number:	127553
Protocol Number:	DS8201-A-U201
Investigational Product:	DS-8201a
Active Ingredient(s)/INN:	DS-8201a consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA-1181a.
Study Title:	A Phase 2, Multicenter, Open-Label Study of DS-8201a, an Anti-HER2-Antibody Drug Conjugate (ADC) for HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated with T-DM1.
Study Phase:	Phase 2
Indication Under Investigation:	Unresectable/metastatic breast cancer with HER2 positive expression
Study Objectives:	Primary Objectives: • To determine the objective response rate (ORR) of DS-8201a in HER2-positive, unresectable and/or metastatic breast cancer subjects who are resistant or refractory to T-DM1 Secondary Objectives: • To evaluate duration of response, best percent change in the sum of the longest diameters (SLD) of measurable tumors, disease control rate (DCR), clinical benefit rate (CBR), progression-free survival (PFS), and overall survival (OS) • To further evaluate the safety of DS-8201a • To determine the pharmacokinetics (PK) of DS-8201a • To determine the recommended Phase 2 dose (RP2D) Exploratory Objectives • To evaluate duration of stable disease, and time to response • To evaluate potential biomarkers of response, such as serum HER2-extracellular domain (ECD) • To evaluate exposure-response relationships for efficacy and safety endpoints

Study Design:	Phase 2, open-label, 2-part, global, multicenter trial. **Study Design Schema of DS8201-A-U201** 
Study Duration:	Enrollment is planned to occur over approximately 12 months Treatment and follow-up projected to be completed within approximately 10 months thereafter. Anticipated duration of the study is at least 22 months.
Study Centers and Location:	Approximately 110 sites possibly including but not limited to: North America, Europe, Japan and other Asian countries. Other countries may also be also considered.
Subject Eligibility Criteria:	Key Inclusion Criteria: • Men or women ≥ 20 years old in Japan and Korea, ≥ 18 years old in the United States (for other countries, please follow the reference[1]) • Pathologically documented breast cancer that: is unresectable or metastatic has confirmed HER2 positive expression (estrogen receptor (ER)/progesterone receptor (PR) positive subjects may be enrolled if they are HER2 positive) as determined according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines evaluated at a Central Laboratory. See Laboratory Manual for details • Subjects must have an adequate tumor sample available for confirmation of HER2 status by Central Laboratory (based on most recent tumor tissue sample). • Subject must have breast cancer which is resistant or refractory to T-DM1 (all parts except Part 2b) For Part 2b, an exploratory portion of the study, subjects must have discontinued treatment with T-DM1 for reasons other than resistant or refractory disease • Presence of at least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

[1] https://hrpo.wustl.edu/wp-content/uploads/2015/01/5-Determining-Legal-Age-to-Consent.pdf

	• Left ventricular ejection fraction (LVEF) ≥ 50% • Males and females of reproductive/childbearing potential must agree to follow instructions for method(s) of contraception. • Adequate renal function, defined as: Creatinine clearance ≥ 30 mL/min, as calculated using the modified Cockcroft Gault equation, ([{140 – age in years} × {actual weight in kg}] divided by [{72 × serum creatinine in mg/dL} multiplied by 0.85 if female]), or serum creatinine ≤ 1.5 × upper limit of normal (ULN) • Adequate hepatic function, defined as: Total bilirubin ≤ 1.5 × ULN or < 3 × ULN in the presence of documented Gilbert's syndrome or liver metastases at baseline; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 5 × ULN Key Exclusion Criteria: • Medical history of myocardial infarction within 6 months before randomization/registration, symptomatic congestive heart failure ([CHF], New York Heart Association Class II to IV), troponin levels consistent with myocardial infarction as defined according to the manufacturer, unstable angina, or serious cardiac arrhythmia requiring treatment within 28 days before randomization/registration. • Has a corrected QT interval (QTc) prolongation to > 470 msec (females) or >450 msec (male) based on screening triplicate 12-lead electrocardiogram (ECG) • Has a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening • Brain metastases that are untreated, symptomatic, or require therapy to control symptoms, as well as any history of radiation, surgery, or other therapy, including steroids or anticonvulsants, to control symptoms from brain metastases within 2 months (60 days) of randomization/registration. After approximately 30 subjects with inactive brain metastases (20% of the 150 planned to receive the RP2D) have been enrolled at the RP2D, subsequent subjects with any current or past history of brain metastases will be excluded • Has clinically significant corneal disease
Dosage Form, Dose and Route of Administration:	DS-8201a [redacted] FL-DP2) to be administered as a 5.4 mg/kg, 6.4 mg/kg or 7.4 mg/kg intravenous (IV) dose for Part 1 of the trial. The dose for Part 2 will be 5.4 mg/kg. A DS-8201a [redacted] Lyo-DP) and administered as a 5.4 mg/kg, 6.4 mg/kg or 7.4 mg/kg IV dose.

Study Endpoints:	Primary Endpoints: • ORR assessed by independent central imaging facility review based on RECIST version 1.1. Secondary Endpoints: • Efficacy Endpoints: Duration of response Best percent change in the SLD of measurable tumors DCR CBR PFS OS ORR assessed by the investigator based on RECIST version 1.1 • Safety Endpoints: Serious adverse events (SAEs) Treatment-emergent adverse events (TEAEs) TEAEs leading to discontinuations Adverse events of special interest Elevated troponin levels Physical examination findings (including Eastern Cooperative Oncology Group Performance Status (ECOG PS) Vital sign measurements Standard clinical laboratory parameters ECG parameters Echocardiogram (Echo)/ multigated acquisition (MUGA) findings Ophthalmologic findings, and; Anti-drug antibodies (ADA) • Pharmacokinetic Endpoints (DS-8201a, total anti-HER2 antibody and MAAA-1181a): PK parameters (Cycle 1): maximum serum concentration (Cmax), time to Cmax (Tmax), area under the concentration-time curve from dosing until the last quantifiable concentration (AUClast), AUC from the time of dosing until day 21 (AUC0-21d)and, if appropriate, AUC from 0 through

	infinity (AUCinf), terminal elimination half-life (T1/2), clearance (CL) and volume of distribution at steady-state (Vss) Serum concentrations. Exploratory endpoints: • Efficacy endpoints Duration of stable disease Time to response Evaluate exposure-response relationships for efficacy and safety endpoints • Potential biomarkers of response, such as serum HER2ECD concentrations
Planned Sample Size:	The estimated total number of subjects planned is approximately 230.
Statistical Analyses:	A data cut-off date for the primary analysis will be identified during Part 2. <u>Efficacy analyses</u>: The primary efficacy analysis will be performed for all subjects who initially received the RP2D of DS-8201a and had measurable tumors assessed by independent central imaging facility review at baseline. The primary efficacy endpoint is ORR assessed by independent central imaging facility review based on RECIST version 1.1. ORR will be summarized with its two-sided 95% exact confidence interval (CI). The secondary efficacy parameters include duration of response, best percent change in the SLD of measurable tumors, DCR, CBR, PFS, OS, and ORR assessed by the investigator based on RECIST version 1.1. DCR, CBR, ORR assessed by the investigator based on RECIST version 1.1 will be analyzed for each part/dose group in the same manner as the primary ORR analysis. Duration of response, PFS, and OS will be summarized with median event times and their 2-sided 95% CIs using the Brookmeyer and Crowley method. <u>Safety analyses</u>: Safety endpoints will include SAEs, treatment-emergent adverse events (TEAEs), physical examination findings, ECOG PS, vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings, ADA and ophthalmologic findings. TEAEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. <u>Pharmacokinetic analyses</u>: Serum concentrations for DS-8201a, total anti-HER2 antibody and

	MAAA-1181a will be listed, plotted, and summarized using descriptive statistics by Part (and Stage)/dose level/study day at each time point. PK parameters will be listed and summarized using descriptive statistics by Part (and Stage)/dose level.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ADA	anti-drug antibody(ies)
ADC	antibody drug conjugate
[redacted]	[redacted]
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase (transaminase)
ANC	absolute neutrophil count
ASCO-CAP	American Society of Clinical Oncology – College of American Pathologists
AST	aspartate aminotransferase (transaminase)
AUC	area under the concentration-time curve
BI	before infusion
CBR	clinical benefit rate
cfDNA	cell free deoxyribonucleic acid
CHF	congestive heart failure
CL	clearance
Cmax	maximum plasma/serum concentration
CR	complete response
CRF	case report form
eCRF	electronic case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAR	drug-to-antibody ratio
DCR	disease control rate
DS1	drug substance manufactured using MAAL-9001 [redacted]
DS2	drug substance manufactured using MAAL-9001 [redacted]

ABBREVIATION	DEFINITION
EC	ethics committee
ECG	electrocardiogram
Echo	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EDC	electronic data capture
FAS	Full Analysis Set
FL-DP1	[redacted]
FL-DP2	[redacted]
GCP	Good Clinical Practice
HER2	human epidermal growth factor receptor 2
HER2ECD	extracellular domain of HER2
hERG	human ether-a–go-go related gene
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgG1	immunoglobin G1
ILD	interstitial lung disease
INN	international non-proprietary name
IRB	institutional review board
IV	intravenous(ly)
IXRS	interactive web/voice response system
LVEF	left ventricular ejection fraction
[redacted]DP	[redacted] drug product
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival

ABBREVIATION	DEFINITION
PD	disease progression
PFS	progression-free survival
PK	pharmacokinetic(s)
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
Q3W	once every 3 weeks
QoL	quality of life
QTc	corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SLD	sum of the longest diameters
SOC	system organ class
SOP	standard operating procedure
SpO2	peripheral oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	terminal elimination half-life
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
Vss	volume of distribution at steady-state

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Background

Breast cancer is the most common cancer worldwide in women: there were approximately 1.67 million new diagnoses and 520,000 deaths worldwide in 2012. Human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20% of breast cancers and an estimated 100,000 breast cancer-related deaths per year are expected in this subject population.[1,2] Despite the benefits in progression-free survival (PFS) and overall survival (OS) obtained with currently approved HER2-targeted therapies, the majority of subjects with HER2-positive unresectable and/or metastatic breast cancer eventually acquire resistance to these drugs.[3] Therefore, HER2 unresectable and/or metastatic breast cancer is still considered a serious and life-threatening disease with an unmet medical need.

DS-8201a is an antibody drug conjugate (ADC) targeting HER2. In the ongoing Phase 1 clinical study, DS8201-A-J101, in subjects with advanced solid tumors, DS-8201a was well tolerated at repeated doses up to 8.0 mg/kg intravenously (IV) once every 3 weeks (Q3W).

1.1.1. Investigational Product

1.1.1.1. Name

DS-8201a

1.1.1.2. Description

DS-8201a consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA-1181a. MAAL-9001 is an in-house humanized immunoglobin G1 (IgG1) monoclonal antibody having the same amino acid sequence as trastuzumab. MAAA-1181a, an exatecan derivative,[4,5,6] is a topoisomerase I inhibitor, cell-membrane permeable, and more potent than SN-38 (active metabolite of irinotecan). This ADC achieves a high drug-to-antibody ratio (DAR) (7 to 8) with homogeneous conjugation with MAAA-1181a.[7] DS-8201a is cleaved by lysosomal enzymes and releases MAAA-1181a in the cytoplasm after it binds to HER2 receptor and gets internalized in tumor cells.

The DS-8201a Phase 1 clinical study DS8201-A-J101 was initiated with the antibody component, MAAL-9001, [redacted] (drug substance 1 [DS 1]). To support new clinical studies, [redacted], transition is being made to MAAL-9001 [redacted] (DS 2). Analytic comparison of the two [redacted] products has shown comparability across a wide range of variables. [redacted] Following single IV administration of DS-8201a to cynomolgus monkeys, mean maximum plasma/serum concentration Cmax of DS-8201a was similar, while area under the concentration-time curve (AUC) was approximately 15% lower, for DS 2 material as compared to DS 1 material. However, in a xenograft study, no difference was seen in cytotoxicity between the two products. Further analysis to assess the

comparability of FL-DP2 used in this study to FL-DP1 data reported from the DS8201-A-J101 study will be performed as detailed in Section 1.2.

1.1.1.3. Intended Use Under Investigation

This study will examine the anti-tumor activity of DS-8201a in subjects with HER2-positive, unresectable and/or metastatic breast cancer who are resistant or refractory to trastuzumab emtansine (T-DM1).

1.1.1.4. Nonclinical Studies

1.1.1.4.1. Pharmacology

DS-8201a inhibits tumor growth by mainly topoisomerase I inhibition-derived deoxyribonucleic acid damage, and induces apoptosis by the MAAA-1181a that is released from DS-8201a after internalization in cancer cells via HER2. In vitro nonclinical pharmacology studies have confirmed that DS-8201a exhibits HER2 expression-dependent cell growth inhibition, and in vivo studies using tumor-bearing mouse models suggest that the administration of DS-8201a results in the regression of a broad array of HER2-expressing tumors, including multiple models unresponsive to T-DM1. In addition, in vivo studies in tumor-bearing mouse models have confirmed that DS-8201a has antitumor activity against HER2 low-expressing tumors which are insensitive to T-DM1. Moreover, DS-8201a demonstrated potent efficacy in mice inoculated with a mixture of HER2-positive and negative cells while T-DM1 did not, due to more potent bystander killing and higher cell membrane permeability of the conjugated toxin.[7,8] The effect therefore supports the efficacy of DS-8201a against tumors with HER2 heterogeneity.

1.1.1.4.2. Safety Pharmacology

In a safety pharmacology study in monkeys treated with single IV doses of DS-8201a, no effects on the cardiovascular system, the respiratory system, or the central nervous system were observed under the study condition. In addition, in human ether a-go-go related gene (hERG) studies of MAAA-1181a, the drug component, MAAA-1181a did not inhibit the hERG channel current.

1.1.1.4.3. Pharmacokinetics and Drug Metabolism

The plasma DS-8201a concentrations decreased exponentially following a single IV administration of DS-8201a at 0.1 mg/kg to 3.0 mg/kg to cynomolgus monkeys. The volume of distribution at steady-state (Vss) was close to the plasma volume. The clearance (CL) decreased as the dose increased, and the pharmacokinetics (PK) was found to be non-linear. Both DS-8201a and the total antibody, bound and unbound antibody combined, exhibited similar plasma concentration-time profiles at all dose levels, as well as similar AUC. All individual plasma concentrations of MAAA-1181a, the released drug from DS-8201a, were below the lower limit of quantification (0.100 ng/mL) at 0.1 and 0.3 mg/kg. A low-plasma level of MAAA-1181a was detected at limited time points at 1.0 and 3.0 mg/kg. No anti-DS-8201a antibody was detected in any of the animals.

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

The release rates of MAAA-1181a from DS-8201a increased gradually throughout the incubation period in mouse, rat, and monkey plasma with the release rates from 1.2% to 3.9% on Day 21. On the other hand, the release rate reached a plateau on Day 14 in human plasma with the release rates from 2.2% to 2.4%. These results indicate that most DS-8201a is stable in plasma.

No major differences were found among the metabolite profiles of DS-8201a in rat, monkey, and human hepatocytes. MAAA-1181a was metabolized by cytochrome P450 (CYP) enzymes; CYP3A4 was the primary CYP enzyme in the metabolism, CYP3A5 and CYP2D6 were also involved in the metabolism. MAAA-1181a did not inhibit organic anion transporter (OAT) 3, organic cation transporter (OCT) 1, OCT2, organic anion- transporting polypeptide (OATP) 1B3, multidrug and toxin extrusion (MATE) 1, MATE2-K, P-glycoprotein, breast cancer resistance protein (BCRP), and bile salt export pump (BSEP) (IC50 >30 μmol/L). MAAA-1181d inhibited OAT1 and OATP1B1 with the IC50 values of 12.7 and 14.4 μmol/L, respectively, however the values were much higher than the Cmax of MAAA-1181a in humans (9.25 ng/mL [0.019 μmol/L] at 8.0 mg/kg of DS-8201a). In addition, OATP1B were considered to contribute to the human hepatic uptake of MAAA-1181a.

