CLINICAL STUDY PROTOCOL

PHASE 1, MULTICENTER, OPEN-LABEL, MULTIPLE-DOSE STUDY OF DS-8201A TO ASSESS THE EFFECT ON THE QT INTERVAL AND PHARMACOKINETICS IN SUBJECTS WITH HER2-EXPRESSING METASTATIC AND/OR UNRESECTABLE BREAST CANCER

DS8201-A-J102

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DAIICHI SANKYO

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INVESTIGATOR AGREEMENT

PHASE 1, MULTICENTER, OPEN-LABEL, MULTIPLE-DOSE STUDY OF DS-8201A TO ASSESS THE EFFECT ON THE QT INTERVAL AND PHARMACOKINETICS IN SUBJECTS WITH HER2-EXPRESSING METASTATIC AND/OR UNRESECTABLE BREAST CANCER

Sponsor Approval:

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

PPD

Print Name	**Signature**
Clinical Study Leader	
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

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

PROTOCOL SYNOPSIS

EudraCT:	Not applicable
IND Number:	127553
Protocol Number:	DS8201-A-J102
Investigational Product:	DS-8201a
Active Ingredient(s)/INN:	Trastuzumab deruxtecan
Study Title:	Phase 1, multicenter, open-label, multiple-dose study of DS-8201a to assess the effect on the QT Interval and pharmacokinetics in subjects with HER2-expressing metastatic and/or unresectable breast cancer.
Study Phase:	Phase 1
Indication Under Investigation:	DS-8201a will be assessed in subjects with human epidermal growth factor receptor 2 (HER2)-expressing metastatic and/or unresectable breast cancer.
Study Objectives:	<u>Primary Objectives</u> · To assess the effect of DS-8201a on the corrected QT interval (QTc interval) · To assess pharmacokinetics (PK) after multiple dosing of DS-8201a <u>Key Secondary Objectives</u> · To assess the safety of DS-8201a · To assess the serum concentrations of DS-8201a at the time of electrocardiogram (ECG) measurement <u>Other Secondary Objectives</u> · To evaluate the efficacy of DS-8201a
Study Design:	This is a Phase 1, multicenter, open-label, multiple dose study of DS-8201a designed to assess the effect on the QTc interval and pharmacokinetics after multiple dosing in subjects with HER2-expressing metastatic and/or unresectable breast cancer.

	The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or completed at least 3 cycles, whichever comes first. After the primary analysis, the main study will be closed and transition to the extension period.
Study Duration:	Enrollment is planned to occur over approximately 7 months, with the data cutoff for the primary analysis projected to be completed within approximately 3 months thereafter. Subjects experiencing clinical benefit will continue to receive study treatment in the extension period of the study. The follow-up (F/U) for post treatment subjects will also continue at the sponsor's discretion to collect more data. Thus, the anticipated duration of the study is 2 years and 6 months. The screening period is up to 28 days. Each cycle of treatment will be 21 days. The number of treatment cycles with DS-8201a is not fixed.
Study Sites and Location:	This study is planned to be conducted at approximately seven study sites in Japan.
Subject Eligibility Criteria:	<u>Key inclusion criteria</u> · Man or Woman ≥ 20 years old. · Has a pathologically documented unresectable or metastatic breast cancer with HER2 expression (immunohistochemistry [IHC] 3+, IHC 2+, IHC 1+ and/or in situ hybridization [ISH]* +) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. *ISH: fluorescent in situ hybridization (FISH) or dual in situ hybridization (DISH) · Left ventricular ejection fraction (LVEF) ≥ 50%. <u>Key exclusion criteria</u> · Has a medical history of myocardial infarction within 6 months before enrollment. · Has a medical history of ventricular arrhythmias, other than rare, occasional premature ventricular contractions. · Has uncontrolled or significant cardiovascular disease, including: - Symptomatic congestive heart failure (New York Heart Association [NYHA] class II-IV, Section 17.4).

	- Troponin levels consistent with myocardial infarction as defined according to manufacturer. - Unstable angina or serious cardiac arrhythmia requiring treatment. - Clinically significant bradycardia. - Uncontrolled hypertension. - Corrected QT interval by Fridericia's formula (QTcF interval) prolongation to > 450 ms, heart rate of > 100 beats per minute or heart rate of < 50 beats per minute based on average of the screening triplicate 12-lead ECG. - Any abnormal ECG findings identified by central assessment. - Atrial fibrillation or flutter. - National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03 grade ≥2 atrioventricular block, left bundle branch block or prolonged QRS. - Pulmonary embolism or deep vein thrombosis. · Has an implantable pacemaker or automatic implantable cardioverter defibrillator or cardiac resynchronization therapy device. · Has a congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death. · Has received ≥ 500 mg/m^2 of cumulative anthracyclines as doxorubicin-equivalent dose. · 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.
Dosage Form, Dose and Route of Administration:	DS-8201a will be administered as a sterile intravenous (IV) injection solution at 6.4 mg/kg once every 3 weeks.
Study Endpoints:	<u>Primary Endpoints</u> · Baseline-adjusted QTcF interval · Serum concentration and PK parameters of DS-8201a, total anti-HER2 antibody and MAAA-1181a <u>Key Secondary Endpoints</u>

	• Serious adverse events (SAEs) • Treatment emergent adverse events (TEAEs) • Physical examination findings (including Eastern Cooperative Oncology Group performance status [ECOG PS]) • Vital sign measurements • Standard clinical laboratory parameters • 12-lead ECG parameters such as RR, PR and QRS duration • Echocardiogram (ECHO)/multiple-gated acquisition (MUGA) findings • Ophthalmologic findings • Anti-drug antibody (ADA) <u>Other Secondary Endpoints</u> • Concentration-QT • Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DoR) • Duration of stable disease (SD) • Clinical benefit rate (CBR) • Time to response (TTR) • Progression-free survival (PFS) • Overall survival (OS) • Percent change in target lesion
Planned Sample Size:	A total of 50 subjects are expected to participate in this study.
Statistical Analyses:	<u>QTc prolongation analyses</u> QTc prolongation analyses will be performed for cardiac safety analysis set. The baseline QTcF interval for each subject will be subtracted from QTcF interval to create a baseline-adjusted QTcF interval for each subject at each time point. The baseline-adjusted QTcF will be averaged across subjects at each time point and a pointwise two-sided 90% confidence interval (CI) will also be calculated. <u>Pharmacokinetic Analyses</u>

PK analysis will be performed for PK analysis set. Serum concentration-time data for DS-8201a, total anti-HER2 antibody and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics at each time point.

PK parameters of DS-8201a, total anti-HER2 antibody and MAAA-1181a will be listed and summarized using descriptive statistics.

Safety Analyses

Safety endpoints will be based on AEs, physical examination findings, vital sign measurements, clinical laboratory measurements, ECG recordings, ADA, ECHO/MUGA findings, and ophthalmologic findings. AEs will be graded according to the NCI-CTCAE version 4.03.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

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

Efficacy Analyses

Efficacy endpoints will include ORR (the sum of complete response [CR] and partial response [PR] rates); DCR (the sum of CR rate, PR rate, and SD rate for a minimum of 5 weeks from the first dosing date), DoR, duration of SD, CBR, TTR, PFS, OS, and percent change in target lesion using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BI	before infusion
CBR	clinical benefit ratio
CHF	congestive heart failure
CI	confidence interval
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DISH	dual in situ hybridization
DNA	deoxyribonucleic acid
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOI	end of infusion
EOT	end of treatment
FISH	fluorescent in situ hybridization

ABBREVIATION	DEFINITION
F/U	follow-up
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
Hb	hemoglobin
HER2	human epidermal growth factor receptor 2
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 Council for Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	investigational new drug
INN	international non-proprietary name
IRB	Institutional Review Board
ISH	in situ hybridization
IV	intravenous
IVRS	interactive voice response systems
IWRS	interactive web response system
IXRS	interactive web/voice response system
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labour and Welfare
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NE	not evaluable