The plasma concentration time profiles following repeated administration of DS-8201a Q3W for 3 cycles (Q3W × 3) to humans were simulated on the basis of the pharmacokinetics of DS-8201a in cynomolgus monkeys. These estimates were compared to the plasma concentrations of DS-8201a in the studies in tumor-bearing mice. As a result, the minimum effective dose and the pharmacologically active dose were expected to be 0.8 and 4.8 mg/kg, respectively, with a dosage Q3W in humans.

1.1.1.4.4. Toxicology

In a study of intermittent IV dosing of DS-8201a in rats (Q3W dosing for 6 weeks), no deaths or moribund animals were found at dose levels up to 197 mg/kg, the maximum dose. The major observed findings included testicular and intestinal toxicity at dose levels of 20 mg/kg and greater, and lymphatic/hematopoietic, skin, and incisor tooth, and renal toxicity at dose levels of 60 mg/kg and greater. Except for the testicular and incisor tooth changes, these changes were all found to recover.

In an intermittent IV dosing study of DS-8201a in cynomolgus monkeys (Q3W, 6 weeks), one female was sacrificed moribund at 78.8 mg/kg, the highest dose level. The major toxicity findings in this moribund animal were observed in the intestine, hematopoietic system, skin, and kidney. The cause of the moribundity appeared to be the deteriorated condition of the animal which included decreased body weight and food consumption, as well as bone marrow toxicity and intestinal toxicity. The major findings of toxicity in the surviving animals were observed in the intestine at dose levels of 10 mg/kg and greater, and in the lung, testes, and skin at dose levels of 30 mg/kg and greater. In addition, hematopoietic system toxicity, renal toxicity, and electrocardiogram (ECG) abnormalities (shortened PR interval and corrected QT interval [QTc] prolongation) were found at 78.8 mg/kg. Except for the pulmonary and skin toxicity (pigmentation), these findings tended to recover.

Thus, as described above, the severely toxic dose in 10% of the animals (STD_{10}) in a rat intermittent IV dosing study of DS-8201a was found to be greater than 197 mg/kg. In the monkey study, due to observed moribundity at 78.8 mg/kg and evidence of critical pulmonary toxicity (eg, interstitial inflammation and/or alveolar edema) in the surviving animals, it was concluded that the highest non-severely toxic dose (HNSTD) is 30 mg/kg.

In an intermittent IV dose toxicity study of MAAA-1181a (morning dosing for 4 weeks), findings in the lymphatic/hematopoietic system, intestinal tract, and the cornea of the eye were observed at 3 mg/kg and greater in rats and there was no death or moribundity at up to 30 mg/kg. Findings similar to those in rats were observed in cynomolgus monkeys at dose levels of 1 mg/kg and greater. In addition, 1 female monkey died and 1 male monkey was sacrificed moribund at 12 mg/kg. Although effects on the heart (focal myocardial cell degeneration/necrosis) were found in the moribund male along with the above mentioned toxicities, there were no abnormal heart findings in the female that died even though both animals exhibited worsening clinical conditions associated with sustained decreases in food consumption, bone marrow toxicity, and intestinal toxicity. These changes were considered to be the cause of the death and moribundity. The common adverse findings with both DS-8201a and MAAA-1181a studies were intestinal and lymphatic/hematopoietic system toxicities. For DS-8201a treatment, pulmonary, testicular, skin and renal toxicities were observed while heart, liver, and corneal toxicities were found only when MAAA-1181a was administered.

In a human cross-reactivity study of DS-8201a with a panel of human tissues, DS-8201a-related cell membrane staining was found only in the placenta. In a cross-reactivity study of DS-8201a with selected cynomolgus monkey tissues (eg, brain, liver, kidney, lung, heart, intestines, lymphoid organs, testis, and skin), neither membranous nor cytoplasmic staining was noted in any tissues.

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

For additional nonclinical data supporting DS-8201a use in nonclinical studies, please refer to the current Investigator's Brochure (IB).

1.1.1.5. Clinical Experience

The DS-8201a first-in-human (FIH) study (Protocol DS8201-A-J101) is an open-label, dose finding study to assess the safety and tolerability of DS-8201a in subjects with advanced solid tumors. The study is being conducted in 2 parts; dose escalation (Part 1) and dose expansion (Part 2): Part 1 was a dose escalation phase in subjects with either advanced breast cancer or gastric/ gastro-esophageal junction (GEJ) adenocarcinoma. Part 2 is the expansion phase and focuses on HER2 expressing breast (previously treated T-DM1 HER2 positive breast cancer) and gastric/GEJ junction adenocarcinoma, HER2 low-expressing breast cancer, as well as other HER2 expressing solid cancers. Preliminary results from Part 1 indicate that DS-8201a has a favorable safety and PK profile and robust antitumor activity in breast cancer subjects, with tumors that were previously treated with T-DM1. Events of special interest detailed in the Phase 1 protocol included infusion reactions, cardiac events, and pneumonitis. Periodic cardiac assessments are performed including echocardiogram (Echo) or multigated acquisition (MUGA) performed at every 2 cycles (42 days) and 12-lead triplicate ECGs performed at least every cycle

(21 days). As of 08 Jun 2017, a total of 148 subjects, 24 in Part 1 and 124 in Part 2, have received DS-8201a in this study. In Part 1, no dose limiting toxicities were reported and the maximum tolerated dose (MTD) was not reached. Two doses were chosen for expansion in Part 2: 5.4 mg/kg and 6.4 mg/kg.

For 148 subjects who have received DS-8201a in the study, the most common AEs (>20%) of any grades were nausea (65%), decreased appetite (53%), vomiting (34%), platelet count decreased (31%), anemia (28%), alopecia (26%), diarrhea (24%), constipation (24%), neutrophil count decreased (24%), white blood cell count decreased (24%), and malaise (22%). The majority of the AEs were of Grade 1 or 2 severity; 52 (35.1%) of 148 subjects experienced Grade 3 AEs and 10 subjects (6.8%) experienced Grade 4 AEs as the worst grade experienced. A total of 3 subjects died due to an AE; 1 due to mechanical ileus, 1 due to extradural hematoma/traumatic intracranial hemorrhage occurring more than 28 days after last dose of study drug, and 1 due to disease progression reported as an AE. All these fatal events were considered not related to study drug by the investigators.

As of 08 Jun 2017, 13 (8.7%) of 148 subjects experienced treatment-emergent adverse events (TEAEs) relating to cardiotoxicity in this on-going study. Of these 13 subjects, 9 experienced QT prolongation (7 Grade 1 and 2 Grade 2, all non-serious), all considered related to the study therapy. Two subjects experienced ejection fraction decreased (Grade 2, non-serious, related), 1 subject experienced Grade 2 tachycardia and 1 subject experienced heart rate decreased (related). No action was taken regarding the study drug therapy and no subjects discontinued study therapy.

Irrespective of the investigator/Sponsor causality, of the 148 treated subjects, there were 3 subjects (where one received 8.0 mg/kg and the other 2 received 6.4 mg/kg) who had experienced one serious and 2 non-serious pneumonitis (one was Grade 1 and the other as Grade 2). There were also 2 subjects who experienced interstitial lung disease (ILD; 1 serious and Grade 3 in severity, and the other non-serious; with Grade 1 severity).

Of the 148 subjects, a total of 2 subjects (1.4%) experienced infusion-related reactions (both Grade 1, non-serious) and 1 subject experienced infusion site extravasation (Grade 1, non-serious). Study drug administration was interrupted for 1 of 3 reported events. The outcome was reported as resolved in all subjects.

Overall efficacy results from all cohorts in Part 1 demonstrated an objective response rate (ORR) of 34.8% and disease control rate (DCR) of 91.3%. Subjects in the higher dose levels (≥5.4 mg/kg, 15 subjects) showed ORR of 53.3%. Overall efficacy results from all cohorts in Part 2 demonstrated an ORR of 48.8% and DCR of 85.7%. Breast cancer cohorts with HER2 positive and low expression, Part 2a and 2c, showed ORR of 61.5% and 50.0%, and DCR of 96.2% and 90.0% respectively. The HER2 positive gastric cancer cohort showed ORR of 48.4% and DCR of 80.6%.

Please see the current IB for an updated summary of clinical studies.

1.1.1.6. Summary of Clinical Pharmacokinetics

PK was evaluated in 22 Japanese subjects who received DS-8201a. Following a single IV administration, the systemic exposure of DS-8201a increased approximately proportional to dose. The pharmacokinetic (PK) parameters at 5.4, 6.4, and 8.0 mg/kg are shown in Table 1.1, Table 1.2, and Table 1.3. The maximum serum concentration (Cmax) of DS-8201a at 6.4 mg/kg

was achieved with a median time to Cmax (Tmax) of 2.16 h. Cmax and AUC from the time of dosing to 21 days ($AUC_{0\ 21d}$) at 6.4 mg/kg were 181 µg/mL and 900 µg·day/mL, respectively. The systemic exposure at 6.4 mg/kg in subjects in Cycle 1 was observed to exceed the systemic efficacious exposure observed during the non-clinical pharmacology evaluation. At this dose, the mean terminal elimination half-life ($T_{1/2}$) of DS-8201a was 7.33 days at 6.4 mg/kg, and Vss was 58.6 mL/kg which is similar to the serum volume.

PK parameters of total antibody were close to that of DS-8201a.

Cmax and AUC for the dosing interval ($AUC_{0\ 21d}$), which were quite low, of MAAA-1181a was 6.80 ng/mL and 31.0 ng·day/mL at 6.4 mg/kg, respectively. The $T_{1/2}$ of MAAA-1181a was similar to that of DS-8201a.

Table 1.1: PK Parameters of DS-8201a (± standard deviation)

	Cmax (µg/mL)	Tmax[a] (h)	AUC_{0-21d} (µg·day/mL)	AUCinf (µg·day/mL)	$T_{1/2}$ (day)	CL (mL/day/kg)	Vss (mL/kg)
5.4 mg/kg (N 6)	127 ±17.2	1.92 (1.92, 2.16)	542 ±163	590 ±186	6.03 ±0.603	10.1 ±3.90	75.2 ±24.2
6.4 mg/kg (N 6)	181 ±33.1	2.16 (1.44, 4.08)	900 ±155	1030 ±209	7.33 ±1.64	6.41 ±1.12	58.6 ±11.0
8.0 mg/kg (N 3)	216 ±52.0	1.92 (1.92, 2.16)	914 ±235	1020 ±279	6.97 ±0.357	8.17 ±1.93	69.7 ±13.1

AUC area under the concentration time curve; AUC_{0-21d} AUC from the time of dosing to 21 days; AUCinf AUC from 0 through infinity; CL clearance; Cmax maximum plasma/serum concentration; N number of evaluable subjects; $T_{1/2}$ terminal elimination half life; Tmax time to Cmax; Vss volume of distribution at steady state.
[a] range

Table 1.2: PK Parameters of Total Antibody (± standard deviation)

	Cmax (µg/mL)	Tmax[a] (h)	AUC_{0-21d} (µg·day/mL)	AUCinf (µg·day/mL)	$T_{1/2}$ (day)
5.4 mg/kg (N=6)	116 ±13.9	1.92 (1.92, 6.96)	606 ±147	682±172	6.78 ±2.39
6.4 mg/kg (N=6)	146 ±18.9	3.84 (2.16, 6.96)	877±97.0	1050±149	8.25 ±2.16
8.0 mg/kg (N=3)	178 ±18.5	2.16 (1.92, 6.72)	1090 ±213	1270±296	7.35 ±0.417

AUC area under the concentration time curve; AUC_{0-21d} AUC from the time of dosing to 21 days; AUCinf AUC from 0 through infinity; Cmax maximum plasma/serum concentration; N number of evaluable subjects; $T_{1/2}$ terminal elimination half life; Tmax time to Cmax.
[a] range

Table 1.3: PK Parameters of MAAA-1181a (± standard deviation)

	Cmax (ng/mL)	Tmax (h)[a]	$AUC_{0\text{-}21d}$ (ng·day/mL)	AUCinf (ng·day/mL)	$T_{1/2}$ (day)
5.4 mg/kg (N=6)	10.8 ±7.56	5.28 (3.84, 23.76)	40.4 ±19.7	43.6 ±21.2	6.11 ±0.811
6.4 mg/kg (N=6)	6.80 ±1.72	6.72 (4.08, 7.20)	31.0 ±5.10	34.2 ±5.63	6.28 ±1.17
8.0 mg/kg (N=3)	9.25 ±3.18	6.72 (6.72, 6.96)	39.4 ±6.43	43.4 ±9.16	6.36 ±1.53

AUC area under the concentration time curve; $AUC_{0\text{-}21d}$ AUC from the time of dosing to 21 days; AUCinf AUC from 0 through infinity; Cmax maximum plasma/serum concentration; N number of evaluable subjects; $T_{1/2}$ terminal elimination half life; Tmax time to Cmax.
[a] range

1.2. Study Rationale

HER2 is a member of the HER superfamily that initiates signal transduction via the PI3K/AKT and RAS/MAPK pathways.[9,10] In human advanced solid tumors, expression of HER2 protein has been reported in various tumor tissues and a variety of cultured tumor cell lines including breast cancer,[11] gastric cancer,[12,13] pancreatic cancer,[14] lung cancer,[15] colorectal cancer,[16] and ovarian cancer.[17] There are also many reports demonstrating an association between expression of HER2 protein and poor clinical prognosis. In normal human tissue, low expression of HER2 protein has been reported on cell membranes of epithelial cells in the gastro-intestinal, respiratory, reproductive, and urinary tract as well as in the skin, breast, and placenta.[18]

Advanced HER2 positive breast cancer resistant or refractory to T-DM1 treatment remains an area of high unmet medical need. For the past few decades, the main approaches to treatment of subjects with unresectable and/or metastatic breast cancer depended on the use of conventional cytotoxic chemotherapies and molecularly targeted agents, with no biomarkers that could potentially identify responsive subjects and/or safety risks. Therefore, both efficacy and safety advances are needed in the treatment approaches for subjects with unresectable and/or metastatic breast cancer.

In an effort to expand the treatments for subjects with unresectable and/or metastatic breast cancer, HER2-targeted drugs (eg, trastuzumab, pertuzumab, T-DM1) have been developed as individualized molecularly targeted therapy for HER2-positive breast cancer. Anti-HER2 drugs have been reported to prolong PFS and OS, with higher levels of efficacy and safety in HER2-positive breast cancer subjects, compared with conventional cytotoxic chemotherapies. Anti-HER2 drugs have also been reported to improve quality of life (QoL). However, none of these treatments are curative and there are still many HER2-positive breast cancer subjects who have tumors that are unresponsive to approved HER2-targeted drugs, or acquire resistance to these drugs during treatment.

Based on the results of the CLEOPATRA trial, current recommendations for HER2 positive metastatic breast cancer are for first line therapy with trastuzumab, pertuzumab, and a taxane.[19] In 2016, United States (US) prescribing patterns indicated that the large majority of HER2 positive subjects received pertuzumab in the first or second line setting. Slightly lower rates

were reported in Europe and Japan. The current study design attempts to replicate this rate of approximately 2/3 of subjects having received pertuzumab by setting a minimum on the number of such subjects enrolled. In the 2nd line, T-DM1 has solidified its position as the next anti-HER2 therapy based on results of the EMILIA trial.[20] There are no anti-HER2 therapies specifically approved in the 3rd line setting.

Other than marginally effective cytotoxic chemotherapy, there is no HER2 targeted drug with a favorable evidence of benefit/risk for breast cancer subjects who do not respond to T-DM1 treatment, or acquire resistance to T-DM1 treatment. Therefore, there is an unmet medical need in this subject population, and new agents and/or strategies need to be established in order to improve outcomes for these subjects.

DS-8201a is a HER2-targeting ADC with a high DAR (7 to 8), and a novel topoisomerase I inhibitor. DS-8201a is expected to inhibit tumor growth on the basis of the following reasons: [redacted] the MAAA-1181a that is released from DS-8201a after the internalization induces apoptosis by inhibiting topoisomerase I. Compelling preclinical evidence demonstrates that the HER2 targeting of DS-8201a is highly specific. In preclinical models, DS-8201a showed a much broader antitumor spectrum than T-DM1, including efficacy against T-DM1 resistant and HER2 low-expressing tumors. In vivo studies using a tumor-bearing mouse model suggest that administration of DS-8201a results in the regression of HER2-positive tumors.

DS-8201a has a different mechanism of cytotoxic drug component from that of T-DM1 and is expected to show activity in the tubulin inhibitor insensitive tumors, so it is anticipated to be of benefit in the T-DM1-refractory subject population.

The DS-8201a drug is being studied in clinical trials in three forms. The earlier Phase 1 trial DS8201-A-J101 provided DS-8201a using FL-DP1 material whereas this study will provide DS-8201a as [redacted] or [redacted] material. [redacted] FL-DP2 and Lyo-DP are the same formulation and differ mainly in dosage form [redacted]

DS8201-A-U201 is designed in three stages to determine the efficacy of the recommended Phase 2 dose (RP2D) for FL-DP2 and Lyo-DP drug product in this population. In the first stage, three dose levels, 5.4, 6.4, and 7.4 mg/kg were selected for comparison with the FL-DP1 drug product doses (5.4 mg/kg and 6.4 mg/kg) used in the Phase1 trial. As described in Section 1.1.1.2, non-clinical comparative evaluation suggested no apparent difference in antitumor activity between FL-DP1 material and FL-DP2 material was detected in a xenograft mouse model. The [redacted]L-DP1 doses (5.4 mg/kg and 6.4 mg/kg) investigated in the Phase 1 expansion will therefore be used at the start of DS8201-A-U201. Considering the lower AUC observed in monkeys for FL-DP2 material as compared to FL-DP1, a higher dose of 7.4 mg/kg will be added as a third dose for investigation. Therefore, in the PK Stage, DS-8201a with FL-DP2 material will be administered at 5.4, 6.4 or 7.4 mg/kg to approximately 20 subjects per dose. PK samples will be collected and two doses, with PK profiles matching those from the administration of 5.4 and 6.4 mg/kg with FL-DP1 material in study DS8201-A-J101, will be selected for further evaluation in the Dose Finding Stage.

In the second stage, a second dose selection analysis will be conducted. This population PK and exposure-response analysis will be conducted, utilizing all available PK, efficacy (tumor size and ORR) and safety (thrombocytopenia and neutropenia) data from both PK, Dose Finding Stages and study DS8201-A-J101 to select the final RP2D for evaluation.

[redacted]-DP2 [redacted] will be supplied at the start of the trial with a planned transition to [redacted]-DP [redacted] material once [redacted] becomes available. This transition is expected to occur at approximately the start of Part 2 of this trial.

1.3. Risks and Benefits for Study Subjects

One study, DS8201-A-J101, with DS-8201a is currently ongoing. DS8201-A-J101 is a two-part Phase 1 trial exploring the dose and safety/efficacy profile of DS-8201a (see Section 1.1.1.5).

Overall, the reported AEs (see Section 1.1.1.5) were consistent with the safety profile of DS-8201a expected based on the nonclinical toxicology data. Subjects receiving DS-8201a should be monitored for signs and symptoms of any of the toxicities observed in nonclinical studies and to other products of the same class which is discussed below.

In nonclinical toxicology studies, intestinal, hematopoietic, pulmonary (interstitial inflammation and/or alveolar edema), testicular, skin, and renal toxicities were found in association with the administration of DS-8201a. Ophthalmologic safety monitoring, which includes visual acuity, slit lamp exam, and fundoscopy will also be part of the overall evaluation. These assessments will be performed at baseline and specific intervals described within the protocol and at the end of treatment, when an additional exam will also be performed. Moreover, at the discretion of the investigator, ophthalmologic testing can be performed at any time during the study.

In addition to these toxicities, similar to other products of the same class, the possibility of cardiotoxicity, relative to the potential for QT prolongation in association with the administration of DS-8201a, cannot be excluded. Left ventricular ejection fraction (LVEF) will be measured by either Echo or MUGA scan. All Echos/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.

Pulmonary toxicity was observed in association with the administration of DS-8201a and cannot be excluded. Based on clinical data and safety information available from other sources as of 13 Dec 2017 and the 2 fatal cases confirmed by the ILD Adjudication Committee (AC) as ILD and related to DS-8201a, ILD and pneumonitis are added as adverse drug reactions associated with the use of DS-8201a.

Additional safety assessments should be conducted as needed, at the investigator's discretion. Hepatotoxicity, embryo-fetal toxicity, visual disturbances/corneal toxicity, or occurring in subjects receiving DS-8201a also cannot be excluded. As with any therapeutic antibodies, there is a possibility of infusion-related reactions, immune responses causing allergic or anaphylactic reactions of DS-8201a. Subjects receiving DS-8201a should be monitored for signs and symptoms of any of the toxicities observed in nonclinical studies (see section 6.13 of the IB) and clinical studies with other products of the same class.

Based on the efficacy and safety data observed in the nonclinical studies, the current clinical experience from phase 1 study, DS8201-A-J101, and the information from other products of the

same class, the benefit-risk balance supports clinical development of DS-8201a in this subject population.

For up-to-date assessments of risks and benefits to subjects, please refer to the current IB for DS-8201a.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

- To determine ORR of DS-8201a in HER2-positive, unresectable and/or metastatic breast cancer subjects who are resistant or refractory to T-DM1.

2.1.2. Secondary Objectives

- To evaluate duration of response, best percent change in the sum of the longest diameters (SLD) of measurable tumors, DCR, clinical benefit rate (CBR), PFS, and OS
- To further evaluate the safety of DS-8201a
- To determine the PK of DS-8201a
- To determine the RP2D of DS-8201a

2.1.3. Exploratory Objectives

- To evaluate duration of stable disease, and time to response
- To evaluate potential biomarkers of response, such as the serum HER2-extracellular domain (ECD)
- To evaluate exposure-response relationships for efficacy and safety endpoints

2.2. Study Hypothesis

DS-8201a confers a significant benefit in ORR in human epidermal growth factor receptor 2 positive (HER2+) breast cancer subjects who are resistant or refractory to T-DM1.

2.3. Study Endpoints

2.3.1. Primary Endpoints

ORR assessed by independent central imaging facility review based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

2.3.2. Secondary Endpoints

- Efficacy Endpoints (based on central assessments unless otherwise stated):

  Duration of response

  Best percent change in the SLD of measurable tumors

  DCR

  CBR

PFS

OS

ORR assessed by the investigator based on RECIST version 1.1.

- Safety Endpoints will include:

  serious adverse events (SAEs)

  TEAEs

  TEAEs leading to discontinuations

  Adverse events of special interest (AESIs)

  Elevated troponin levels

  physical examination findings (including Eastern Cooperative Oncology Group performance status [ECOG PS])

  vital sign measurements

  standard clinical laboratory parameters (central lab)

  ECG parameters

  Echo/MUGA findings

  ophthalmologic findings, and

  anti-drug antibody (ADA).

- Pharmacokinetic Endpoints (DS-8201a, total anti-HER2 antibody and MAAA-1181a):

  PK parameters (Cycle 1): Cmax, Tmax, AUClast, $AUC_{0\ 21d}$, and, if appropriate, AUCinf, $T_{1/2}$, CL and Vss

  Serum concentrations

2.3.3. Exploratory Endpoints

- Exploratory efficacy endpoints:

  Duration of stable disease

  Time to response

  Evaluate exposure-response relationships for efficacy and safety endpoints

- Potential biomarkers of response, such as serum HER2ECD concentrations

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

This is Phase 2, open-label, multicenter, 2-part, study designed to investigate the anti-tumor activity as well as the safety and efficacy of DS-8201a in HER2-positive, unresectable and/or metastatic breast cancer subjects who are resistant or refractory to T-DM1.

Part 1 will enroll 120 subjects in a 2 stage design: a PK Stage and a Dose Finding Stage designed to define the RP2D that will be evaluated in Part 2.

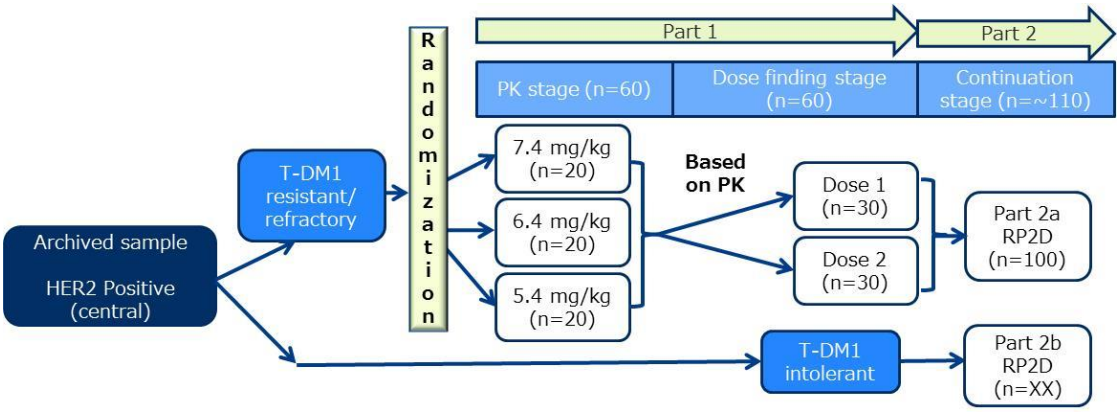
- PK Stage: approximately 20 subjects at 7.4 mg/kg dosing, 20 subjects at 6.4 mg/kg dosing and 20 subjects at 5.4 mg/kg dosing will be randomized in a 1:1:1 ratio. Two dose levels will be selected based on the PK results.
- Dose Finding Stage: approximately 30 subjects at each dose level will be randomized in a 1:1 ratio into 1 of 2 treatment groups selected after the PK analysis. A dose selection analysis will be performed to evaluate both safety and efficacy in order to determine the optimal dose for DS-8201a.

Part 2a will continue to enroll approximately 100 subjects at the RP2D of 5.4 mg/kg (see Section 11.5) as well as the Phase 1 trial DS8201-A-J101. Part 2b will enroll an open-ended number of subjects that received T-DM1 but are not eligible for the primary analysis. This is an exploratory cohort with the objective to explore the efficacy of DS-8201a in subjects who discontinued prior T-DM1 therapy for reasons other than progression of disease. Part 2b will enroll an open-ended number of subjects. The enrollment duration of Part 2b is determined based on enrollment in Part 2a. Part 2a and Part 2b will begin enrollment simultaneously and complete enrollment when the target of approximately 100 subjects enrolled is reached for Part 2a. Approximately 10 to 15 subjects would be expected to enroll in Part 2b. The exploratory analysis for Part 2b will be performed at the same time as the primary analysis cohort including all subjects in Part 1 and Part 2a treated at the RP2D of 5.4 mg/kg.

DS-8201a will be administered [redacted] at a dose of 7.4 mg/kg, 6.4 mg/kg or 5.4 mg/kg every 3 weeks.

The study treatment will be continued according to the dosing criteria to derive clinical benefit in the absence of withdrawal of subject consent, PD, or unacceptable toxicity. If the study treatment is delayed more than 4 weeks from the planned date of administration, the subject will be withdrawn from the study drug (see Section 5.7.3).

Figure 3.1: Study Design Schema of DS8201-A-U201



History of past treatment with pertuzumab will be collected for all study subjects. The study plans to enroll 100 or more subjects with history of prior pertuzumab treatment in the metastatic/advanced breast cancer setting. If after 150 subjects have been enrolled at the RP2D (20 from the PK stage, 30 from the dose finding stage and 100 from Part 2a), less than 100 such subjects have been enrolled, the study may continue to enroll subjects but only those meeting this criteria, and until at least 100 such subjects have been enrolled. This study also has a cap for subjects with moderate hepatic impairment at approximately 10 subjects (See Section 4.1, #10).

3.1.2. Duration of the Study

Enrollment is planned to occur over approximately 12 months, with treatment, and follow-up projected to be continued for at least 10 months after last subject enrolled. Thus, the anticipated duration of the study is at least 22 months.

Sponsor may terminate the study at any time and study termination may also be requested by (a) competent authority(ies).

3.1.3. Duration of Subject Participation

The screening period is up to 28 days. Once subject is randomized, Cycle 1 Day 1 (first dose) should occur within 7 days from the randomization date. Each cycle of treatment will be 21 days. The number of treatment cycles with DS-8201a is not fixed. Upon commencing study treatment, subjects may continue receiving study drug until the occurrence of any of the events defined in Section 5.7.1. Most subjects are expected to receive between 10 and 20 cycles of treatment.

Regardless of reason for discontinuation from study treatment, all subjects, may be contacted every 3 months until death or until follow-up data collection is no longer of scientific value or otherwise needed (at the Sponsor's discretion), to obtain information about subsequent treatment(s) and survival status.

3.1.4. Definition of the End of the Study

The end of the study is defined as the last subject visit or contact, including telephone contacts, for collection of any study-related data.

3.2. Discussion of Study Design

It is estimated that approximately 230 subjects will be enrolled in the study at approximately 110 sites in North America, Japan and other Asian countries, and Europe. Other countries may also be considered.

3.2.1. Selection of Dose

The dose selection was based on clinical data from DS8201-A-J101 and subsequent exposure-response analysis. Dose up to 8.0 mg/kg was shown to be tolerable in DS8201-A-J101, and modeling results on efficacy and safety endpoints supported the selection of 5.4, 6.4, and 7.4 mg/kg, given the risk benefit considerations.

4. STUDY POPULATION

Each subject will sign an Informed Consent Form (ICF) provided by the site. A subject is considered enrolled in the study upon the investigator or designee obtaining written informed consent from the subject, (Section 15.2) at the time of Screening and upon determination that all inclusion and exclusion criteria have been satisfied.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited subject information (initials, age, gender) and outcome of screening process (ie, enrollment in the study, reason for ineligibility, refused to participate).

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

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

4.1. Inclusion Criteria

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

1. Men or women ≥ 20 years old in Japan and Korea, ≥ 18 years old in the US (for other countries, please follow the reference[2])
2. Pathologically documented breast cancer that:
   - is unresectable or metastatic;
   - has confirmed HER2 positive expression (estrogen receptor/progesterone receptor positive subjects may be enrolled if they are HER2 positive) according to American Society of Clinical Oncology College of American Pathologists (ASCO-CAP) guidelines[21] evaluated at a Central Laboratory. See Laboratory Manual for details.
3. Subjects must have an adequate tumor sample available for confirmation of HER2 status by Central Laboratory (based on most recent tumor tissue sample, see Section 6.1)
4. Subject must have breast cancer which is resistant or refractory to T-DM1 with documented clinical or radiographic progression of disease during or after treatment with T-DM1
   - For Part 2b, subjects must have discontinued treatment with T-DM1 for reasons other than resistant or refractory disease
5. Presence of at least one measurable lesion per RECIST version 1.1
6. LVEF ≥ 50%
7. ECOG PS 0 or 1
8. Adequate bone marrow function, defined as:

[2] https://hrpo.wustl.edu/wp-content/uploads/2015/01/5-Determining-Legal-Age-to-Consent.pdf

- Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (G-CSF administration is not allowed within 1 week prior to screening assessment)
- Platelet count ≥ 100 × 10^9/L (Platelet transfusion is not allowed within 1 week prior to screening assessment)
- Hemoglobin level ≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)

9. Adequate renal function, defined as:
    - Creatinine clearance ≥ 30 mL/min, as calculated using the Cockcroft Gault equation (Section 17.1), ([{140 age in years} × {actual weight in kg}] divided by [{72 × serum creatinine in mg/dL} multiplied by 0.85 if female])
10. Adequate hepatic function, including mild-moderate hepatic impairment defined as the following:
    - Normal hepatic function to mild hepatic dysfunction: Total bilirubin ≤ 1.5 × ULN or < 3 × ULN in the presence of documented Gilbert's syndrome or liver metastases at baseline and aspartate transaminase (AST)/alanine transaminase (ALT) ≤ 5 × ULN
    - Moderate hepatic dysfunction: total bilirubin > 1.5 × ULN and ≤ 3 × ULN and aspartate transaminase (AST)/alanine transaminase (ALT) ≤ 5 × ULN. *After approximately 10 subjects with moderate hepatic dysfunction have been enrolled, subsequent subjects with moderate hepatic dysfunction will be excluded*
11. Adequate blood clotting function, defined as:
    - International normalized ratio and activated partial thromboplastin time ≤ 1.5 × ULN
12. If <100 of the planned 150 subjects (20 from the PK stage, 30 from the dose finding stage and 100 from Part 2a) enrolled and dosed with the RP2D have a history of pertuzumab treatment in the metastatic setting, enrollment may continue to achieve this number, and prior 1st or 2nd line pertuzumab treatment in the advanced/metastatic breast cancer setting will be required for these additional subjects.
13. Subjects should be able and willing to comply with protocol visits and procedures
    - Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 4.5 months after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception including:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

        Oral

        Intravaginal

        Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:

  Oral

  Injectable

  Implantable

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 4.5 months after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] > 40 mIU/mL and estradiol < 40 pg/mL [< 147 pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for women of childbearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.