ABBREVIATION	DEFINITION
NRU	neutral red uptake
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival
OTC	over the counter
PD	progressive disease
PFS	Progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	Preferred Term
Q3W	once every 3 weeks
QTc interval	corrected QT interval
QTcF interval	corrected QT interval by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2, ie COVID-19
SAVER	serious adverse event report
SCR	screening
SD	stable disease
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	standard operating procedure
SpO_2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse event reaction
SD	standard deviation
TBL	total bilirubin
T-DM1	trastuzumab emtansine

ABBREVIATION	DEFINITION
TEAE	treatment emergent adverse event
TTR	time to response
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Reference

LIST OF PHARMACOKINETIC PARAMETERS

PARAMETER	DEFINITION
AUC	area under the plasma/serum concentration-time curve
AUC_{21d}	area under the plasma/serum concentration-time curve from the time of dosing to 21 day
AUCinf	area under the plasma/serum concentration-time curve up to infinity
AUClast	area under the plasma concentration-time curve up to the last quantifiable time
AUCtau	area under the plasma/serum concentration-time curve during dosing interval
CL	total body clearance
Cmax	maximum plasma/serum concentration
Ctrough	trough plasma/serum concentration
Tmax	time to reach maximum plasma/serum concentration
$t_{1/2}$	terminal elimination half-life
Vss	volume of distribution at steady state

LIST OF DEFINITIONS OF TERMS

TERM	DEFINITION
MAAA-1181a	The drug component of DS-8201a – a derivative of exatecan, a topoisomerase I inhibitor, free form
MAAL-9001	The antibody component of DS-8201a – a humanized IgG1 monoclonal antibody produced in-house with reference to the same amino acid sequence of trastuzumab

1. INTRODUCTION

1.1. Background

Human epidermal growth factor receptor 2 (HER2) is a member of the HER superfamily that initiates signal transduction via the PI3K/AKT and RAS/MAPK pathways.[1,2] 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,[3] gastric cancer,[4,5] pancreatic cancer,[6] lung cancer,[7] colorectal cancer,[8] and ovarian cancer.[9] There are also many reports demonstrating an association between expression of HER2 protein and clinical poor 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.[10]

As an antibody targeting HER2, trastuzumab has been approved in the United States for the indication of HER2 overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma,[11] in Europe for HER2 positive metastatic breast cancer and HER2 positive metastatic adenocarcinoma of the stomach or GEJ,[12] and in Japan for HER2-overexpressing breast cancer and HER2-overexpressing unresectable or advanced/recurrent gastric cancer.[13] Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate (ADC) targeting HER2 that has been approved in the United States for the indication of HER2-positive metastatic breast cancer,[14] in Europe for the indication of HER2-positive unresectable locally advanced or metastatic breast cancer,[15] and in Japan for HER2-positive unresectable or advanced breast cancer.[16]

DS-8201a is an ADC targeting HER2. DS-8201a is currently under investigation in a two-part Phase 1 study (DS8201-A-J101): Part 1 is the dose escalation study in patients with either advanced breast cancer or gastric/GEJ adenocarcinoma. Part 2 is the expansion phase and focuses on HER2-expressing breast and gastric/GEJ adenocarcinoma, as well as other HER2-expressing solid tumors.

1.1.1. Study Drug

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 immunoglobulin G1 (IgG1) monoclonal antibody having the same amino acid sequence as trastuzumab. MAAA-1181a, an exatecan derivative,[17,18,19] 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 (7 to 8) with homogeneous conjugation with MAAA-1181a.[20] 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.

1.1.1.3. Nonclinical Studies

1.1.1.3.1. Pharmacology

DS-8201a inhibits tumor growth by mainly topoisomerase I inhibition-derived DNA damage and 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 even against HER2 low-expressing tumors which are insensitive to T-DM1. DS-8201a is therefore expected to be effective against HER2 low-expressing tumors which are insensitive to T-DM1, and is also expected to be effective against T-DM1-insensitive tumors with HER2 high-expressing and HER2 low-expressing tumors for which T-DM1 has not been approved. 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 effect and higher cell membrane permeability of the conjugated toxin. The effect therefore supports the efficacy of DS-8201a against tumors with HER2 heterogeneity.

1.1.1.3.2. Safety Pharmacology

In a safety pharmacology study in monkeys treated with single intravenous (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.

1.1.1.3.3. 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 Vss was close to the plasma volume. The CL decreased as the dose increased, and the pharmacokinetics (PK) were found to be non-linear. Both DS-8201a and the total anti-HER2 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 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.

The plasma concentration time profiles following repeated administration of DS-8201a once every 3 weeks (Q3W) for 3 cycles (Q3W × 3) to humans were simulated on the basis of the PK 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.

1.1.1.3.4. 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 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 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 is 30 mg/kg.

In an intermittent IV dose toxicity study of MAAA-1181a (once weekly 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 neutral red uptake (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-1181a 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).

1.1.1.4. Clinical Study

1.1.1.4.1. Clinical Experience

The DS-8201a first-in-human study (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 patients with either advanced breast cancer or gastric/ 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, 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 patients, with tumors that were previously treated with T-DM1. Adverse events of special interest detailed in the Phase 1 study (DS8201-A-J101) 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 haemorrhage 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 the 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 (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 refer to the current IB for additional information.

1.1.1.4.2. Summary of Clinical Pharmacokinetics

As of 08 Jun 2017, preliminary PK data are available from the 24 subjects in the 0.8 mg/kg to 8.0 mg/kg cohorts in Part 1. The PK parameters of DS-8201a are shown in Table 1.1, Table 1.2 and Table 1.3. Following a single IV administration of DS-8201a at 6.4 mg/kg, peak serum concentration (Cmax) of DS-8201a was achieved with a median Tmax of 2.16 h and mean $t_{1/2}$ of 7.33 days. The Vss for DS-8201a was approximately

45 mL/kg to 70 mL/kg (approximating plasma/serum volume), suggesting that DS-8201a is primarily limited to the vascular compartment.

The total anti-HER2 antibody profile is similar to the PK profile for DS-8201a, and the PK parameters of total antibody were comparable to those of DS-8201a.

Serum MAAA-1181a concentrations gradually increased and reached peak concentrations with longer Tmax (6 h to 7 h, median Tmax) compared to those for DS-8201a. The systemic exposure (Cmax and AUCs as reported in ng/mL and ng·day/mL, respectively) to MAAA-1181a was much lower than that of DS-8201a (as reported in µg/mL and µg·day/mL, respectively), where DS-8201a exposure was >10,000-fold to that of MAAA-1181a. The elimination ($t_{1/2}$) appeared to be similar to that of DS-8201a. This reflects the intrinsic stability of the linker when DS-8201a is in circulation systemically.

Table 1.1: Pharmacokinetic Parameters of DS-8201a

	Cmax (µg/mL)	**Tmax[a] (h)**	**AUClast (µg·d/mL)**	**AUCinf (µg·d/mL)**	**$t_{1/2}$ (day)**	**CL (mL/d/kg)**	**Vss (mL/kg)**
0.8 mg/kg (N = 3)	22.9 (3.76)	1.92 (1.68, 1.92)	51.7 (13.1)	55.0 (11.9)	2.18 (0.671)	15.0 (2.89)	45.0 (8.96)
1.6 mg/kg (N = 3)	36.2 (4.98)	4.08 (1.92, 4.08)	116 (58.7)	121 (58.9)	3.07 (1.22)	16.1 (9.27)	58.3 (10.0)
3.2 mg/kg (N = 3)	78.2 (16.1)	4.08 (1.92, 6.96)	325 (142)	340 (150)	4.23 (1.24)	11.3 (6.52)	56.8 (14.4)
5.4 mg/kg (N = 6)	127 (17.2)	1.92 (1.92, 2.16)	544 (165)	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)	901 (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)

Mean (SD)
a: Tmax reported as median (min, max)

Table 1.2: Pharmacokinetic Parameters of Total Anti-HER2 Antibody

	Cmax (μg/mL)	Tmax[a] (h)	AUClast (μg•d/mL)	AUCinf (μg•d/mL)	$t_{1/2}$ (day)
0.8 mg/kg (N = 3)	19.3 (4.30)	1.68 (1.68, 1.92)	83.8 (73.4)	93.5 (82.1)	3.49 (2.51)
1.6 mg/kg (N = 3)	41.2 (12.7)	1.92 (1.68, 4.08)	200 (191)	227 (225)	4.35 (2.77)
3.2 mg/kg (N = 3)	67.5 (13.8)	4.08 (4.08, 6.96)	302 (97.8)	313 (102)	3.93 (0.863)
5.4 mg/kg (N = 6)	116 (13.9)	1.92 (1.92, 6.96)	609 (151)	682 (172)	6.78 (2.39)
6.4 mg/kg (N = 6)	146 (18.9)	3.84 (2.16, 6.96)	878 (97.1)	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)

Mean (SD)
a: Tmax reported as median (min, max)

Table 1.3: Pharmacokinetic Parameters of MAAA-1181a

	Cmax (ng/mL)	Tmax[a] (h)	AUClast (ng•d/mL)	AUCinf (ng•d/mL)	$t_{1/2}$ (day)
0.8 mg/kg (N = 3)	1.17 (0.757)	6.72 (6.72, 22.32)	4.84 (1.89)	4.89 (1.89)	2.50 (0.579)
1.6 mg/kg (N = 3)	1.72 (0.193)	6.96 (6.72, 24.00)	8.53 (2.15)	8.76 (2.34)	3.48 (1.09)
3.2 mg/kg (N = 3)	5.69 (0.530)	6.96 (4.08, 6.96)	24.0 (7.58)	24.9 (7.98)	4.68 (0.969)
5.4 mg/kg (N = 6)	10.8 (7.56)	5.28 (3.84, 23.76)	40.6 (19.8)	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 (5.11)	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)

Mean (SD)
a: Tmax reported as median (min, max)

1.2. Study Rationale

DS-8201a is an ADC that targets HER2. A humanized IgG1 monoclonal antibody with reference to the amino acid sequence of trastuzumab is used as the antibody component

and a derivative of exatecan, a topoisomerase I inhibitor, is used as the drug component. The results of nonclinical studies have not indicated an effect of DS-8201a on cardiac ventricular repolarization.

The detailed study of drug-induced cardiac arrhythmias is addressed in the current ICH-E14 guidelines, which recommend evaluation of the effect of non-antiarrhythmic drugs in clinical development on QT intervals and QTc. This guidance has been provided due to the potentially fatal complication of torsades de pointes resulting from prolongation of the QT interval, an effect seen in a wide variety of drugs. In this study, QT prolongation will be assessed in breast cancer patients based on the ICH-E14 guidance because DS-8201a is an anti-cancer drug and cannot be studied in healthy volunteer due to the possibility that MAAA-1181a has genotoxicity.

In the Phase 1 study (DS8201-A-J101), PK parameters after single dosing were assessed but not those after multiple dosing. The peak plasma concentrations of DS-8201a and MAAA-1181a were observed at approximately 1.44 h to 4.08 h and 3.84 h to 23.76 h after single dose, respectively (see Section 1.1.1.4.2). Exposure of MAAA-1181a, the drug component of DS-8201a, was quite low and $t_{1/2}$ of MAAA-1181a was similar to that of DS-8201a (see Section 1.1.1.4.2). In this study, PK parameters after multiple dosing will be assessed, though the Cmax will be some different between Cycle 1 and subsequent cycles due to the difference of infusion rate.

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 1.1.1.4).

Overall, the reported adverse events (AEs) were consistent with the safety profile of DS-8201a expected based on the nonclinical toxicology data (see Section 1.1.1.4.1). 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 (phototoxicity), 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 (EOT), when an additional exam will also be performed. In addition, at the discretion of the Investigator, ophthalmologic testing can be performed at any time during the study.

As of 08 Jun 2017, 13 (8.7%) of 148 subjects experienced TEAEs relating to cardiotoxicity in the Phase 1 study (DS8201-A-J101, see Section 1.1.1.4.1). Similar to other products of the same class, the possibility of cardiotoxicity, relative to the potential for QT prolongation were found in association with the administration of DS-8201a and 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 were observed in association with the administration of DS-8201a and cannot be excluded.

Additional safety assessments should be conducted as needed, at the Investigator's discretion. Hepatotoxicity, embryo-fetal toxicity, visual disturbances/corneal toxicity or phototoxicity 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 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 patient 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 assess the effect of DS-8201a on the QTc interval
- To assess PK after multiple dosing of DS-8201a

2.1.2. Secondary Objectives

2.1.2.1. Key Secondary Objectives

- To assess the safety of DS-8201a
- To assess the serum concentrations of DS-8201a at the time of ECG measurement

2.1.2.2. Other Secondary Objectives

- To evaluate the efficacy of DS-8201a

2.2. Study Hypotheses

DS-8201a will not show an effect on the QTc interval (baseline-adjusted corrected QT interval by Fridericia's formula [QTcF interval] < 10 ms) in HER2-expressing breast cancer subjects.

2.3. Study Endpoints

2.3.1. Primary Endpoints

- Baseline-adjusted QTcF interval
- Serum concentration and PK parameters of DS-8201a, total anti-HER2 antibody and MAAA-1181a

2.3.2. Secondary Endpoints

2.3.2.1. Key Secondary Endpoints

Key secondary endpoints are the following safety endpoints.

- Serious adverse events (SAEs)
- TEAEs
- Physical examination findings (including Eastern Cooperative Oncology Group performance status [ECOG PS])
- Vital sign measurements
- Standard clinical laboratory parameters

- 12-lead ECG parameters such as RR, PR and QRS duration
- ECHO/MUGA findings
- Ophthalmologic findings
- Anti-drug antibody (ADA)

2.3.2.2. Other Secondary Endpoints

Other secondary endpoints are the following endpoints.

- Concentration-QT
- ORR
- DCR
- Duration of response (DoR)
- Duration of stable disease (SD)
- Clinical benefit ratio (CBR)
- Time to response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Percent change in target lesion

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

This is a Phase 1, multicenter, open-label, multiple dose study of DS-8201a designed to assess the effect on the QTc interval and PK after multiple dosing in subjects with HER2-expressing metastatic and/or unresectable breast cancer. A total of 50 subjects are expected to participate in this study.

DS-8201a will be administered as a sterile IV solution at 6.4 mg/kg Q3W. The study treatment will be continued according to the dosing criteria (See Section 5.4) to derive clinical benefit in the absence of withdrawal of subject consent, progressive disease (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.

The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or completed at least 3 cycles, whichever comes first. After the primary analysis, the main study will be closed and transition to the extension period.

3.1.2. Duration of the Study

Enrollment is planned to occur over approximately 7 months, with the data cutoff for the primary analysis projected to be completed within approximately 3 months thereafter.

Subjects experiencing clinical benefit will continue to receive study treatment in the extension period of the study. The follow-up (F/U) for post treatment subjects will also continue at the sponsor's discretion to collect more data. During the extension period, the number and frequency of non-safety study procedures may be reduced. In addition, the extent of data collection will be reduced. The study may be terminated at any time at the sponsor's discretion.

Thus, the anticipated duration of the study is 2 years and 6 months.

3.1.3. Duration of Subject Participation

The screening period is up to 28 days. 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.

After discontinuation from study treatment, all subjects, regardless of whether they discontinued prior to or subsequent to disease progression, may be contacted every 3 months until death or until F/U 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. Planned Study period

01 Oct 2017 to 31 Mar 2021.

3.2. Discussion of Study Design

3.2.1. Selection of Dose

DS-8201a was administered in 0.8 mg/kg to 8.0 mg/kg once every 3 weeks in the prior Phase 1 study (DS8201-A-J101) and the MTD was not reached up to 8.0 mg/kg. However, the highest dose 8.0 mg/kg is considered not to be appropriate to assess the QT interval at the steady state because the dose reduction rate at the earlier time point was high (67%). In addition, due to the possibility that MAAA-1181a has genotoxicity, QT assessment of DS-8201a is not able to be conducted at a supra therapeutic dose, and will be studied in breast cancer subjects, not healthy volunteers.