14. Men who are fertile and sexually active should be willing to use highly effective methods of contraception if their partners are of reproductive potential.
15. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4.5 months after the final study drug administration. Preservation of sperm should be considered prior to enrollment in this study.
16. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 4.5 months after the final study drug administration.
17. Must have provided informed consent for study participation (see Section 15.2) before performance of any study-specific procedures or tests.

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Medical history of myocardial infarction within 6 months before randomization/registration, symptomatic congestive heart failure (CHF) (New York

Heart Association Class II to IV, Section 17.4), troponin levels consistent with myocardial infarction as defined according to the manufacturer, unstable angina, or serious cardiac arrhythmia requiring treatment within 28 days before randomization/registration

2. Has a corrected QT interval (QTc) prolongation to > 470 msec (females) or >450 msec (males) based on average of the screening triplicate12-lead ECG
3. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening
4. Brain metastases that are untreated, symptomatic, or require therapy to control symptoms, as well as any history of radiation, surgery, or other therapy, including steroids or anticonvulsants, to control symptoms from brain metastases within 2 months (60 days) of randomization/registration. After approximately 30 subjects with inactive brain metastases [20% of the 150 planned to receive the RP2D] have been enrolled at the RP2D, subsequent subjects with any current or past history of brain metastases will be excluded
5. Has clinically significant corneal disease in the opinion of the investigator
6. History of severe hypersensitivity reactions to other monoclonal antibodies
7. Substance abuse or medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results
8. Social, familial, or geographical factors that would interfere with study participation or follow-up
9. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals
10. Known human immunodeficiency virus (HIV) infection, or active hepatitis B surface antigen or C infection. Subjects should be tested for HIV prior to randomization if required by local regulations or institutional review board (IRB)/ethics committee (EC)
11. History of other malignancy(ies), except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated, with no evidence of disease for ≥ 3 years
12. Prior treatment with an ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor.
13. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to grade ≤ 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator after consultation with the Sponsor Global Clinical Lead or designee (eg, Grade 2 chemotherapy-induced neuropathy)
14. Therapeutic radiation therapy or major surgery within 4 weeks before study drug treatment or palliative radiation therapy within 2 weeks before study drug treatment

15. Systemic treatment with anticancer therapy, antibody-based therapy, retinoid therapy, or hormonal therapy within 3 weeks before study drug treatment; or treatment with nitrosoureas or mitomycin C within 6 weeks before study drug treatment; or treatment with small-molecule targeted agents within 2 weeks, or 5 half-lives before study drug treatment, whichever is longer
16. Current treatment with CYP3A4 strong inhibitors and OATP1B inhibitors (Section 17.5) (washout period of ≥ 3 elimination half-lives of the inhibitor is required)
17. Participation in a therapeutic clinical study within 3 weeks before study drug treatment (for small-molecule targeted agents [eg, inhibitors], this non-participation period is 2 weeks or 5 half-lives, whichever is longer), or current participation in other investigational procedures
18. Pregnant or breastfeeding, or planning to become pregnant
19. Subject must not be a family member of study site personnel or of Sponsor personnel.
20. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments

5.1.1. Treatment Group(s)

There will be subjects randomized to 3 different treatment groups: 5.4 mg/kg, 6.4 mg/kg, and 7.4 mg/kg Q3W in the PK stage and two treatment groups in the dose finding stage. Once assigned, subjects will remain on study in their treatment group and will not change dose groups. There will be 1 treatment group in Part 2 of this study (at the RP2D of 5.4 mg/kg).

5.1.2. Method of Treatment Allocation

For the PK Stage of Part 1, eligible subjects will be randomized by the interactive web/voice response system (IXRS) in a 1:1:1 ratio into 1 of 3 treatment groups: 5.4 mg/kg, 6.4 mg/kg, and 7.4 mg/kg.

For the Dose Finding Stage of Part 1, eligible subjects will be randomized by the IXRS in a 1:1 ratio into 1 of 2 treatment groups selected after the PK Stage.

Randomization will be stratified by region (Asia, rest of world).

For Part 2, eligible subjects will not be randomized, but will instead be registered in IXRS.

5.1.3. Blinding

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

5.2. Study Drug(s)

5.2.1. Description

Two dosage forms of DS-8201a drug product will be supplied.

The DS-8201a drug product containing 100 mg of DS-8201a is either provided as:

[redacted]**-DP2)**

The DS-8201a drug product [redacted] Each vial is designed for single use only and is not to be used to treat more than one subject.

or

[redacted]**-DP)**

The DS-8201a drug product [redacted] Each vial is designed for single use only and is not to be used to treat more than one subject. [redacted]

5.2.2. Labeling and Packaging

DS-8201a will be supplied by the Sponsor. DS-8201a Injection study drug will be clinical-labeled in compliance with regulatory requirements and packaged. The packaging will clearly display the name of the investigational product, the investigational product manufacturing code, storage condition and other required information in accordance with local regulations.

5.2.3. Preparation

The drug for IV infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight in a volume of 100 mL. Prepared medicinal solutions should be used immediately. The preparation will be conducted in accordance with the Pharmacy Manual provided by the Sponsor. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study site. Refer to the Pharmacy Manual for detailed information about preparation and administration of DS-8201a.

5.2.4. Administration

The investigational drug will be administered initially as a 7.4 mg/kg, 6.4 mg/kg, or 5.4 mg/kg IV every 3 weeks. The initial dose of DS-8201a will be infused for 90 ± 10 minutes. If there is no infusion-related reaction, after the initial dose, the next dose of DS-8201a will be infused for 30 ± 5 minutes. The subject's weight at screening (baseline) will be used to calculate the initial dose. If during the course of treatment the subject's weight changes by ± 10% of the baseline weight, the subject's dose will be recalculated based on the subject's updated weight. Two drug materials will be used in this study. [redacted] The transition from [redacted] to [redacted] is expected to occur at approximately the start of Part 2 of the trial.

5.2.5. Storage

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

- Stored [redacted]
- Stored [redacted]

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

5.2.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be signed and the original form will be retained at the site. In addition, the investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the investigational product. The record must be kept current and should contain the following:

- dates and quantities of drug received,
- subject's identification number and/or initials or supply number (as applicable),
- the date and quantity of investigational product dispensed and remaining (if from individual subject drug units),
- the initials of the dispenser.

At the end of the study, as per local laws and/or directed by Sponsor, all unused DS-8201a will be returned or destroyed as per local laws or site policy and only after the study monitor has completed a final inventory. As applicable, the study site must file a copy of the appropriate institution policy within their investigator site file and provide a copy to the Sponsor. Please see Pharmacy Manual for details.

All investigational product inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors.

5.3. Control Treatment

Not applicable.

5.4. Dose Interruptions and Reductions

The investigator will evaluate which toxicities are attributed to the study drug and adjust the dose of the drug as recommended below. All dose modifications should be based on the worst preceding toxicity (common toxicology criteria [CTC]AE version 4.03). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of DS-8201a are listed in Table 5.2. All interruptions or modifications must be recorded on the AE and drug administration case report form (CRF). Appropriate clinical experts should be consulted as deemed necessary.

For Grade 3 or Grade 4 events, monitoring (including local laboratory tests when appropriate) should be performed at intervals no greater than 7 days until AE is determined to be resolving or subject is discontinued at end of treatment.

Prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs will be as per treating physician discretion and institutional guidelines.

Dose Reduction Guidelines:

NOTE: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in Table 5.2.

Two dose reductions will be permitted. The adjustment for reduced dosing of DS-8201a is as shown in Table 5.1.

Table 5.1: Dose Reduction Levels of DS-8201a

Starting Dose	Dose Level -1	Dose Level -2
7.4 mg/kg	6.4 mg/kg	5.4 mg/kg
6.4 mg/kg	5.4 mg/kg	4.4 mg/kg
5.4 mg/kg	4.4 mg/kg	3.2 mg/kg

Once the dose of DS-8201a has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. More than 2 dose reductions are not allowed and the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs. DS-8201a dose increases are not allowed in the study.

Dose can be interrupted for up to 28 days from the planned date of administration. If a subject is assessed as requiring a dose delay longer than 28 days, the subject will be withdrawn from the study.

Treatment cycles for a subject for whom DS-8201a dosing was temporarily withheld for any reason may have future cycles scheduled based on the date of the last DS-8201a dose.

Investigators may contact the Sponsor's Global Clinical Lead or designee to discuss questions regarding dose modification or discontinuation of study drug.

Table 5.2: Dose modification for DS-8201a

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
No toxicity	Maintain dose and schedule
Infusion Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion-related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 h)	Administration of DS-8201a should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, intravenous fluids). If the event resolves or improves to grade 1, infusion can be re-started at a 50% reduced infusion rate. Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	Administration of DS-8201a should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation etc., should be administered.

Table 5.2: Dose modification for DS-8201a (Continued)

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4	Delay dose until resolved to ≤ Grade 2, Reduce dose 1 level
Febrile Neutropenia (absolute neutrophil count < 1×10^9/L, fever > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)	Delay dose until resolved, Reduce dose by 1 level
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (< 0.2×10^9/L)	Delay dose until resolved to ≤ Grade 2: • If resolved in ≤ 14 days, maintain dose • If resolved in > 14 days, reduce dose 1 level
Anemia	
Grade 3 (Hemoglobin (Hg) <8.0 g/dL); transfusion indicated	Transfuse. Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 (Hg <8.0 g/dL) Life threatening consequences; urgent intervention indicated	Transfuse. Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (platelets <50 to 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days, maintain dose • If resolved in > 7 days, reduce dose 1 level
Grade 4 (platelets < 25×10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure (CHF)	Discontinue subject from study treatment
Decrease in left ventricular ejection fraction (LVEF) 10-20% (absolute value), but LVEF > 45%	Continue treatment with DS-8201a
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	Continue treatment with DS-8201a Repeat LVEF assessment within 3 weeks

Table 5.2: Dose modification for DS-8201a (Continued)

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
LVEF 40% to ≤ 45% and decrease is ≥ 10% (absolute value) from baseline	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% from baseline, discontinue subject from study treatment
LVEF < 40% or > 20% (absolute value) drop from baseline	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue subject from study treatment
Corrected QT (QTc) Prolongation	
Grade 3 (QTc> 500 ms on 2 separate electrocardiograms)	Delay dose until resolved to ≤ Grade 1 (QTc ≤ 480 ms), determine if another medication the subject was taking may be responsible and can be adjusted, then if attributed to DS-8201a, reduce dose 1 level
Grade 4 (QTc > 500 or > 60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment
Troponin	
Grade 1 (Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer)	If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3 Repeat troponin testing at 3 ± 1 hours after initial troponin test. • If repeat troponin level at 3 ± 1 hours rises significantly per institutional guidelines, - perform ECG in triplicate; - repeat troponin testing at 6 ± 1 hours after initial troponin test; - follow institutional guidelines for management of detectable troponin testing. • If repeat troponin level at 3 ± 1 hours does not rise significantly per institutional guidelines, - repeat troponin testing at 6 ± 1 hours or at 24 ± 2 hours after initial troponin test. Continue treatment with DS-8201a.
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	Perform ECG in triplicate Repeat troponin testing at 6 hours and 12 hours after initial troponin test. Follow institutional guidelines for management of detectable troponin testing. If AMI confirmed, discontinue subject from study therapy. Delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days, maintain dose • If resolved in > 7 days, reduce dose 1 level

Table 5.2: Dose modification for DS-8201a (Continued)

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Pulmonary Toxicity	If a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: • High resolution CT • Pulmonologist consultation • Pulmonary function tests and pulse oximetry (SpO2) • Arterial blood gases if clinically indicated • One blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible Other tests could be considered as needed. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (Kubo K, et al 2013 for guidance[22]). If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.
Grade 1	The administration of DS-8201a must be interrupted for any ILD event regardless of grade. For Grade 1 events, DS-8201a can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤ 28 days from day of onset, maintain dose • If resolved in > 28 days from day of onset, reduce dose 1 level
Grade2, 3, or 4	Permanently discontinue subject from study treatment.
Ocular	
Grade 3	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days, maintain dose • If resolved in > 7 days, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Renal Toxicity (serum creatinine)	
Grade 3 (> 3 to 6 × upper limit of normal [ULN])	Delay dose until resolved to ≤ Grade 2 or baseline, then reduce dose 1 level
Grade 4 (> 6 × ULN)	Discontinue subject from study treatment

Table 5.2: Dose modification for DS-8201a (Continued)

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Hepatic Toxicity	
Aspartate Transaminase (AST) or Alanine Transaminase (ALT) with Simultaneous Total Bilirubin (TBL) Increased	
AST/ALT ≥3.0 × ULN with simultaneous TBL >2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.
Aspartate Transaminase (AST) or Alanine Transaminase (ALT)	
Grade 2 (> 3.0 - 5.0 × ULN)	No action for Grade 2 AST/ALT
Grade 3:> 5.0 - 20.0 × ULN In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 × ULN:	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days from day of onset, maintain dose • If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 3 (> 8.0 - 20.0 × ULN) In subjects with liver metastases, if the baseline level was > 3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: • If resolved in ≤ 7 days from day of onset, maintain dose • If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 4 (> 20 × ULN)	Discontinue subject from study treatment
Total Bilirubin	
Grade 2 (> 1.5 - 3.0 × ULN)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days from day of onset, maintain dose • If resolved in > 7 days from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (> 3.0 – 10.0 × ULN)	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days from day of onset, reduce dose 1 level • If resolved in > 7 days from day of onset, discontinue DS-8201a If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 2: • If resolved in ≤ 7 days from day of onset, reduce dose 1 level • If resolved in > 7 days from day of onset, discontinue DS-8201a
Grade 4 (> 10.0 × ULN)	Discontinue subject from study treatment
Alkaline Phosphatase Increased	
Grade 3 or 4 (>5.0 × ULN)	No modification unless determined by the investigator to be clinically significant or life-threatening

Table 5.2: Dose modification for DS-8201a (Continued)

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	Dose or schedule modification for DS-8201a
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 7 days, maintain dose • If resolved in > 7 days, reduce dose 1 level
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤ 3 days, maintain dose • If resolved in > 3 days, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Other Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline level: • If resolved in ≤ 7 days, maintain dose • If resolved in > 7 days, reduce dose 1 level
Grade 4	Discontinue subject from study treatment
Other Non-laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline: • If resolved in ≤ 7 days, maintain dose • If resolved in > 7 days, reduce dose 1 level
Grade 4	Discontinue subject from study treatment

All dose modifications should be based on the worst preceding toxicity.
CTCAE: Common Terminology Criteria for Adverse Events.

In addition, investigators may consider dose reductions or discontinuations of the study drug according to the subject's condition and after discussion with the Sponsor Global Clinical Lead or designee.

5.5. Method of Assessing Treatment Compliance

DS-8201a will be administered IV only to subjects participating in the study and under the supervision of clinical study personnel at the site. Start and stop times of injection and amount of drug administered are to be recorded by clinical study personnel.

5.6. Concomitant Medications, Treatments, And Procedures

Medications used from the time the subject signs the informed consent form to 40 days (+ 7 days) after the last administration of DS-8201a will be recorded. All concomitant medications will be recorded on the CRF.

The following medications, treatment and procedures will be prohibited during the treatment period (see Section 4.2 for required washout periods):

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anti-cancer hormonal treatment.
- Other investigational therapeutic agents.
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in dose modification section).
- Radiotherapy to the thorax.
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications. (Inhaled steroids or intra articular steroid injections are permitted in this study.)
  - Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.
- CYP3A4 strong inhibitors (eg, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, saquinavir, telaprevir, telithromycin, voriconazole). Please consult with your local resources as needed to evaluate potential CYP3A4 inhibitors (see Section 17.5 for more extensive list).