On the basis of efficacy, tolerability and PK profile established in the Phase 1 study and pre-clinical studies, 6.4 mg/kg have been considered as the dosage for this study.

4. STUDY POPULATION

4.1. Inclusion Criteria

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

- No.1: Man or woman ≥ 20 years old.
- No.2: Has a pathologically documented unresectable or metastatic breast cancer with HER2 expression (immunohistochemistry [IHC] 3+, IHC 2+, IHC 1+ and/or in situ hybridization [ISH]* +) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.
  *ISH: fluorescent in situ hybridization (FISH) or dual in situ hybridization (DISH)
- No.3: LVEF ≥ 50%.
- No.4: Has an ECOG PS 0 or 1.
- No.5: Has adequate organ function, defined as:

Item	Laboratory value
Platelet count	≥ 100 000/mm^3 (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin (Hb)	≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count (ANC)	≥ 1500/mm^3 (G-CSF administration is not allowed within 1 week prior to screening assessment)
Creatinine	Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation (see Section 17.1)
AST/ALT	≤ 3 × upper limit of normal (ULN) (if liver metastases are present, ≤ 5 × ULN)
Total bilirubin (TBL)	≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline
Prothrombin time and activated partial thromboplastin time	≤ 1.5 × ULN
Serum Ca, K and Mg	Within normal range

- No.6: Has adequate treatment washout period before enrollment, defined as:

Treatment	Washout period
Major surgery	≥ 4 weeks
Radiation therapy	≥ 4 weeks (if palliative stereotactic radiation therapy without abdominal, ≥ 2 weeks)
Autologous transplantation	≥ 3 months
Chemotherapy (including antibody drug therapy, retinoid therapy and hormonal therapy)	≥ 3 weeks (≥ 2 weeks or 5 half-lives before study drug treatment, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; > 6 weeks for nitrosureas or mitomycin C)
Immunotherapy	≥ 4 weeks
CYP3A4 strong inhibitor	≥ 3 elimination half-lives of the inhibitor (See Supplement 4)
Organic anion transporting polypeptide (OATP) inhibitor	≥ 3 elimination half-lives of the inhibitor (See Supplement 4)

- No.7: Is able to provide written informed consent. Subject must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible toxicities) and must sign and date an Institutional Review Board (IRB) approved ICF before performance of any study-specific procedures or examinations.
- No.8: Is willing to provide one of the following:
  - Pre-existing diagnostic or resected tumor samples.
  - HER2 status data confirmed by a central laboratory in another DS-8201a clinical study.
- No.9: Has a life expectancy of ≥ 3 months.
- No.10: Is 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 7 months for females and 4 months for males after the last dose of study drug. Methods considered as highly effective methods of contraception include:
    - 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
- Intrauterine hormone-releasing system
- 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 7 months for females and 4 months for males after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

  Non-child-bearing 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 > 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 child-bearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 weeks to 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 post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

- Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to enrollment in this study.
- 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 7 months after the final study drug administration.

4.2. Exclusion Criteria

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

- No.1: Has a medical history of myocardial infarction within 6 months before enrollment.
- No.2: Has a medical history of ventricular arrhythmias, other than rare, occasional premature ventricular contractions.
- No.3: Has uncontrolled or significant cardiovascular disease, including:
  - Symptomatic congestive heart failure (CHF) (New York Heart Association [NYHA] class II-IV, Section 17.4).
  - Troponin levels consistent with myocardial infarction as defined according to manufacturer.
  - Unstable angina or serious cardiac arrhythmia requiring treatment.
  - Clinically significant bradycardia.
  - Uncontrolled hypertension.
  - QTcF interval prolongation to > 450 ms, heart rate of > 100 beats per minute or heart rate of < 50 beats per minute based on average of the screening triplicate 12-lead ECG.
  - Any abnormal ECG findings identified by central assessment.
  - Atrial fibrillation or flutter.
  - National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03 grade ≥2 atrioventricular block, left bundle branch block or prolonged QRS.
  - Pulmonary embolism or deep vein thrombosis.
- No.4: Has an implantable pacemaker or automatic implantable cardioverter defibrillator or cardiac resynchronization therapy device.
- No.5: Has a congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death.
- No.6: Has received ≥ 500 mg/m^2 of cumulative anthracyclines as doxorubicin-equivalent dose.
- No.7: 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.
- No.8: Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.

- No.9: Has human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection.
- No.10: Is a lactating mother (Women who are willing to temporarily interrupt breastfeeding will also be excluded), planning to become pregnant or pregnant as confirmed by pregnancy tests performed within 7 days before enrollment.
- No.11: Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated, or contralateral breast cancer.
- No.12: Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with clinically inactive brain metastases may be included in the study. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and enrollment.
- No.13: Has 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 (eg, Grade 2 chemotherapy-induced neuropathy).
- No.14: Has a clinically significant corneal disease in the opinion of the Investigator.
- No.15: Prior treatment with an ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor.
- No.16: Has a concomitant medical condition that would induce QTc prolongation and increase the risk of toxicity in the opinion of the Investigator.
- No.17: Has history of severe hypersensitivity reactions to the drug substances or inactive ingredients in the drug product, or other monoclonal antibodies.
- No.18: Has substance abuse or any other medical conditions that would increase the safety risk to the subject or interfere with participation of the subject or evaluation of the clinical study in the opinion of the Investigator.

Rationale for Exclusion Criteria:

These criteria are included to minimize the risk for subject safety.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)/Sequences

Study treatment and procedure is the same among all subjects enrolled in this study.

5.1.2. Method of Treatment Allocation

Each subject will be provided with information about the study, will have all questions answered to their satisfaction, and will sign and date an ICF. This will be completed before any study-specific procedures are performed. Additional information about informed consent procedures is provided in Section 15.3.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, gender), date and outcome of screening process (eg, enroll 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 Subject Number.

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

5.1.2.1. Subject Number Assignment

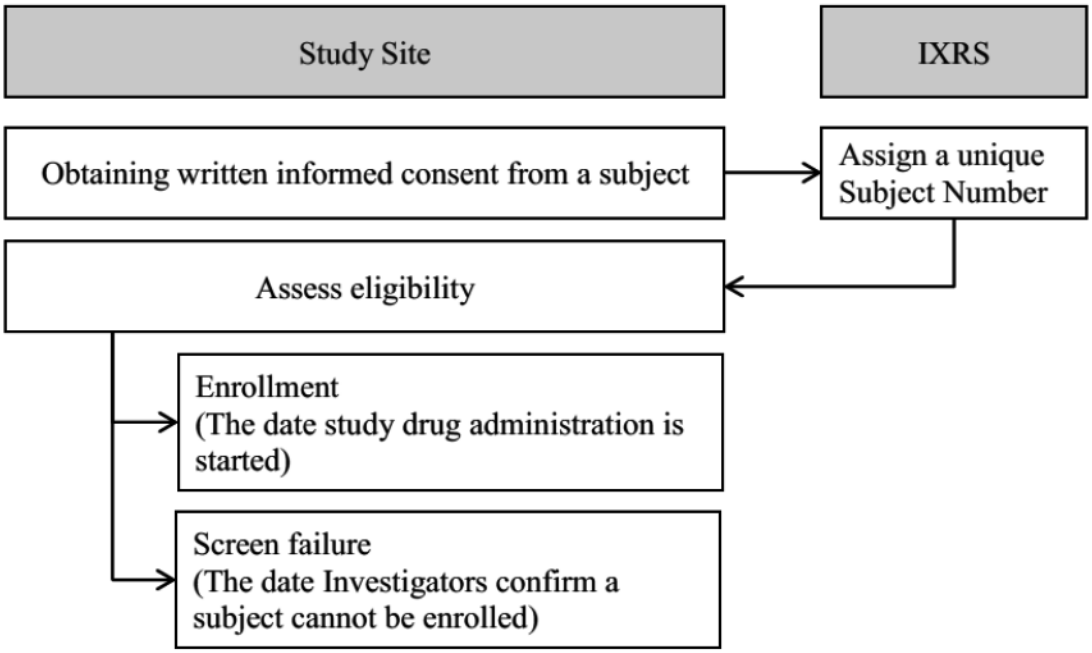
The unique Subject Number will be assigned to all subjects who provide written informed consent. After obtaining written informed consent, Investigators will assign the unique Subject Number to the subject by interactive web/voice response system (IXRS), encompassing both interactive voice response systems utilizing the telephone or tone dialers and interactive web response systems utilizing the internet (see Figure 5.1).