  If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying DS-8201a treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is co-administered and DS-8201a treatment cannot be delayed, subjects should be closely monitored for adverse reactions.
- Organic anion transporting polypeptide (OATP)1B inhibitors including but are not limited to: atazanavir, clarithromycin, cyclosporine, erythromycin, gemfibrozil, lopinavir, rifampin, ritonavir, simeprevir. Consult with your local resources as needed to evaluate potential OATP1B inhibitors (see Section 17.5 for more extensive list).
- If concomitant use of OATP1B inhibitors is unavoidable, consider delaying DS-8201a treatment until the OATP1B inhibitors have cleared from the circulation (approximately 3 × the elimination half-life of the inhibitors) as long as possible.
- If an OATP1B inhibitor is co-administered and DS-8201a treatment cannot be delayed, subjects should be closely monitored for adverse reactions.
- Foods or beverages containing grapefruit;

Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the investigator.

Prophylactic or supportive treatment of study-drug induced AEs will be otherwise as per investigator's discretion and institutional guidelines.

Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged, but not prohibited.

5.7. Removal of Subjects From Treatment and/or Study

5.7.1. Reasons for Discontinuation of Study Treatment

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

- Progressive disease per criteria set forth in RECIST version 1.1;
- Clinical progression (definitive clinical signs of (PD), but a recent radiographic assessment did not meet the criteria for Progressive Disease according to RECIST version 1.1);
- Adverse event;
- Withdrawal of consent by subject;
- Physician Decision;
- Death;
- Pregnancy;
- Study terminated by Sponsor;
- Lost to follow-up;
- Other, specify.

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

All subjects who are withdrawn from study treatment should complete protocol-specified withdrawal procedures (Section 5.7.3) and follow-up procedures (Section 6.6).

Record the reason for any subject who discontinues study treatment. Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

5.7.2. Reasons for Discontinuation of Study Participation

- Subject withdraws consent to participate in study procedures;
- Subject dies;
- Study is terminated;
- Subject is lost to follow-up;
- Other, specify.

Note: All subjects will be followed for survival status even after consent for study procedures is withdrawn. Subjects discontinued from the study because of withdrawal of consent will be followed for survival by collecting public records (eg, death certificates) every 3 months from the last study visit, unless prohibited by local laws.

5.7.3. Withdrawal Procedures

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

If the subject is withdrawn from the study treatment due to an AE, the investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study treatment should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be obtained during the end of treatment visit (+7 days) and the follow-up 40 day visit (+7 days) conducted after the last administration of DS-8201a (Section 6.5 and Section 6.6).

5.7.4. Subject Replacement

Subjects that have been enrolled and administered study medication will not be replaced. However, it is allowable to replace a subject that was enrolled but was not administered any study medication.

5.7.5. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet eligibility criteria upon initial screening. The subject identification (SID) number **must remain the same** at the time of re-screening. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for a subject who is re-screened.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided below in Table 6.1 and Table 6.2.

6.1. Tissue Screening

To determine eligibility, subjects must meet tumor biomarker criteria.

Note: Subjects may continue on prior therapy while tissue testing takes place.

Please refer to the study Laboratory Manual for required tumor sample specifications and shipping instructions.

The following procedures will be conducted:

- Obtain a signed and dated written consent from the subject to collect tissue and/or perform a biopsy as needed.
- If a tumor biopsy is needed, record any SAEs directly related to tissue screening procedure (ie, tumor biopsy).
- Obtain adequate archived or recent tumor tissue sample for HER2 testing. Most recent tumor tissue sample should be submitted. If prior tissue specimen is submitted, document reason why most recent tumor sample is unavailable.
- Send the sample to the Central Laboratory to confirm HER2 status
- Additional slides for exploratory biomarker assessment are requested (see Laboratory Manual).
- For subjects who sign only the Informed Consent Form for tissue screening, report only serious adverse events (SAEs) directly related to tissue screening procedure (ie, tumor biopsy). Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

6.2. Screening

Obtain a signed and dated ICF before any study-related procedures or assessments are conducted.

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

Within 28 days before registration/randomization

- Perform a human immunodeficiency virus (HIV) antibody test. HIV antibody test must be performed for Japanese subjects, and is optional for other subjects unless required by local regulations or IRB/ECs.
- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, and fundoscopy.
- Perform an Echo or MUGA (note: the same test must be used for the subject throughout the study).

- Perform tumor assessment by computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and any other sites of disease. A CT or MRI of the brain is to be included for all subjects.

NOTE: To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use it as comparator for subsequent measurement. Therefore, all lesions (target and non-target) have to be assessed at Screening according to RECIST version 1.1 (Section 17.3).

The following activities and/or assessments will be performed during the screening period within 14 days before starting study drug except as indicated:

- Obtain demographics (eg, birth date, sex, race, ethnicity), medical and surgical history, including all previous, now resolved, significant medical conditions, date of diagnosis, extent of disease, disease staging, estrogen/progesterone receptor status, previous cancer therapies (including prior radiation therapy) and oncology surgical history.
- Perform a complete physical examination (see Section 9.11) including weight and height.
- Assess AEs throughout the screening period (from the time the subject signed the ICF).
- Record concomitant medications (from the time the subject signed the ICF)
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and SpO2).
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Obtain urine sample for urinalysis (protein, glucose, blood, microscopy assessment [if indicated], and specific gravity) and blood sample for coagulation testing (prothrombin time and activated partial thromboplastin time).
- Obtain blood samples for hematology and blood chemistry tests (includes calculated creatinine clearance. See Section 9.8, Section 17.1), troponins (preferably troponin-T) and HER2ECD.
- Perform a 12-lead ECG in triplicate*.

*ECGs will be taken in close succession, approximately 3 minutes apart, while in a supine/semi-recumbent position.

- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential. Test must be confirmed negative within 72 hours prior to randomization/registration. For postmenopausal subjects (no childbearing potential, as indicated by an elapse of at least 12 months after the last menstruation) or subjects who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of childbearing potential and required to undergo the pregnancy test.
- Review inclusion/exclusion criteria.

6.3. Randomization

For the PK Stage of Part 1, eligible subjects will be randomized by the IXRS in a 1:1:1 ratio into 1 of 3 initial treatment groups: 5.4 mg/kg, 6.4 mg/kg, and 7.4mg/kg.

For the Dose Finding Stage of Part 1, an additional of approximately 30 subjects per dose will be randomized by the IXRS in a 1:1 ratio into 1 of 2 treatment groups selected after the PK Stage.

Randomization will be stratified by region (Asia, rest of world).

For Part 2, eligible subjects will not be randomized, but will instead be registered in IXRS.

Once the subject is randomized, first dose / Cycle 1 Day 1 should occur within 7 days from the randomization date.

6.4. Treatment Period

6.4.1. Cycle 1 to Cycle 4 and Subsequent Cycles

Treatment and procedures performed on Day 1 of Cycle 1 and beyond are specified in Table 6.1 and Table 6.2 below. Procedures are to be performed within 3 days of the Day 1 visit of each cycle unless otherwise specified.

Physical examination, weight, ECOG PS assessment, 12-lead ECG, hematology, blood chemistry, coagulation test, and vital signs (including SpO2) evaluations do **not** need to be repeated at the Cycle 1, Day 1 visit **if** performed within 3 days before the first dose of study drug. However, vital sign information must be collected at EOI of Cycle 1, 2, and 3.

Before Dosing:

- Record concomitant medications
- Blood plasma samples for exploratory biomarkers, such as cell free deoxyribonucleic acid (cfDNA) analysis in plasma, will be collected before treatment on Day 1 of Cycle 1 and every 3 cycles thereafter(eg, Cycle 4, Cycle 7, etc.).
- Physical examination (Section 9.11) will be performed on the scheduled day even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Ophthalmologic assessments to include visual acuity testing, slit lamp examination and fundoscopy will be performed at Day 1 of Cycle 2 (within 3 days before administration) and every 4 cycles (±7 days) thereafter (Day 1 Cycle 2, 6, 10, 14, etc). If the planned date of study drug administration is delayed after examination of ophthalmologic assessments, and there are no abnormal findings on the examination, it is up to the investigator's judgment as to whether ophthalmologic assessments need to be repeated.
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and SpO2) will be performed as per the Schedule of Events. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- ECOG PS will be assessed as per the Schedule of Events.

- Safety will be monitored by assessment as well as by collection of the AEs at every visit. For details on AE collection and reporting, refer to Section 9.
- Blood samples for hematology and blood chemistry assessments will be collected as per the Schedule of Events. Refer to Section 9.8 for a list of parameters to be evaluated.
- Triplicate 12-lead ECG will be performed as per the Schedule of Events, approximately 3 minutes apart. ECGs should be performed before PK blood draws at respective time points.
- Perform an Echo or MUGA scan assessment (note: the same test must be used for the subject throughout the study) every 4 cycles (±7 days) (Cycle 5, 9, 13, etc). If the planned date of study drug administration is delayed after examination of Echo or MUGA, and there are no abnormal findings on the examination, it is up to the investigator's judgment as to whether Echo or MUGA need to be repeated.
- Obtain a blood sample for pharmacogenetic assessment within Cycle 1 only. (This sample is not required for study participation and will be collected from subjects who have provided consent by signing the pharmacogenetics sample banking consent form.)
- Blood samples for PK assessments will be obtained before infusion (-8 hours) on Day 1 of each cycle through Cycle 4; then at Day 1 of Cycle 6 and Cycle 8.
- Blood samples for ADA will be obtained according to the time points indicated in the Schedule of Events.
- Blood samples for HER2ECD assessment will be collected on Cycle 3 Day 1 and every other cycle thereafter (eg, Cycle 3, 5, 7, 9...).

Dosing and Postinfusion Assessments:

- Administer DS-8201a IV infusion 90 ± 10 minutes for the initial dose and, if no infusion-related reaction after the initial dose, infuse subsequent doses over 30 ± 5 minutes. Record start and stop times. DS-8201a is to be administered every 3 weeks ± 2 days.
- Collect blood samples within 15 minutes after end of infusion (EOI) for PK analysis for on Day 1 of each cycle through Cycle 4; then at Day 1 of Cycle 6 and Cycle 8.
- Collect blood samples for troponin (preferably high sensitivity troponin-T) 2-3 hours after end of infusion. The test used to test troponin should remain the same throughout the course of a subject's time on study. An additional sample should be submitted for central laboratory troponin-T testing.

  Repeat troponin testing at 3 ± 1 hours after initial troponin test.

  If repeat troponin level at 3 ± 1 hours rises significantly per institutional guidelines,

  perform ECG in triplicate;

  repeat troponin testing at 6 ± 1 hours after initial troponin test;

follow institutional guidelines for management of detectable troponin testing.

If repeat troponin level at 3 ± 1 hours does not rise significantly per institutional guidelines,

repeat troponin testing at 6 ± 1 hours or at 24 ± 2 hours after initial troponin test.

If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG testing in triplicate, repeat troponin testing 6 ± 1 hours and 12 ± 1 hours after initial troponin test was drawn, and follow institutional guidelines.

If troponin levels are above the upper limit of normal at baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin level is not Grade 3.

- Collect vital signs at EOI of Cycle 1, 2, and 3.

Part 1 PK Stage Only: Obtain blood sample for PK assessments at the following time points:

- Cycle 1 Day 1

  2 hours after the start of drug administration (± 15 minutes)

  4 hours after the start of drug administration (± 15 minutes)

  7 hours after the start of drug administration (± 15 minutes)

- Cycle 1 Day 2 and Day 4: Obtain blood sample for PK assessments at the following time points

  24 hours (Day 2) and 72 hours (Day 4) after the start of drug administration (± 2 hours)

- Cycle 1 Day 8 (± 1 day) and Day 15 (± 1 day):
- Cycle 3 Day 1:

  4 hours after the start of drug administration (± 15 minutes)

  7 hours after the start of drug administration (± 15 minutes)

All subjects dose finding stage and continuation stage: Obtain blood sample for PK assessments at the following time points

- Cycle 1 Day 1

  4 hours after the start of drug administration (± 15 minutes)

  7 hours after the start of drug administration (± 15 minutes)

- Cycle 1 Day 8 (± 1 day) and Day 15 (± 1 day):
- Cycle 3 Day 1:

  4 hours after the start of drug administration (± 15 minutes)

7 hours after the start of drug administration (± 15 minutes)

If the schedule on Day 1 of Cycles 2, 3 or 4 is delayed for 3 days or more, or if the subject cannot continue onto the next cycle, PK blood sample will be collected on Day 22 of Cycle 1, Cycle 2 or Cycle 3 as per the Schedule of Event (Table 6.1 and Table 6.2) and Section 8.1.

6.4.2. Every 6 Weeks (±7 days)

- Record concomitant medications and AEs at every visit.
- Tumor assessments, based on sites of disease identified at Screening and any additional newly suspected sites of progressive disease, will be conducted every 6 weeks (± 7 days) from Cycle 1 Day 1, independent of treatment cycle. CT or MRI scans of the suspected sites of disease in the chest, abdomen and pelvis are mandatory. Computerized tomography and/or MRI (spiral CT or MRI with ≤ 5 mm cuts) of chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions. The same assessment modality should be used throughout the study for all assessments for each subject unless prior approval is obtained from Sponsor or its designee. Unscheduled tumor assessments may be performed if progression is suspected.
- A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated.

Imaging results will be reviewed by an independent radiologic facility.

6.5. End of Treatment

The EOT is defined as the date the investigator decides to discontinue study treatment (+7 days). The following procedures will be performed as specified in the Schedule of Events. However, if the EOT assessments have been performed within 30 (±7) days of their last treatment, they can be considered to be the EOT data and there is no need to repeat them, otherwise these assessments need to be repeated.

- Physical examination. Weight will be recorded.
- Ophthalmologic assessments to include visual acuity testing, slit lamp examination, and fundoscopy.
- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and SpO2).
- ECOG PS.
- AEs and concomitant medications will be recorded.
- Blood samples for hematology, troponin, and blood chemistry assessments will be collected. Refer to Section 9.8 for a list of parameters to be evaluated.
- Blood plasma sample for exploratory biomarkers, such as cfDNA analysis in plasma, will be collected.

- Blood sample for HER2ECD assessment.
- Triplicate 12-lead ECG, approximately 3 minutes apart, while in a supine/semi-recumbent position.
- Echo or MUGA (note: the same test must be used for the subject throughout the study).
- Serum or urine sample for pregnancy testing in women of childbearing potential.
- Follow-up evaluations should include all sites of disease identified at screening and any other locations if progressive disease is suspected (eg, MRI of the brain if brain metastases are suspected) should also be imaged, per RECIST 1.1 (Section 17.3). If the previous scan was within the last 6 weeks, this assessment does not need to be performed at the EOT Visit.
- An MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need brain scan for tumor assessment unless clinically indicated.

6.6. Follow-up

Forty days (+7 days) after last study drug administration or before starting new anticancer treatment, whichever comes first, the following procedures will be performed as specified in the Schedule of Events. If EOT is > 40 (+7) days after last treatment, then the EOT assessments can also function as the follow-up visit.

- Vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature and SpO2).
- Physical examination. Weight will be recorded.
- ECOG PS.
- Hematology, blood chemistry, and troponin assessments will be performed.
- AEs and concomitant medications will be recorded.
- For subjects with positive ADA at the follow-up visit, additional serum ADA samples must be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or until the ADA becomes negative, or until the ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

Subjects will also be assessed every three months (±14 days), from the date of follow-up visit, for survival and subsequent anticancer therapy until death, withdrawal of consent, loss to follow-up, or study closure; whichever occurs first. This information may be collected in a visit or via phone contact, or (as necessary for survival status, in the case of withdrawal of consent or loss to follow-up) from public records as allowed by law.

Further follow-up may be required for ongoing AEs (see Section 9.1).