5.1.2.2. Enrollment

Investigators will assess the eligibility of a subject based on the inclusion and exclusion criteria after obtaining written informed consent from the subject.

Enrollment date is defined as the date study drug administration is started upon the Investigator's or designee's obtaining written informed consent from a subject (see Section 15.3) and upon determination of all inclusion and exclusion criteria having been satisfied. The date of screen failure is defined as the date that Investigators confirm a subject cannot be enrolled in the study (see Figure 5.1).

Figure 5.1: Process for Subject Number Assignment and Enrollment



5.1.3. Blinding

Not applicable.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug(s)

5.2.1. Description

The DS-8201a drug product will be provided as a lyophilized powder containing 100 mg of DS-8201a in a glass vial (Lyo-DP). Each glass vial should be reconstituted to a concentration of 20 mg/mL (ie, 100 mg / 5 mL). Each vial is designed for single use only and is not to be used to treat more than one subject.

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 instructions 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 study drug will be administered at a dose of 6.4 mg/kg. The initial dose of DS-8201a will be infused for approximately 90 minutes. If there is no infusion related reaction, after the initial dose, the next dose of DS-8201a will be infused for approximately 30 minutes.

The subject's weight at screening will be used to calculate the initial dose. If during the course of treatment the subject's weight changes by more than 10% of the baseline weight, the subject's dose will be recalculated based on the subject's updated weight.

5.2.5. Storage

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

- Stored at 2°C to 8°C (protected from light).

If storage conditions are not maintained per specified requirements, the 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 by the Sponsor. 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 study drug. The record must be kept current and should contain the dates and quantities of study drug received, subject's information (the site subject identifier and the subject number), for whom the study drug was dispensed, the date and quantity of study drug dispensed and remaining, as well as the initials or seal of the dispenser.

At the end of the study, or as directed by the Sponsor, all unused study drugs will be returned to a designee as instructed by the Sponsor. Study drug will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation included in the shipment. At the end of the study, a final study drug reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor.

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 (NCI-CTCAE version 4.03). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of DS-8201a are listed in Table 5.2. For Grade 3 or Grade 4 events, monitoring (including local lab tests when appropriate) should be performed at intervals no greater than 7 days until AE is determined to be resolving or discontinuation of study treatment is decided.

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

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.

Dose Reduction Guidelines:

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

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

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.

Table 5.1: Dose Reduction Levels of DS-8201a

Starting Dose	Dose Level −1	Dose Level −2
6.4 mg/kg	5.4 mg/kg	4.4 mg/kg

Dose Interruption and Schedule Modification Guidelines:

A dose can be delayed for up to 28 days (49 days from the last infusion date) from the planned date of administration. If a subject is assessed as requiring a dose delay of longer than 28 days, the subject will be withdrawn from the study.

In case DS-8201a dosing is temporarily withheld for any reason, next planned date of administration will be scheduled based on the date of dose resumption.

All confirmed or suspected SAR-CoV-19 infection events must be recorded in the eCRF. Please refer to Section 17.6 for additional information on dose modification.

Table 5.2: Dose or Schedule Modification for DS-8201a

Worst toxicity NCI-CTCAE version 4.03 Grade (unless otherwise specified)	**Management Guidelines for DS-8201a**
No toxicity	Maintain dose and schedule.
Infusion-related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	· If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during 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, 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, IV 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, IV fluid therapy, oxygen inhalation etc., should be administered.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	Delay dose until resolved to ≤ Grade 2: · Maintain dose
Grade 4	Delay dose until resolved to ≤ Grade 2: · Reduce dose 1 level
Febrile Neutropenia	
Grade 3 (absolute neutrophil count < 1 x 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 1 level
Grade 4	Discontinue subject from study treatment.
Lymphocyte Count Decreased	

Grade 1 to 3	No dose modification.
Grade 4 (< 0.2 x 10^9/L)	Delay dose until resolved to ≤ Grade 2: · If resolved in ≤ 14 days from day of onset, maintain dose · If resolved in > 14 days from day of onset, reduce dose 1 level
Anaemia	
Grade 3 (Hb <8.0 g/dL; transfusion indicated)	Delay dose until resolved to ≤ Grade 2: · Maintain dose
Grade 4 (Life threatening consequences; urgent intervention indicated)	Delay dose until resolved to ≤ Grade 2: · Reduce dose 1 level
Platelet Count Decreased	
Grade 3 (<50 to 25 x 10^9/L)	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
Grade 4 (< 25 x 10^9/L)	Delay dose until resolved to ≤ Grade 1: · Reduce dose 1 level
Cardiac Toxicity	
CHF	Discontinue subject from study treatment.
Decrease in LVEF 10% to 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.
LVEF 40% to ≤ 45% and decrease is ≥ 10-20% (absolute value) from baseline	Interrupt DS-8201a dosing. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment. If LVEF recovers to within 10% from baseline, resume study drug 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.
Electrocardiogram QT prolonged	
Grade 3 (QTc> 500 ms on 2 separate ECGs)	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 or if there are any changes in serum electrolytes that can be corrected, 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 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 End of infusion (EOI) 3-hour troponin test if the troponin level is not Grade 3. If troponin levels are not above the upper limit of normal at baseline, for new diagnosed grade 1, repeat troponin testing at 3 ± 1 hours (~ 6 hours post-infusion) after initial troponin test. · If repeat troponin level at 3 ± 1 hours (~ 6 hours post-infusion) rises significantly per institutional guidelines, - perform ECG in triplicate; - repeat troponin testing at 6 ± 1 hours (~9 hours post-infusion) after initial troponin test; - follow institutional guidelines for management of detectable troponin testing. · If repeat troponin level at 3 ± 1 hours (~ 6 hours post-infusion) does not rise significantly per institutional guidelines, - repeat troponin testing at 6 ± 1 hours (~9 hours post-infusion) or at 24 ± 2 hours (~27 hours post-infusion) 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 ± 1 hours (~9 hours post-infusion) and 12 ± 1 hours (~15 hours post-infusion) after initial troponin test. Follow institutional guidelines for management of detectable troponin testing. If acute myocardial infarction confirmed, discontinue subject from study therapy. Otherwise, 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
Pulmonary Toxicity If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If 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.	

<table>
<tr><td colspan="2">Evaluations should include:
· high resolution CT
· pulmonologist consultation (infectious disease consultation as clinically indicated)
· blood culture and CBC. Other blood tests could be considered as needed
· consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
· pulmonary function tests and pulse oximetry (SpO_2)
· arterial blood gases if clinically indicated
· one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.
Other tests could be considered, as needed.
If the AE is confirmed to be ILD/pneumonitis, follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.</td></tr>
<tr><td>Grade 1</td><td>The administration of DS-8201a must be interrupted for any ILD/pneumonitis events regardless of grade.
· Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry
· Consider follow-up imaging in 1-2 weeks (or as clinically indicated).
· Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks.
· If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.*
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
However, if the event grade 1 ILD/pneumonitis occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued.
* If subject is asymptomatic, then subject should still be considered as Grade 1 even if steroid treatment is given</td></tr>
<tr><td>Grade 2</td><td>Permanently discontinue subject from study treatment.
· Promptly start and treat with systemic steroids (e.g., at least 1 mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks.
· Monitor symptoms closely.</td></tr>
</table>

	· Re-image as clinically indicated.
	· If worsening or no improvement in clinical or diagnostic observations in 5 days,
	  · Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone).
	  · Re-consider additional work-up for alternative etiologies as described above.
	  · Escalate care as clinically indicated.

Grade 3 and 4	Permanently discontinue subject from study treatment.
	· Hospitalization required.
	· Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks.
	· Re-image as clinically indicated.
	· If still no improvement within 3 to 5 days,
	  · Re-consider additional work-up for alternative etiologies as described above.
	  · Consider other immuno-suppressants and/or treat per local practice.

Ocular	
Grade 3	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
Grade 4	Discontinue subject from study treatment.
Blood creatinine increased	
Grade 3 (> 3.0 to 6.0 x ULN)	Delay dose until resolved to ≤ Grade 2 or baseline. · Reduce dose 1 level
Grade 4 (> 6.0 x ULN)	Discontinue subject from study treatment.
Hepatic Toxicity	
Aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT) with simultaneous TBL	

AST/ALT ≥ 3.0 x ULN with simultaneous TBL > 2.0 x 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 aminotransaminase (AST) or alanine aminotransaminase (ALT) increased	
Grade 2 (>3.0 to 5.0 x ULN)	No action for Grade 2 AST/ALT.
Grade 3 (> 5.0 to 20.0 x ULN) In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 x ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1 if baseline ≤ 3 x ULN, otherwise delay dose until resolved to ≤ baseline, 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 to 20.0 x ULN) In subjects with liver metastases, if the baseline level was > 3 x ULN	Repeat testing within 3 days. Delay dose until resolved to baseline level: · 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 (> 20.0 x ULN)	Discontinue subject from study treatment.
TBL increased	
Grade 2 (> 1.5 to 3.0 x 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 to 10.0 x 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 x ULN)	Discontinue subject from study treatment.

Blood Alkaline Phosphatase (ALP) Increased	
Grade 3 to 4 (>5.0 x ULN)	No modification unless determined by the Investigator to be clinically significant or life-threatening.
Gastrointestinal	
Nausea	
Grade 3	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
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1: · If resolved in ≤ 3 days from day of onset, maintain dose · If resolved in > 3 days from day of onset, 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 from day of onset, maintain dose · If resolved in > 7 days from day of onset, 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 from day of onset, maintain dose · If resolved in > 7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment.

5.5. Method of Assessing Treatment Compliance

All drugs used for the study treatment will be administered by the Investigator or other designated study personnel. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for the administration of study treatment. Start and stop date/time of injection, amount of drug administered, and reason for dose reduction/interruption (if applicable) will be recorded in medical record by clinical study personnel. These data will be recorded on the electronic case report form (eCRF).

5.6. Prior and Concomitant Medications

5.6.1. Concomitant Medications

Medications used from the time the subject signs the ICF to 40-Day F/U visit (+ 7 days) will be recorded. All concomitant medications will be recorded in the eCRF.

5.6.2. Prohibited Concomitant Medications/Activities

With the exception of medications that are under investigation in the study (e.g. standard of care, comparators, or combination therapies, the following medications, treatment and procedures will be prohibited during the treatment period. The Sponsor must be notified if a subject receives any of these during the study:

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or hormonal treatment [concurrent use of hormones for noncancer-related conditions (e.g. insulin for diabetes and hormone replacement therapy) is acceptable].
- 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 except for managing AEs; 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.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. Refer to 17.6 for further details.
- Concomitant use of drugs which would induce QT prolongation (see Supplement 3).

Permitted Therapies/Products

- 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.
- Based on the currently available clinical safety data, it is recommended that subjects receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-hydroxytryptamine receptor (5-HT3) antagonists or Neurokinin-1 (NK1) receptor antagonists and/or steroids (e.g. dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

Restricted Products

- Use of e-cigarettes and vaping is strongly discouraged but not prohibited.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal from Study Treatment

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

- PD per criteria set forth in Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
- Clinical progression (definitive clinical signs of disease progression, but a recent radiographic assessment did not meet the criteria for Progressive Disease according to RECIST Version 1.1)
- Adverse event
- Withdrawal of consent to study treatment
- Physician Decision
- Death
- Pregnancy
- Protocol violation
- Study terminated by the sponsor
- Lost to F/U
- 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 Sponsor.

All subjects who are withdrawn from study treatment should complete protocol-specified withdrawal procedures (see Section 6.4) and F/U procedures (see Section 6.5 and 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 Withdrawal from Study Participation

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

- Withdrawal of consent to participate in study procedures

- Death
- Lost to F/U
- Study terminated by the sponsor
- Other, specify

5.7.3. Withdrawal Procedures

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

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be performed during the EOT visit (+7 days, Section 6.4) and the 40-Day F/U visit (+7 days, Section 6.5).

5.7.4. Subject Replacement

Subjects that have been enrolled and received study drug will not be replaced.

5.7.5. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet eligibility criteria upon initial screening. The unique Subject 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 rescreened.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 17.7.

6.1. Screening

Obtain of 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:

Before enrollment

- Assign a Site Subject Identifier.
- Assign an unique Subject Number by IXRS
- Record demographic (eg, birth date, sex, race), primary cancer history, significant medical history information and prior treatment history information for cancer.
- Record historical HER2 status.
- If a subject has HER2 status data confirmed by a central laboratory in another DS-8201a clinical study, identify the unique Subject Number for the study and provide it to the central laboratory of the DS8201-A-J102 study.
- Review Inclusion/Exclusion criteria.
- Record concomitant medications.
- Assess subjects for AEs.

Within 90 days before enrollment

- Perform a HIV antibody test.

Within 28 days before enrollment

- Ophthalmologic assessments.
  The assessments will include visual acuity testing, slit lamp examination, and fundoscopy.
- Perform either ECHO or MUGA (LVEF).
- Perform tumor assessment by computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain, chest, abdomen, pelvis, and any other sites of disease (Section 17.3).

Within 7 days before enrollment

- Perform a 12-lead ECG in triplicate (Section 9.10).
  ECGs will be taken in close succession, no more than approximately 2 min apart, and after at least 10 min of quiet rest in the supine position. Any study

procedures such as blood sampling are not allowed during quiet rest and prior to ECG measurement.

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Obtain blood samples for safety laboratories (Section 9.8 and Section 17.1), prothrombin time and activated partial thromboplastin, troponin (preferably high-sensitivity troponin-T) testing by study site, and troponin-T testing by central lab (Section 8.5.2).
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential.
  For postmenopausal subjects (no childbearing potential, as indicated by an elapse of at least 12 months after the last menstruation) or female subjects who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of child-bearing potential and required to undergo the pregnancy test.
- Perform urinalysis test (Section 9.8).

Before the first dose of study drug administration

- Perform a complete physical examination and record height.
- If there is no archived sample, Investigator performs a tumor biopsy before the first dose of study drug. Tumor slides for assessment of HER2 by IHC/FISH are needed. The detailed procedures for preparing and submitting tumor samples will be provided in Section 8.2. If a subject has HER2 status data confirmed by a central laboratory in another DS-8201a clinical study, there is no need to collect and submit tumor samples.

6.2. Randomization

Not applicable.

6.3. Treatment Period

6.3.1. Tumor Assessment

The same imaging tumor assessment as at the time of screening by CT or MRI scans will be performed every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks (± 7 days) regardless of delay in dosing. The assessment will be conducted before Day 1 of each Cycle as possible. CT or MRI scans of the chest, abdomen and pelvis are mandatory. However, if there is no brain metastasis at the time of screening, CT or MRI should only be done when symptoms associated with brain

metastasis occur. If no clinical symptoms are observed, brain CT or MRI is not mandatory (Section 17.3).

6.3.2. Other Study Procedure in Treatment Period

NOTE: The triplicate 12-lead safety ECGs will be performed at the each time point in close succession, no more than approximately 2 min apart, and after at least 10 min of quiet rest in the supine position. Any study procedures such as blood sampling are not allowed during quiet rest and prior to ECG measurement.