Table 6.1: Schedule of Events – Part 1 PK Stage

			Cycle 1							Cycle 2			Cycle 3			Cycle 4 and subsequent cycles					
		SCR	Day 1		Day 2	Day 4	Day 8	Day 15	Day 22[v]	Day 1		Day 22[v]	Day 1		Day 22[v]	Day 1		Every 6 wks (±7 days)	EOT (a)	40-day F/U (b)	q3mo F/U (±14 days)
	Tissue Screen	(-14 d or as noted)	BI	EOI			(±1 day)	(±1 day)	(±2 days)	BI	EOI	(±2 days)	BI	EOI	(±2 days)	BI	EOI				
Informed Consent (may sign	●	●																			
Administer DS 8201a			●							●			●			●					
Medical		●																			
Demograp		●																			
Pregnancy		●(																	●		
Vital Signs		●	●(	●			●	●		●(	●		●(	●		●(			●	●	
Physical		●	●(							●(			●(			●(			●	●	
SpO2		●	●(d)							●(d)			●(d)			●(d)			●	●	
Inclusion/Exclusion		●																			
Height		●																			
Weight,		●	●(							●(			●(			●(			●	●	
Urinalysis and coagulation testing		●																			
Hematology & Blood Chemistry Tests		●	●(d)				●	●		●(d)			●(d)			●(d)			●	●	
Troponin (e)		●		●							●			●			●		●	●	
Biomarker Blood Samples (f)			●													●			●		
Pharmacogenomics Blood Sample			●(g)																		
PK Blood (Serum) Sample			●(h)	●(i,j)	●(k)	●(k)	●	●	●(l)	●(h)	●(i)	●(l)	●(h)	●(i,j)	●(l)	●(h)	●(i)				
ADA Blood Sample			●(m)							●(m)						●(m)				●	●(n)
HIV Antibody Test (as required by local regulations		●(o)																			

	Tissue Screen	SCR (-14 d or as noted)	Cycle 1 Day 1 BI	Cycle 1 Day 1 EOI	Day 2	Day 4	Day 8 (±1 day)	Day 15 (±1 day)	Day 22[v] (±2 days)	Cycle 2 Day 1 BI	Cycle 2 Day 1 EOI	Day 22[v] (±2 days)	Cycle 3 Day 1 BI	Cycle 3 Day 1 EOI	Day 22[v] (±2 days)	Cycle 4 and subsequent cycles Day 1 BI	Cycle 4 and subsequent cycles Day 1 EOI	Every 6 wks (±7 days)	EOT (a)	40-day F/U (b)	q3 mo F/U (±14 days)
)																					
Blood Sample for		●											●(p)			●(p)			●		
Echo or MUGA		●(o)														●			●		
12 lead ECG in		●	●(d)							●(d)			●(d)			●(d)			●		
CT/MRI of		●(																●(s	●(		
Tumor		●(																●	●		
Ophthalmologic		●(o)								●(d,t)						●(d,t			●		
Tumor Sample for HER2 Status and	●(u)																				
Concomitant Medication		●																			
Adverse	●(	●																			
Survival																					●

AE = adverse event; ACC = American College of Cardiologists; BI = before infusion, cfDNA = cell free deoxyribonucleic acid; CT = computed tomography; d = days; Echo = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOT = end of treatment; F/U = follow-up; ADA = anti-drug antibody; HER2 = human epidermal growth factor receptor 2; HER2ECD = extracellular domain of HER2; HIV = human immunodeficiency virus; IXRS = interactive web/voice response system; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PK = pharmacokinetic; q3 mo = every 3 months; SCR: screening; SpO2 = peripheral oxygen saturation.

a The date the investigator decides to discontinue study treatment (+ 7 days). See Section 6.5 for whether new tests need to be conducted.

b 40 days (+ 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. See Section 6.6 for whether new tests need to be conducted.

c Within 72 hours before randomization

d Within 3 days before administration. The blood collections should be done after ECG (if performed on the same day as ECG).

e Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2-3 hours after end of infusion (EOI). An additional sample should be submitted for central laboratory troponin-T testing. Repeat troponin testing at 3 ± 1 h after initial troponin test. If repeat troponin level at 3 ± 1 h rises significantly per institutional guidelines, perform ECG in triplicate; repeat troponin testing at 6 ± 1 h after initial troponin test; and follow institutional guidelines for management of detectable troponin testing. If repeat troponin level at 3 ± 1 h does not rise significantly per institutional guidelines, repeat troponin testing at 6 ± 1 h or at 24 ± 2 h after initial troponin test. If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG testing in triplicate, repeat troponin testing 6 ± 1 h and 12 ± 1 h after initial troponin test was drawn, and follow institutional guidelines. If troponin levels are above the upper limit of normal at

baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin level is not Grade 3.

f Samples will be collected at Cycle 1 and then every 3 cycles (Cycles 4, 7, etc) until EOT for exploratory biomarkers such us cfDNA in plasma.

g Participation in this part of the study is optional for all subjects.

h Within 8 hours BI on Day 1 of each cycle through Cycle 4 and then every 2 cycles until Cycle 8 (Cycle 1, 2, 3, 4, 6, 8).

i Within 15 minutes of EOI on Day 1 of each cycle through Cycle 4 (Cycle 1, 2, 3 and 4) and then at Day 1 of Cycle 6 and Cycle 8.

j 2 h, 4 h and 7 h after the start of administration (± 15 minutes) for Cycle 1 and 4 h and 7 h after the start of administration (± 15 minutes) for Cycle 3.

k 24 h and 72 h after the start of administration (± 2 hours).

l If treatment of next cycle is delayed for 3 days or more, or subject is discontinued, collect PK blood on this day, Day 22 of the current cycle (± 2 days). Also see footnote v.

m Within 8 hours BI on Day 1 in Cycles 1, 2 and 4, and then every 4 cycles.

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

o Within 28 days before randomization/registration.

p Before administration at every 2 cycles from Cycle 3 (Cycle 3, 5, 7, 9, etc).

q Echo or MUGA scan assessments (note: the same test must be used for the subject throughout the study) will be performed at Screening and every 4 cycles (±7 days) (Cycle 5, 9, 13, etc)

r ECGs will be taken in close succession, approximately 3 minutes apart, while in a supine/semi-recumbent position.

s An MRI of the brain is mandatory for all subjects who were enrolled with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated.

t Ophthalmologic assessments to include visual acuity testing, slit lamp examination and fundoscopy will be performed at Day 1 of Cycle 2 (within 3 days before administration) and every 4 cycles (±7 days) thereafter (Day 1 Cycle 2, 6, 10, 14, etc).

u Archived tissue appropriate for central laboratory HER2 testing. If archived tissue is not available, fresh biopsy is required. Up to 5 additional slides are requested for optional biomarker analysis.

v Based on no delays and a 21-day cycle, Day 22 should be the same as Day 1 of the next cycle. In the event that there is a delay in the start of the next cycle, the goal is to still obtain the PK sample on Day 22 of the earlier cycle.

w DS-8201a is to be administered every 3 weeks ± 2 days unless discontinuation criteria are required.

x For subjects who sign only the Informed Consent Form for tissue screening, report only serious adverse events (SAEs) directly related to tissue screening procedure (ie, tumor biopsy). Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

For suspected ILD/pneumonitis, treatment with study drug should be interrupted pending evaluation.
Evaluations should include:

- High resolution CT
- Pulmonologist consultation
- Pulmonary function tests and pulse oximetry (SpO2)
- Arterial blood gases if clinically indicated
- One blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

Table 6.2: Schedule of Events – Part 1 Dose Finding Stage and Part 2 Stage

			Cycle 1					Cycle 2			Cycle 3			Cycle 4 and subsequent cycles					
		SCR	Day 1		Day 8	Day 15	Day 22[u]	Day 1		Day 22[u]	Day 1		Day 22[u]	Day 1		Every 6 wks (± 7 days)	EOT (a)	40-day F/U (b)	q3mo F/U (± 14 days)
	Tissue Screen	(-14 days or as noted)	BI	EOI	(± 1 day)	(± 1 day)	(± 2 days)	BI	EOI	(± 2 days)	BI	EOI	(± 2 days)	BI	EOI				
Informed Consent (may sign >	●	●																	
Administer			●					●			●			●					
Medical History		●																	
Demographi		●																	
Pregnancy		●(c															●		
Vital Signs		●	●(	●	●	●		●(d	●		●(	●		●(d			●	●	
Physical		●	●(					●(d			●(			●(d			●	●	
SpO2		●	●(d)					●(d)			●(d)			●(d)			●	●	
Inclusion/Exclusion		●																	
Height		●																	
Weight,		●	●(					●(d			●(			●(d			●	●	
Urinalysis and coagulation testing		●																	
Hematology & Blood Chemistry Tests		●	●(d)		●	●		●(d)			●(d)			●(d)			●	●	
Troponin (e)		●		●					●			●			●		●	●	
Biomarker Blood Samples (f)			●											●			●		
Pharmacogenomics Blood Sample			●(g)																
PK Blood (Serum) Sample			●(h)	●(i,j)	●	●	●(k)	●(h)	●(i)	●(k)	●(h)	●(i,j)	●(k)	●(h)	●(i)				
ADA Blood Sample			●(l)					●(l)						●(l)				●	●(m)
HIV Antibody Test (as required by local regulations)		●(n)																	

			Cycle 1					Cycle 2			Cycle 3			Cycle 4 and subsequent cycles					
		SCR	Day 1		Day 8	Day 15	Day 22[u]	Day 1		Day 22[u]	Day 1		Day 22[u]	Day 1		Every 6 wks (± 7 days)	EOT (a)	40-day F/U (b)	q3 mo F/U (± 14 days)
	Tissue Screen	(-14 days or as noted)	BI	EOI	(± 1 day)	(± 1 day)	(± 2 days)	BI	EOI	(± 2 days)	BI	EOI	(± 2 days)	BI	EOI				
Blood Sample for		●									●(o)			●(o)			●		
Echo or MUGA		●(n)												●			●		
12 lead ECG in		●	●(d)					●(d)			●(d)			●(d)			●		
CT/MRI of		●(n														●(r)	●(r		
Tumor		●(n														●	●		
Ophthalmologic		●(n)						●(d,s)						●(d,s)			●		
Tumor Sample for HER2 Status and	●(t)																		
Concomitan		●																	
AEs	●(w	●																	
Survival																			●

AE = adverse event; ACC = American College of Cardiologists; ADA = anti-drug antibodies; BI = before infusion, cfDNA = cell free deoxyribonucleic acid; CT = computed tomography; d = days; Echo = echocardiogram; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOI = end of infusion; EOT = end of treatment; F/U = follow-up; HER2 = human epidermal growth factor receptor 2; HER2ECD = extracellular domain of HER2; HIV = human immunodeficiency virus; IXRS = interactive web/voice response system; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition (scan); PK = pharmacokinetic; q3 mo = every 3 months; SCR: screening; SpO2 = peripheral oxygen saturation.

a The date the investigator decides to discontinue study treatment (+ 7 days). See Section 6.5 for whether new tests need to be conducted.

b 40 days (+ 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. See Section 6.6 for whether new tests need to be conducted.

c Within 72 hours before randomization.

d Within 3 days before administration. The blood collections should be done after ECG (if performed on the same day as ECG).

e Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2-3 hours after end of infusion (EOI). An additional sample should be submitted for central laboratory troponin-T testing. Repeat troponin testing at 3 ± 1 h after initial troponin test. If repeat troponin level at 3 ± 1 h rises significantly per institutional guidelines, perform ECG in triplicate; repeat troponin testing at 6 ± 1 h after initial troponin test; and follow institutional guidelines for management of detectable troponin testing. If repeat troponin level at 3 ± 1 h does not rise significantly per institutional guidelines, repeat troponin testing at 6 ± 1 h or at 24 ± 2 h after initial troponin test. If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG testing in triplicate, repeat troponin testing 6 ± 1 h and 12 ± 1 h after initial troponin test was drawn, and follow institutional guidelines. If troponin levels are above the upper limit of normal at baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin level is not Grade 3.

f Samples will be collected at Cycle 1 and then every 3 cycles (Cycles 4, 7, etc) until EOT for exploratory biomarkers such us cfDNA in plasma.
g Participation in this part of the study is optional for all subjects.
h Within 8 hours BI on Day 1 of each cycle through Cycle 4 and then every 2 cycles until Cycle 8 (eg, Cycle 1, 2, 3, 4, 6, 8).
i Within 15 minutes of EOI on Day 1 of each cycle until Cycle 4 (eg, Cycle 1, 2, 3 and 4) and then at Day 1 of Cycle 6 and Cycle 8.
j 4 h and 7 h after the start of administration (± 15 minutes).
k If treatment of next cycle is delayed for 3 days or more, or subject is discontinued, collect PK blood on this day, Day 22 of the current cycle (± 2 days). Also refer to footnote u for further explanation.
l Within 8 hours BI on Day 1 in Cycles 1, 2 and 4, and then every 4 cycles.
m For subjects with positive ADA at F/U visit, additional serum ADA samples must be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or until the ADA becomes negative, or until ADA titer becomes less than baseline (applicable when pre-existing ADA was observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
n Within 28 days before randomization/registration.
o Before administration at every 2 cycles from Cycle 3 (eg, Cycle 3, 5, 7, 9...).
p Echo or MUGA scan assessments (note: the same test must be used for the subject throughout the study) will be performed at Screening and every 4 cycles (±7 days) (eg, Cycle 5, 9, 13…).
qECGs will be taken in close succession, approximately 3 minutes apart, while in a supine/semi-recumbent position.
r An MRI of the brain is mandatory for all subjects who were enrolled with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated.
s Ophthalmologic assessments to include visual acuity testing, slit lamp examination and fundoscopy will be performed at Day 1 of Cycle 2 (within 3 days before administration) and every 4 cycles (±7 days) thereafter (Day 1 Cycle 2, 6, 10, 14, etc).
t Archived tissue appropriate for central laboratory HER2 testing. If archived tissue is not available, fresh biopsy is required. Up to 5 additional slides are requested for optional biomarker analysis.
u Based on no delays and a 21-day cycle, Day 22 should be the same as Day 1 of the next cycle. In the event that there is a delay in the start of the next cycle, the goal is to still obtain the PK sample on Day 22 of the earlier cycle.
v DS-8201a is to be administered every 3 weeks ± 2 days unless discontinuation criteria are required.
w For subjects who sign only the Informed Consent Form for tissue screening, report only serious adverse events (SAEs) directly related to tissue screening procedure (ie, tumor biopsy). Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

For suspected ILD/pneumonitis, treatment with study drug should be interrupted pending evaluation.
Evaluations should include:

- High resolution CT
- Pulmonologist consultation
- Pulmonary function tests and pulse oximetry (SpO2)
- Arterial blood gases if clinically indicated
- One blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

7. EFFICACY ASSESSMENTS

7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is ORR assessed by independent central imaging facility review based on RECIST version 1.1. Refer to Section 17.3 for details regarding RECIST for radiological tumor assessments.

7.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include duration of response, best percent change in the SLD of measurable tumors, DCR, clinical benefit ratio (CBR), PFS, OS, and ORR assessed by the investigator based on RECIST version 1.1.

7.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include duration of stable disease, time to response, evaluation of exposure-response relationships for efficacy and safety endpoints, and potential biomarkers of response, such as serum HER2ECD concentrations.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK)

Blood samples for DS-8201a PK analyses will be obtained at the time points specified in the Schedule of Events (Table 6.1 and Table 6.2) and in Table 8.1 and Table 8.2 below.