6.3.2.1. Cycle 1, Day 0

The following procedures will be performed on Day 0 (Within 3 days before Day 0).

- Record concomitant medications.
- Assess subjects for AEs.
  The Investigator must confirm any clinically significant AEs have not been occurred before performing a 12-lead ECG.
- Perform a 12-lead ECG in triplicate at the following time points (Section 9.10):
  - 15 minutes before the planned start time of administration on Cycle 1, Day 1 (Acceptable range of ECG measurement start time: ± 10 minutes)
  - 30 minutes after the planned start time of administration on Cycle 1, Day 1 (Acceptable range of ECG measurement start time: ± 10 minutes)
  - 2 hours after the planned start time of administration on Cycle 1, Day 1 (Acceptable range of ECG measurement start time: ± 10 minutes)
  - 4 hours after the planned start time of administration on Cycle 1, Day 1 (Acceptable range of ECG measurement start time: ± 10 minutes)
  - 7 hours after the planned start time of administration on Cycle 1, Day 1 (Acceptable range of ECG measurement start time: ± 10 minutes)

6.3.2.2. Cycle 1, Day 1

Before infusion

The following procedures will be completed at pre-dose on Day 1.

- Record concomitant medications.
- Assess subjects for AEs.

Latest data within 3 days before administration

Physical examination, weight, ECOG PS Scale assessment, hematology, blood chemistry and vital signs evaluations do NOT need to be repeated if performed within 3 days before the first dose of study drug.

- Perform a complete physical examination and record weight.

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and peripheral oxygen saturation [SpO_2]).
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Obtain blood samples for safety laboratories (Section 9.8).

Within 8 hours before administration

- Obtain blood sample for ADA (Section 8.6).

15 minutes before administration

- Perform a 12-lead ECG in triplicate (Acceptable range of ECG measurement start time: ± 10 minutes) (Section 9.10).
- Obtain PK blood sample (Within 10 minutes after completing ECG measurement) (Section 8.3).

Administration and after Infusion

- Administer DS-8201a per Section 5.2.4.

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate at the following time points (Section 9.10):
  - 2 hours after the start of administration
    (Acceptable range of ECG measurement start time: ± 10 minutes)
  - 4 hours after the start of administration
    (Acceptable range of ECG measurement start time: ± 10 minutes)
  - 7 hours after the start of administration
    (Acceptable range of ECG measurement start time: ± 10 minutes)
- Obtain PK blood samples at the following time points (Section 8.3):
  - EOI (Within 10 minutes after EOI)
  - 2 hours after the start of administration (Within 10 minutes after completing ECG measurement)
  - 4 hours after the start of administration (Within 10 minutes after completing ECG measurement)
  - 7 hours after the start of administration (Within 10 minutes after completing ECG measurement)
- Obtain blood samples for troponin (preferably high-sensitivity troponin-T) testing by study site and troponin-T testing by central lab 2 to 3 hours after EOI (Section 8.5.2).

- If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
- 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), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn.
  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.
  - If troponin level at 3 hours (6 hours post-infusion): Significantly increases per institutional guidelines, then perform a 12-lead ECG in triplicate, repeat troponin testing at 6 hours (± 1 hour) and follow institutional guidelines.
  - Otherwise, repeat troponin testing at 6 hours (± 1 hour) or at 24 hours (± 2 hours) after initial troponin test.

- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.3. Cycle 1, Day 2

The following procedures will be performed on Day 2.

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the 24 hours (± 2 hours) after the start of Day 1 administration (Section 8.3).
- Obtain blood samples for safety laboratories (Section 9.8).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.4. Cycle 1, Day 4

The following procedures will be performed on Day 4.

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the 72 hours (± 2 hours) after the start of Day 1 administration (Section 8.3).
- Record concomitant medications.

- Assess subjects for AEs.

6.3.2.5. Cycle 1, Day 8

The following procedures will be performed on Day 8 (± 1 day).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate (Section 9.10).
- Obtain PK blood samples on Day 8 (Within 10 minutes after completing ECG measurement) (Section 8.3).
- Obtain blood samples for safety laboratories (Section 9.8).
- Obtain a blood sample for ADA (Section 8.6).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.6. Cycle 1, Day 15

The following procedures will be performed on Day 15 (± 1 day).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate (Section 9.10).
- Obtain PK blood samples on Day 15 (Within 10 minutes after completing ECG measurement) (Section 8.3).
- Obtain blood samples for safety laboratories (Section 9.8).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.7. Cycle 1, 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, the following procedures will be performed on Day 22 (± 2 days).

- Obtain PK blood samples on Day 22 (Section 8.3).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.8. Cycle 2, Day 1

Before Infusion

The following procedures will be completed at pre-dose on Day 1 (± 2 days).

- Record concomitant medications.
- Assess subjects for AEs.

Latest data within 3 days before administration

- Ophthalmologic assessments.
  The assessments will include visual acuity testing, slit lamp examination, and fundoscopy. If the planned date of study drug administration is delayed after examination of ophthalmologic assessments, and there are no abnormal findings on the examination, ophthalmologic assessments may not be repeated at the Investigator's judgment.
- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Perform a 12-lead ECG in triplicate (Section 9.10).
- Obtain blood samples for safety laboratories (Section 9.8).
- Perform either ECHO or MUGA (LVEF).
  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, ECHO or MUGA may not be repeated at the Investigator's judgment.

Within 8 hours before administration

- Obtain PK blood sample (Section 8.3).
  Even if blood sample is collected on Day 22 of Cycle 1, the blood sample will be collected at before infusion (BI) on Day 1 of Cycle 2 if possible.
- Obtain a blood sample for ADA (Section 8.6).

Administration and after Infusion

- Administer DS-8201a per Section 5.2.4.

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the end of administration within 30 minutes after EOI (Section 8.3).
- Obtain blood samples for troponin (preferably high-sensitivity troponin-T) testing by study site and troponin-T testing by central lab 2 to 3 hours after EOI (Section 8.5.2).
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1

hour) after initial troponin test was drawn, and follow institutional guidelines.

- 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), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn.
  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.
  - If troponin level at 3 hours (6 hours post-infusion): Significantly increases per institutional guidelines, then perform a 12-lead ECG in triplicate, repeat troponin testing at 6 hours (± 1 hour) and follow institutional guidelines.
  - Otherwise, repeat troponin testing at 6 hours (± 1 hour) or at 24 hours (± 2 hours) after initial troponin test.

- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.9. Cycle 2, Day 8

The following procedures will be performed on Day 8 (± 2 days).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories (Section 9.8).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.10. Cycle 2, Day 15

The following procedures will be performed on Day 15 (± 2 days).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories (Section 9.8).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.11. Cycle 2, 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, the following procedures will be performed on Day 22 (± 2 days).

- Obtain PK blood samples during the Cycle 2, Day 22 (Section 8.3).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.12. Cycle 3, Day 1

Before Infusion

The following procedures will be completed at pre-dose on Day 1 (± 2 days).

- Record concomitant medications.
- Assess subjects for AEs.

Latest data within 3 days before administration

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Obtain blood samples for safety laboratories (Section 9.8).
- Perform either ECHO or MUGA (LVEF).
  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, ECHO or MUGA may not be repeated at the Investigator's judgment.

15 minutes before administration

- Perform a 12-lead ECG in triplicate (Acceptable range of ECG measurement start time: ± 10 minutes) (Section 9.10).
- Obtain PK blood sample (Within 10 minutes after completing ECG measurement) (Section 8.3).
  Even 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 if possible.

Administration and after Infusion

- Administer DS-8201a per Section 5.2.4.