Table 8.1: Blood Sampling for PK Analysis – Part 1 PK Stage

Cycle	Day	Sampling Time Point (Acceptable Ranges)
Cycle 1	Day 1	BI (– 8 hours) EOI: Within 15 minutes after EOI 2 hours after the start of drug administration (± 15 minutes) 4 hours after the start of drug administration (± 15 minutes) 7 hours after the start of drug administration (± 15 minutes)
	Day 2	24 hours after the start of drug administration (± 2 hours)
	Day 4	72 hours after the start of drug administration (± 2 hours)
	Day 8	7 days after the start of drug administration (± 1 day)
	Day 15	14 days after the start of drug administration (± 1 day)
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of drug administration (± 2 days)
Cycle 2	Day 1	BI (– 8 hours) If blood sample is collected on Day 22 of Cycle 1, the blood sample will be collected at BI on Day 1 of Cycle 2. EOI: Within 15 minutes after EOI
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample on 21 days after the start of drug administration (± 2 days)
Cycle 3	Day 1	BI (– 8 hours) If blood sample is collected on Day 22 of Cycle 2, the blood sample will be collected at BI on Day 1 of Cycle 3. EOI: Within 15 minutes after EOI 4 hours after the start of drug administration (± 15 minutes) 7 hours after the start of drug administration (± 15 minutes)
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample on 21 days after the start of drug administration (± 2 days)

Cycle	Day	Sampling Time Point (Acceptable Ranges)
Cycle 4, 6, 8	Day 1	BI (– 8 hours) If blood sample is collected on Day 22 of Cycle 3, the blood sample will be collected at BI on Day 1 of Cycle 4. EOI: Within 15 minutes after EOI

BI = before infusion; EOI = end of infusion.

Table 8.2: Blood Sampling for PK Analysis – Part 1 Dose Finding and Part 2

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	BI (– 8 hours) EOI: Within 15 minutes after EOI 4 hours after the start of drug administration (± 15 minutes) 7 hours after the start of drug administration (± 15 minutes)
	Day 8	7 days after the start of drug administration (± 1 day)
	Day 15	14 days after the start of drug administration (± 1 day)
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of drug administration (± 2 days)
Cycle 2	Day 1	BI (– 8 hours) If blood sample is collected on Day 22 of Cycle 1, the blood sample will be collected at BI on Day 1 of Cycle 2. EOI: Within 15 minutes after EOI
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample on 21 days after the start of drug administration (± 2 days)
Cycle 3	Day 1	BI (– 8 hours) If blood sample is collected on Day 22 of Cycle 2, the blood sample will be collected at BI on Day 1 of Cycle 3. EOI: Within 15 minutes after EOI 4 hours after the start of drug administration (± 15 minutes) 7 hours after the start of drug administration (± 15 minutes)
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample on 21 days after the start of drug administration (± 2 days)

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 4, 6, 8	Day 1	BI (– 8 hours) If blood sample is collected on Day 22 of Cycle 3, the blood sample will be collected at BI on Day 1 of Cycle 4. EOI: Within 15 minutes after EOI

BI = before infusion; EOI = end of infusion.

At each time point, blood will be collected for DS-8201a analysis. The actual time of study drug administration and the exact time of blood sampling for DS-8201a PK analysis must be recorded on the electronic case report form (eCRF).

Instructions for the handling of blood samples and shipping of serum samples for DS-8201a PK analyses are included in a separate document (ie, Laboratory Manual). The DS-8201a PK samples will be shipped to a central laboratory for forwarding to a Sponsor designated bioanalytical laboratory.

Serum concentrations of DS-8201a, total anti-HER2 antibody and MAAA-1181a will be measured using validated assays at the bioanalytical laboratory.

The serum PK parameters (listed in Section 2.3.2) for DS-8201a, total anti-HER2 antibody and MAAA-1181a for each subject will be estimated using standard noncompartmental method.

8.2. Pharmacodynamic

Not Applicable.

8.3. Immunogenicity (Anti-Drug Antibodies, ADA)

Blood samples for ADA analyses will be collected at the time points specified in Table 6.1 and Table 6.2. A blood sample will be drawn at each time point. Serum concentrations of DS-8201a and/or total anti-HER2 antibody may be measured using the same ADA samples for purpose of ADA assessment.

Instructions for the handling and shipping of ADA serum samples are included in a separate document (ie, Laboratory Manual). The ADA samples will be shipped to a central laboratory for forwarding to a Sponsor designated bioanalytical laboratory.

The immunogenicity testing will be performed using validated ADA assay following tiered assay steps including screening, confirmatory as well as titer determination. Samples confirmed positive will be banked until availability of the neutralizing anti-drug antibody (NAB) assay.

8.4. Pharmacogenomic Analysis

8.4.1. Tumor Sampling

In addition to the tumor sample required for confirmation of HER2 status, additional slides (up to 5) for exploratory biomarker analysis are requested (if the subject signs the additional optional informed consent form for Pharmacogenomics analysis). The detailed instructions for the handling of tumor samples and shipping of tumor samples are included in the Laboratory Manual.

8.4.2. Genomic or Genetic Banking and Analysis

A single blood sample for pharmacogenomics analysis will be collected from each subject, who consented to this test, before drug administration on Day 1 of Cycle 1. Participation in this part of the study is optional for all subjects.

The following procedures will be used for the long-term preservation (banking) of DNA specimens extracted from subjects' blood samples. Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of DS-8201a. Additionally, samples may be analyzed for genes involved in DS-8201a related signaling pathways, or to examine diseases or physiologic processes related to DS-8201a DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Specimen shipping and handling details will be included in the Laboratory Manual.

8.4.2.1. Disclosure of the Results of Genomic or Genetic Analysis

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

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

Samples will be retained until exhausted or until the Sponsor requests disposition.

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

8.5. Biomarker and Exploratory Variables

Exploratory biomarkers such as HER2EDC in serum may be measured by a central laboratory. Other exploratory biomarkers in tumor tissue or blood such as cfDNA in plasma may be measured.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.4.1 for definitions) occurring after the subject signs the ICF and up to 40 (+ 7) days after last treatment (ie, the follow-up period), whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event CRF page. All SAEs occurring after subject signs the ICF and up to 40 (+ 7) days after last treatment will be recorded on CRF. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history.

All AEs, SAEs, and events of special interest are to be reported according to the procedures in Section 9.5.

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

At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The investigator's assessment must be clearly documented in the site's source documentation with the investigator's signature.

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

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and consequently, should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, "disease progression" should be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to study drug should also be reported and managed as an SAE.

9.2. Safety Endpoint Event(s)

Safety parameters will include SAEs, TEAEs, Echo/MUGA findings; ophthalmologic findings, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters (central lab) (blood chemistry, coagulation, and hematology), anti-drug antibodies (ADA), and ECG parameters. Adverse events will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and abnormal laboratory test results, if applicable, will be graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

9.3. Adverse Events of Special Interest

Information regarding the AESIs, except infusion-related reactions, specified below for the DS-8201a clinical program will be collected through the targeted questionnaires, in-built within the eCRF in the study clinical database.

9.3.1. Interstitial Lung Disease/Pneumonitis

9.3.1.1. Clinical Summary

As of 13 Dec 2017, 3 clinical studies have subjects dosed with DS-8201a: DS8201-A-J101, DS8201-A-U201, and DS8201-A-J202. There have been no events of ILD/pneumonitis reported in the DS8201-A-U201 and DS8201-A-J202 studies. Due to the limited number of subjects dosed and short treatment duration in these 2 studies, ILD/pneumonitis data has been summarized from the DS8201-A-J101 study.

Interstitial lung disease/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the DS8201-A-J101 clinical study as well as the results of potential ILD/pneumonitis cases reviewed by the independent ILD AC, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.

9.3.1.2. Management Guidance

Interstitial lung disease/pneumonitis should be ruled out if a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the designated “Other Non-Laboratory Adverse Events” dose modification section of the study protocol (Section 5.4).

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high resolution CT, pulmonologist consultation, pulmonary function tests and SpO2, arterial blood gases if clinically indicated, and one blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (Kubo K, et al 2013 for guidance[22]).

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated “Pulmonary Toxicity” dose modification section of the study protocol (Section 5.4).

All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

9.3.1.3. Interstitial Lung Disease Adjudication Committee

An independent ILD Adjudication Committee for the DS-8201a program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data collections will cover a more in-depth relevant medical history (eg smoking, radiation, chronic obstructive pulmonary disease and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for adverse events reported using MedDRA preferred terms (PTs) from the current ILD Standardised MedDRA Query (SMQ).

9.3.2. Cardiotoxicity (Cardiac Related Events including QT Prolongation and LVEF Decrease)

9.3.2.1. Clinical Summary

Cardiotoxicity in association with DS-8201a is considered to be an important potential risk based on the available pre-clinical data, literature and available safety information for drugs of similar class.

9.3.2.2. Management Guidance

LVEF will be measured by either Echo or MUGA scan. All Echos/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function. Troponin will be measured at screening and after each infusion and as needed based on subject reported cardiac symptoms. Triplicate ECGs will be performed and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter will be recorded in the eCRF.

9.3.3. Infusion-related Reactions

9.3.3.1. Clinical Summary

As with any therapeutic antibodies, there is a possibility of infusion-related reactions and immune responses causing allergic or anaphylactic reactions following the administration of DS-8201a. Immune responses causing allergic or anaphylactic reactions are considered to be an AESI for the DS-8201a clinical program. Refer to the current IB for a summary of preliminary clinical trial data.

9.3.3.2. Management Guidance

Subjects receiving DS-8201a should be monitored by means of vital signs, physical examination, and signs and symptoms of infusion-related reaction: fever, chills, nausea, vomiting, headache, cough, dizziness, rash, and/or lower back pain usually of mild to moderate severity and may lead to shortness of breath and severe lowering of blood pressure.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

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

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

9.4.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

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

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

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

Note:

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

9.4.3. Severity Assessment

All AEs will be graded (1 to 5; see below) according to the latest NCI-CTCAE version 4.03:

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

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness of an event is based upon a universal and global Regulatory definition for reporting SAEs to regulatory agencies. For example, Grade 4 (life threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the investigator as Grade 1 or 2, but if the subject presents to the emergency facility for evaluation and is hospitalized overnight for observation that immediately makes the event serious based upon hospitalization without regard to the investigator assessment of severity.

9.4.4. Causality Assessment

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

- Related:

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

or

  The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

- Not Related:

  The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.

- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.
- Drug Interrupted: The study drug was temporarily stopped.

9.4.6. Other Action Taken for Event

- None.

  No treatment was required.
- Medication required.

  Prescription and/or over the counter (OTC) medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.

  Hospitalization was required or prolonged due to the AE, whether or not medication was required.
  - Other.

9.4.7. Adverse Event Outcome

- Recovered/Resolved

  The subject fully recovered from the AE with no residual effect observed.
- Recovering/Resolving

  The AE improved but has not fully resolved.
- Not Recovered/Not Resolved

  The AE itself is still present and observable.
- Recovered/Resolved with Sequelae

  The residual effects of the AE are still present and observable.

  Include sequelae/residual effects.
- Fatal

  Fatal should be used when death is a direct outcome of the AE.

9.5. Serious Adverse Events and Adverse Events of Special Interest Reporting–Procedure for Investigators

All AEs, AESIs, SAEs and medication errors including overdose, will be reported in the eCRF.

Additional relevant information regarding the AESIs ILD/pneumonitis and cardiotoxicity (cardiac-related events including QT prolongation and LVEF) for the DS-8201a clinical program regardless of seriousness is to be collected through the targeted questionnaires built within the applicable eCRFs in the clinical study database.

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

clinically anticipated events in the target treatment population, and will be periodically reviewed by the Daiichi Sankyo safety teams to ensure prompt identification of any clinically concerning safety issues.

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

- SAEs (see Section 9.4.2 for definition)
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥3 × ULN and an elevated TBL ≥2 × ULN that may occur at different time points during the study conduct. A targeted questionnaire is in-built as an eCRF to collect relevant additional information for these potential cases.

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

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up. In the event that eCRF is unavailable, report SAEs by faxing the paper Serious Adverse Event Report (SAVER) Form to CRO using the provided fax cover sheet and the appropriate fax number provided for your country. Once eCRF becomes available, please enter SAEs reported on the SAVER Form into eCRF as soon as possible. Please refer to eCRF Completion Guide for additional instructions.

See Section 15.10 for contact information for SAE reporting. Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

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

Daiichi Sankyo and/or CRO will inform investigators IRBs/ECs, and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study centers or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the investigator's responsibility to inform the IRB/EC per Sponsor's instruction.

In the European Economic Area states, it is the Sponsor's responsibility to report SUSARs to all ECs.

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject or their female partner who becomes pregnant while receiving or within 4.5 months of discontinuing the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a female subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

1. Hematology tests
   - Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
2. Blood chemistry tests
   - Total protein, albumin, alkaline phosphatase (ALP), ALT, AST, total bilirubin, blood urea nitrogen (BUN)/urea, calcium, chloride, serum creatinine, lactate dehydrogenase (LDH), potassium, sodium, and magnesium)
   - A coagulation test (prothrombin time and activated partial thromboplastin time) will be performed at screening and thereafter as needed,
   - Creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation (Section 17.1).
3. Urinalysis
   - Protein, glucose, blood, microscopy assessment (if indicated), and specific gravity.

In addition, the following parameters will be analyzed at the visits indicated in the Schedule of Events, Table 6.1 and Table 6.2.

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

All laboratory values must be appraised by the investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered clinically significant by the investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, a SAVER form should be submitted and other

relevant procedures must be followed (see Section 9.5). Abnormal laboratory values (NCI-CTCAE grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Additionally, SpO2 will be measured at Screening, before administration on Day 1 of each cycle, EOT and F/U.

9.10. Electrocardiograms

Standard supine/semi-recumbent 12-lead ECGs in triplicate (taken in close succession, approximately 3 minutes apart) will be performed as described in the Schedule of Events. Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnormalities.

9.11. Physical Examinations

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

9.12. Other Examinations

ECOG PS

Cardiac Assessments

- Either Echo or MUGA will be performed as described in the Schedule of Events (Table 6.1 and Table 6.2). LVEF will be measured.

Ophthalmic Assessments

- Will include visual acuity testing, slit lamp examination and fundoscopy.

Pulmonary Assessments

- Will include CT or MRI of the chest, SpO2 and will be performed as described in schedule of events. For more details please refer to Section 6 of the protocol.
- An ILD AC will review all cases of (potential) ILD on an ongoing basis. Description of the ILD AC is available in Section 9.3.1.3.

10. OTHER ASSESSMENTS

Not applicable

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Full Analysis Set/Safety Analysis Set

The Full Analysis Set (FAS)/Safety Analysis Set will include all subjects enrolled in Part 1 or Part 2 who received at least one dose of study drug.

11.1.2. Response Evaluable Set

The Response Evaluable Set will include all subjects enrolled in Part 1 or Part 2 who received at least one dose of study drug and had measurable tumors assessed by independent central imaging facility review at baseline.

11.1.3. Per Protocol Set

Not Applicable.

11.1.4. Pharmacokinetic Set

The PK Analysis Set will include all subjects enrolled in Part 1 or Part 2 who received at least one dose of study drug and had measurable serum concentrations of DS-8201a.

11.2. General Statistical Considerations

A data cut-off date for the primary analysis will be identified during Part 2.

Data in Part 1 and Part 2a will be combined by the starting dose level. Summary statistics will be presented by part/dose group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency counts and percentages.

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

Analyses of ORR, DCR, and CBR will be performed on the Response Evaluable Set. The other efficacy analyses will be performed on the Full Analysis Set (FAS). Safety analyses will be performed using the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set. All other exploratory analyses will be performed based on the FAS and availability of assessment.

11.3. Study Population Data

Subject disposition will be summarized for the enrolled subjects in each part/dose group. The total number of subjects for each defined analysis set will also be tabulated for each part/dose group. The demographic and baseline characteristics will be summarized descriptively for the

FAS/Safety Analysis Set and Response Evaluable Set. Study drug exposure, treatment duration, and compliance with study therapy as well as prior and concomitant medications will be summarized using descriptive statistics for the Safety Analysis Set.

11.4. Statistical Analysis

11.4.1. Efficacy Analyses

The convention to be followed when assessing response or progression will be to assign a single date to evaluations performed within that time point. The date of response (CR, PR, SD, or NE) will be recorded as the date of the last radiographic evaluation included in the series for that assessment. The date of progression (PD) will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

11.4.1.1. Primary Efficacy Analysis

The primary endpoint is ORR (the proportion of subjects who achieved a best overall response of CR or partial response [PR]). Tumor responses will be assessed by an independent central imaging facility based on RECIST version 1.1. The primary efficacy analysis will be performed for all subjects who initially received the RP2D of DS-8201a in Part 1 and Part 2a of the Response Evaluable Set. Confirmation of CR/PR is required for this study.

The estimate of ORR and its two-sided 95% exact confidence intervals (CI) will be provided. In addition, ORR until fixed time points (eg, 3, 6, 9, 12 months) along with their 2-sided 95% exact CIs will be provided.

11.4.1.2. Secondary Efficacy Analyses

11.4.1.2.1. Analyses of ORR in the Other Dose Levels of Part 1 and Part 2b

The same analyses as described in the primary efficacy analyses (Section 11.4.1.1) will be performed by dose group for subjects from Part 1 and for Part 2b as part of the Response Evaluable Set.

11.4.1.2.2. Other Secondary Efficacy Analyses

The secondary efficacy endpoints include duration of response, best percent change in the SLD of measurable tumors, DCR, (the proportion of subjects who achieved a best overall response of CR or PR or stable disease [SD]), CBR (the proportion of subjects who achieved a best overall response of CR or PR or more than 6 months SD), PFS, OS, and ORR assessed by the investigator based on RECIST version 1.1.

Duration of response is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of PD or death due to any cause. Duration of response will be measured for responding subjects (CR or PR) only. Detailed censoring rules for duration of response will be specified in the statistical analysis plan (SAP).

PFS is defined as the time from the date of randomization/registration to the earlier of the dates of the first objective documentation of radiographic PD via independent radiologic facility review based on RECIST version 1.1 or death due to any cause. Detailed censoring rules for PFS will be specified in the SAP.

OS is defined as the time from the date of randomization/registration to the date of death for any cause. If there is no death reported for a subject before the data cut-off for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive.

Duration of response, PFS, and OS will be summarized with median event times and their 2-sided 95% CI for the median using Brookmeyer and Crowley methods for each part/dose group.

Descriptive statistics for the best (minimum) percent change from baseline in the SLD will be provided by part/dose group.

DCR, CBR, ORR assessed by the investigator based on RECIST version 1.1 will be analyzed for each part/dose group in the same manner as the primary ORR analysis.

11.4.1.3. Exploratory Efficacy Analyses

The exploratory efficacy analyses include subgroup analyses of the primary and secondary endpoints and analyses of exploratory efficacy endpoints. Any additional analysis plans will be specified in the SAP.

11.4.1.3.1. Subgroup Analyses

The subgroup analyses for ORR, duration of response, DCR, CBR, PFS, and OS will be performed. Subgroup analyses will include:

- ERs (positive, negative).
- Progesterone receptors (positive, negative).
- Lines of prior systemic therapy not including hormone therapy (<3, ≥3).
- Prior pertuzumab (yes, no)
- Prior pertuzumab in 1st or 2nd line in advanced/metastatic breast cancer (yes, no)
- Renal impairment at baseline (within normal range, mild/moderate impairment)
- Hepatic impairment at baseline (within normal range, mild-moderate impairment)
- Best response to T-DM1 therapy (CR/PR/SD, PD).
- Brain metastases (brain metastases, no brain metastases)
- Age (<65, ≥ 65 years).
- Race (Asian, others).
- Region (Asia, rest of world).
- Ethnicity (Hispanic/Latino, others).
- ECOG PS (0, 1).

The subgroups are based on baseline values (ie, the last non-missing values before the first drug administration). In each subgroup defined above, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint. These results will be considered exploratory because of smaller sample sizes that cannot be pre-specified.

11.4.1.3.2. Analyses of Exploratory Efficacy Endpoints

Duration of stable disease, time to response, exposure-response relationships for efficacy and safety endpoints, and potential biomarkers of response, such as serum HER2ECD concentrations, will be evaluated and considered as exploratory efficacy endpoints.

Duration of stable disease and time to response will be summarized with median event times and their 2-sided 95% CI for the median by part/dose group using Brookmeyer and Crowley methods.

11.4.2. Pharmacokinetic/Pharmacodynamic Analyses

11.4.2.1. Pharmacokinetic Analyses

Serum concentrations for DS-8201a, total anti-HER2 antibody and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics by Part (and Stage)/dose level/study day at each time point. PK parameters will be listed and summarized using descriptive statistics by Part (and Stage)/dose level. A dose selection analysis will also be conducted based on the data from Part 1, and based on comparative PK results, 2 doses will be selected for dose-finding stage of Part 1.

The population pharmacokinetic and exposure-response analysis will be conducted for all evaluable subjects in the study. An interim population PK and exposure response analysis may also be conducted based on the data from Part 1. Modeling results will be presented in separate reports.

11.4.2.2. Pharmacodynamic Analyses

Not Applicable.

11.4.2.3. Biomarker Analyses

Biomarkers will be listed and summarized using descriptive statistics.

11.4.2.4. Pharmacogenomic Analyses

Not Applicable.

11.4.3. Safety Analyses

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. A summary and display of TEAEs will be performed.

Terminology of the MedDRA will be used to assign system organ class (SOC) and PT classification to AEs and diseases, based on the original terms entered on the eCRF.

The incidence of TEAEs will be summarized by SOC, PT, relationship to the study treatment, and severity for each part/dose group. A by-subject listing will be provided for those subjects who experience an SAE, including death, or experience an AE associated with early withdrawal from the study or study treatment.

11.4.3.1. Adverse Event Analyses

TEAEs are AEs that occur, having been absent before the first dose of study treatment, or have worsened in severity after the initiating the study treatment. TEAEs will be coded using MedDRA and assigned grades based on version 4.03 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE). The number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC), and PT, relationship to the study treatment, and the worst CTCAE grade. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study treatments.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, SOC, PT, CTCAE grade, and relationship to study treatment will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study treatments, will be listed.

11.4.3.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the central clinical laboratory results by scheduled time of evaluation, as well as for the change from baseline. In addition, the change from baseline will be summarized for the maximum and minimum post-treatment values.

Abnormal clinical laboratory results will be graded according to NCI CTCAE version 4.03, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests.

All clinical laboratory test results and abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

11.4.3.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation, as well as for the change from baseline. In addition, the change from baseline will be presented for the maximum and minimum post-treatment values. All vital sign data will be also listed.

11.4.3.4. Electrocardiogram Analyses

Descriptive statistics will be provided for ECG parameters and changes from baseline by scheduled time of evaluation, including the maximum post-treatment values and the values at the EOT Visit. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc $\leq$ 450 ms, > 450 to $\leq$ 480 ms, > 480 ms to $\leq$ 500 ms, and > 500 ms). The QT intervals will be corrected for heart rate by **Fridericia's formula (QTcF $QT/[RR]^{1/3}$)**. ECG data will also be listed.

11.4.3.5. Physical Examination Analyses

Physical examination findings will be listed.

11.4.3.6. Concomitant Medication Analyses

Concomitant medications will be coded using the World Health Organization drug dictionary (most recent version). Number and percentage of subjects taking concomitant medications will be summarized. Concomitant medications will also be listed.

11.4.3.7. Exploratory Safety Analyses

Not applicable.

11.4.3.8. Immunogenicity (Anti-Drug Antibody, ADA) Analyses

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

11.4.3.9. Other Safety Analyses

All other safety variables per Section 9.12 will be listed.

11.4.4. Other Analysis

11.5. Dose Selection Analysis

In the PK Stage, DS-8201a of FL-DP2 material will be administered at 5.4, 6.4 or 7.4 mg/kg to approximately 20 subjects/dose on Day 1 of a 21 day cycle. Serial PK samples will be collected over 21 days in Cycle 1 following each dose administration. Two doses, with PK profiles (eg, Cmax, AUC) matching those from the administration of 5.4 and 6.4 mg/kg of FL-DP1 material in study DS8201-A-J101, will be selected for further evaluation in the Dose Finding Stage. The two dose levels will be selected based on the PK results.

The next dose selection analysis will be conducted during the dose finding stage. The purpose of the analysis is to determine one optimal dose level for Part 2. The optimal dose level will be decided based on overall assessment of efficacy and safety data. The following criteria will be included as part of the information used for dose selection. Additional factors such as depth of response, duration of response, and chronic toxicity will also be included.

- The high dose level will be considered efficacious compared with the low dose level if the posterior probability given the observed ORR data suggest that: Pr (ORR_{high} ORR_{low} > 5% | data) > 80%.
- The high dose level will be considered toxic compared with the low dose level if the posterior probability given the observed percent change from baseline in neutrophil count (PCNC) data suggest that: Pr ($PCNC_{high}$ $PCNC_{low}$ < 10% | data) > 80%.

11.5.1. Data Monitoring Committee

A Data Monitoring Committee is not applicable for this trial given that it is an open label trial. However, measures are put in place for monitoring the safety of the subjects participating in the

study. Individual subject data will be reviewed on an ongoing basis and aggregate safety data will be monitored monthly by the study team across the duration of the trial following the Sponsor's established safety monitoring SOPs. The data review and analysis will be based on the available investigator reported data in the clinical database.

11.6. Sample Size Determination

The sample size of approximately 230 subjects was chosen to further confirm the safety profile and secure adequate accuracy to determine ORR of DS-8201a. A sample size of 150 subjects (50 subjects from Part 1 who receive the optimal dose level and 100 subjects from Part 2a) provides ORR with 95% CI within plus or minus 10% of the ORR. The probabilities of observing the lower bound of the 95% CI > 20% and ORR ≥ 30% are 98.2% and 91.6% under the expected ORR 35%, respectively. The probability values for the sample size are derived based on binomial distribution using SAS® version 9.3 or higher.

11.7. Statistical Analysis Process

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

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

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

12. DATA INTEGRITY AND QUALITY ASSURANCE

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

12.1. Monitoring and Inspections

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

The monitor is responsible for visiting sites at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

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

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

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories, etc.) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.2. Data Collection

All relevant observations and data related to the study, as per the study protocol, will be recorded on eCRF pages. A representative of Daiichi Sankyo or their designee will provide instruction for completing the eCRF. Adequate and accurate case records should be maintained, including the evaluation of inclusion and exclusion criteria, medical history, physical examinations, clinical assessments, a record of clinical safety laboratory sample collection drug administration, AEs, and final evaluation

The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. The information should be entered into the eCRF within 5 days of the visit and should be completed, reviewed, and signed off by the investigator within 2 weeks of the last subject visit. Query resolution should be completed within 48 hours.

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedures. For subjects who are screened but not randomized, minimal data will be recorded on the eCRF, including demography, subject status, and AEs. All study related data for these subjects will be maintained in the medical records at the site.

The investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.3. Data Management

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

To ensure the quality of clinical data across all subjects and study centers, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor or Designee. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

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

Serious Adverse Events in the clinical database will be reconciled with the safety database.

All Adverse Events will be coded using MedDRA.

All concomitant medications and prior cancer therapies will be coded using the World Health Organization Drug Reference List Dictionary and MedDRA.

12.4. Study Documentation and Storage

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

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

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

All essential documentation will be retained by the institution for at least 5 years after completion of the study or for a longer period, where so required by other applicable regulations or requirements. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

12.5. Record Keeping

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

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

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

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until 1 year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that Daiichi Sankyo has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the advice of company patent council and in accord with needs for subject protection.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Subject Confidentiality

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

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

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

15.2. Informed Consent

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

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the EC or IRB prior to being provided to potential subjects.

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

15.3. Regulatory Compliance

The study protocol, subject information and consent form, the IB, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to

the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

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

The investigator and/or Sponsor must submit and, where necessary, obtain approval from the EC or IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the EC or IRB of deviations from the protocol or SAEs occurring at the study center and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after approval by the relevant regulatory bodies.

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

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

15.4. Compliance Statement, Ethics and Regulatory Compliance

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

- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March, 1997 and/or;
- Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal product for human use;
- Other applicable local regulations.

15.5. Protocol Deviations

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

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

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

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

- If applicable, the investigator should notify the IRB/EC of deviations from the protocol in accordance with local procedures.

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

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

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

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

15.7. Protocol Amendments

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

A global protocol amendment will affect study conduct at all study centers in all regions of the world. Such amendments will be incorporated into a revised protocol document. Changes made by such amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A local protocol amendment will affect study conduct at a particular study center(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

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

15.8. Study Termination

The Sponsor has the right to terminate the study at any time and study termination may also be requested by (a) competent authority(ies).

15.9. Data and Safety Monitoring Board

Not applicable

15.10. Address List

See the site Study Manual for all appropriate addresses.

16. REFERENCES

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17. APPENDICES

17.1. Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the modified Cockcroft-Gault equation based on actual weight, where weight is lean body mass in kilograms (1 kilogram 2.2 pounds):

Conventional – serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) – serum creatinine in µmol/L:

Male:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} \quad \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in } \mu\text{mol/L)} \times 72 \times 0.0113} \times 0.85$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

17.2. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

Table 17.1: Eastern Cooperative Oncology Group Performance Status Scale

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

17.3. Response Evaluation Criteria in Solid Tumors, Version 1.1

17.3.1. Measurability of Tumor at Baseline

17.3.1.1. Definitions

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

17.3.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

  10 mm by CT scan (CT scan slice thickness no greater than 5 mm)

  10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

  20 mm by chest X-ray

- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline (ie, screening for this study) and in follow-up (ie, all measurements past screening for this study), only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

17.3.1.1.2. Non-Measurable

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

17.3.1.1.3. Special Considerations Regarding Lesion Measurability

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

17.3.1.1.3.1. Bone Lesions

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

or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

17.3.1.1.3.2. Cystic Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

17.3.1.1.3.3. Lesions with Prior Local Treatment

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

17.3.1.2. Specifications by Methods of Measurements

17.3.1.2.1. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 28 days before randomization/registration.

17.3.1.2.2. Method of Assessment

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

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

17.3.2. Tumor Response Evaluation

17.3.2.1. Assessment of Overall Tumor Burden and Measurable Disease

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

In this study, only subjects with measurable disease at baseline should be included.

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

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

17.3.2.3. Response Criteria

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

17.3.2.3.1. Evaluation of Target Lesions

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

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

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

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

17.3.2.3.2. Special Notes on the Assessment of Target Lesions

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

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

17.3.2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they

need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

PD: Unequivocal progression (see comments below) of existing non-target lesions (Note: the appearance of 1 or more new lesions is also considered progression).

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

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

When the subject also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to 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 subject has only non-measurable disease: The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in 'volume' [which is equivalent to a 20% increase diameter in a measurable lesion]). If 'unequivocal progression' is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

17.3.2.3.5. New Lesions

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

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is

the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

17.3.2.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the EOT. Confirmatory measurement for CR, PR, or SD is required in the study.

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

17.3.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.2 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, see Table 17.2.

Table 17.2: Overall Response: Subjects with Target (+/–Non-target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = in-evaluable.

17.3.2.4.2. Missing Assessments and Inevaluable Designation

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

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

17.3.2.4.3. Best Overall Response: All Time Points

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

Best response determination in this study requires confirmation of CR or PR: Best response is defined as the lesser of the two best responses across 2 consecutive scans (eg, a subject who has PR at first assessment, SD at second assessment, and PD on last assessment; this would report as a best overall response of SD). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, 6 weeks (± 7 days). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

17.3.2.4.4. Special Notes on Response Assessment

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

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

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

The convention to be followed when assessing response or progression will be to assign a single date to evaluations performed within that time point. The date of response (CR, PR, SD, or NE) will be recorded as the date of the last radiographic evaluation included in the series for that assessment. The date of progression (PD) will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

17.3.2.5. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted every 6 weeks (± 7 days) while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to follow-up. Scan dates should not be adjusted or rescheduled due to dose interruption of any type.

Baseline tumor assessments must be performed within 28 days of randomization/registration.

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

The radiographic evaluation must include CT or MRI scanning of chest, abdomen, and pelvis at screening period. An MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Any additional suspected sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. Follow-up evaluations should include all sites of disease identified at screening and any other locations if progressive disease is suspected (eg, MRI of the brain if brain metastases are suspected) should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

17.4. New York Heart Association Functional Classification

Table 17.3: New York Heart Association Functional Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class 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.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: American Heart Association, Inc. Classification of Functional Capacity and Objective Assessment. Available from: http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

17.5. Strong CYP3A4 and OATP1B Inhibitors

CYP3A4 strong inhibitors	boceprevir clarithromycin conivaptan indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole
OATP1B inhibitors	atazanavir cyclosporine eltrombopag gemfibrozil lopinavir rifampin (single-dose) ritonavir saquinavir tipranavir