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate at the following time points (Section 9.10):
  - EOI (Within 15 minutes after EOI)
  - 2 hours after the start of administration
    (Acceptable range of ECG measurement start time: ± 10 minutes)

  - 4 hours after the start of administration
    (Acceptable range of ECG measurement start time: ± 10 minutes)
  - 7 hours after the start of administration
    (Acceptable range of ECG measurement start time: ± 10 minutes)
- Obtain PK blood samples at the following time points (Section 8.3):
  - EOI (Within 10 minutes after completing ECG measurement)
  - 2 hours after the start of administration (Within 10 minutes after completing ECG measurement)
  - 4 hours after the start of administration (Within 10 minutes after completing ECG measurement)
  - 7 hours after the start of administration (Within 10 minutes after completing ECG measurement)
- Obtain blood samples for troponin (preferably high-sensitivity troponin-T) testing by study site and troponin-T testing by central lab 2 to 3 hours after EOI (Section 8.5.2).
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
  - 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), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn.
    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.
    - If troponin level at 3 hours (6 hours post-infusion): Significantly increases per institutional guidelines, then perform a 12-lead ECG in triplicate, repeat troponin testing at 6 hours (± 1 hour) and follow institutional guidelines.
    - Otherwise, repeat troponin testing at 6 hours (± 1 hour) or at 24 hours (± 2 hours) after initial troponin test.
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.13. Cycle 3, Day 2

The following procedures will be performed on Day 2.

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the 24 hours (± 2 hours) after the start of Day 1 administration (Section 8.3).
- Obtain blood samples for safety laboratories (Section 9.8).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.14. Cycle 3, Day 4

The following procedures will be performed on Day 4.

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the 72 hours (± 2 hours) after the start of Day 1 administration (Section 8.3).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.15. Cycle 3, Day 8

The following procedures will be performed on Day 8 (± 1 day).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate (Section 9.10).
- Obtain PK blood samples on Day 8 (Within 10 minutes after completing ECG measurement) (Section 8.3).
- Obtain blood samples for safety laboratories (Section 9.8).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.16. Cycle 3, Day 15

The following procedures will be performed on Day 15 (± 1 day).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Perform a 12-lead ECG in triplicate (Section 9.10).
- Obtain PK blood samples on Day 15 (Within 10 minutes after completing ECG measurement) (Section 8.3).
- Obtain blood samples for safety laboratories (Section 9.8).

- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.17. Cycle 3, 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, the following procedures will be performed on Day 22 (± 2 days).

- Obtain PK blood samples on Day 22 (Section 8.3).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.2.18. Cycle 4 and Subsequent Cycles, Day 1

Before Infusion

The following procedures will be completed at pre-dose on Day 1 (± 2 days).

- Record concomitant medications.
- Assess subjects for AEs.

Latest data within 3 days before administration

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Obtain blood samples for safety laboratories (Section 9.8).
- Perform a 12-lead ECG in triplicate (Section 9.10).

<At Day 1 every 2 cycles from Cycle 5 to the EOT (eg, Day 1 in Cycle 5, 7, 9...)>

- Perform either ECHO or MUGA (LVEF).
  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, ECHO or MUGA may not be repeated at the Investigator's judgment.

Within 8 hours before administration

<At Day 1 in Cycle 4, 6 and 8>

- Obtain PK blood sample (Section 8.3).
  Even if blood sample is collected on Day 22 of Cycle 3, 5 and/or 7, the blood sample will be collected at BI on Day 1 of Cycle 4, 6 and/or 8 if possible.

<At Day 1 every 2 cycles from Cycle 4 to the EOT (eg, Day 1 in Cycle 4, 6, 8, 10...)>

- Obtain a blood sample for ADA (Section 8.6). A portion of ADA blood sample will be used for future central lab analysis for SARS-CoV-2 testing

once protocol version 7.0 is applied for a subject. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 4 (Cycle 4, Cycle 8 etc.).

Administration and after Infusion

- Administer DS-8201a per Section 5.2.4.

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

- Record concomitant medications.
- Assess subjects for AEs.

<Every 2 cycles from Cycle 4 until Cycle 8 at the maximum (eg, Day 1 of cycle 4, 6, 8)>

- Obtain PK blood sample at the end of administration within 30 minutes after EOI (Section 8.3).

6.3.2.18.1. Cycle 5, Day 22 and Cycle 7, 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, the following procedures will be performed on Day 22 (± 2 days).

- Obtain PK blood samples on Day 22 (Section 8.3).
- Record concomitant medications.
- Assess subjects for AEs.

6.4. End of Treatment

The EOT is defined as the date the Investigator decides to discontinue study treatment. The following assessments will be performed at EOT visit (+ 7 days). However, if the following assessments have been performed within 30 days (± 9 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.

- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, and fundoscopy.
- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Perform a 12-lead ECG in triplicate (Section 9.10).
- Obtain blood samples for safety laboratories (Section 9.8), ADA (Section 8.6), troponin (preferably high-sensitivity troponin-T) testing by study site (Section 8.5.2). A portion of ADA blood sample will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 7.0 is applied for a subject.

- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential. For postmenopausal subjects (no childbearing potential, as indicated by an elapse of at least 12 months after the last menstruation) or female subjects who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of child-bearing potential and required to undergo the pregnancy test.
- Perform either ECHO or MUGA (LVEF).
- Perform same imaging tumor assessment as at the time of screening by CT or MRI scans. CT or MRI scans of the chest, abdomen and pelvis are mandatory. However, if there is no brain metastasis at the time of screening, CT or MRI should only be done when symptoms associated with brain metastasis occur. If no clinical symptoms are observed, brain CT or MRI is not mandatory (Section 17.3). If progression is identified in a prior examination, only the chest is examined by CT to monitor the pulmonary status.
- Record concomitant medications.
- Assess subjects for AEs.
- Record reason for treatment discontinuation.

6.5. 40-Day 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. If EOT visit is > 40 days after last treatment, then the EOT assessments can also function as the F/U visit.

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature and SpO_2).
- Perform a complete physical examination and record weight.
- Assess functional status using the ECOG PS Scale (Section 17.2).
- Obtain blood samples for safety laboratories (Section 9.8), ADA (Section 8.6).For subjects with positive ADA at 40-Day F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first. A portion of ADA blood sample will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 7.0 is applied for a subject.
- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential. For postmenopausal subjects (no childbearing

potential, as indicated by an elapse of at least 12 months after the last menstruation) or female subjects who have no possibility of pregnancy due to sterilization surgery, etc., no pregnancy test will be required. Female subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of child-bearing potential and required to undergo the pregnancy test.

- Record concomitant medications.
- Assess subjects for AEs.

6.6. New Cancer Treatment and Survival Follow-up

Subjects will be assessed every 3 months (±14 days), from the date of 40-Day F/U visit, for survival and subsequent anticancer therapy until death, withdrawal of consent, lost to F/U 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 F/U) from public records as allowed by law.

Further F/U may be required for ongoing AEs.

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoint(s)

Efficacy assessments will be based on tumor assessments to be performed at screening and every 6 weeks in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks while the subject remains on study drug. The clinical activity of DS-8201a will be assessed by evaluating tumor response. Tumor response will be evaluated using RECIST version 1.1 (Section 17.3).

CT or MRI (spiral CT or MRI with ≤ 5 mm cuts) of brain, chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions at screening period. Every effort should be made to use the same assessment modality for all assessments for each subject. However, if there is no brain metastasis at the time of screening, CT or MRI should only be done when symptoms associated with brain metastasis occur during study period. If no clinical symptoms are observed, brain CT or MRI is not mandatory during study period.

The following efficacy variables will be assessed.

- ORR (the sum of complete response [CR] rate and partial response [PR] rate)
- DCR (the sum of CR rate, PR rate, and SD rate)
- DoR
- Duration of SD
- CBR
- TTR
- PFS
- OS
- Percent change in target lesion

7.2. Appropriateness of Selected Efficacy Assessment(s)

The efficacy assessments were selected for this study because RECIST is used widely and generally recognized as standard tumor response criteria.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Blood Sampling

Blood samples for PK and ADA will be collected into blood sampling tubes supplied by the Sponsor. The collected blood will be centrifuged to separate the serum. The serum samples will be shipped to a central laboratory.

The detail instructions for the handling of blood samples and shipping of serum samples are included in a separate document (eg, laboratory manual).

8.2. Tumor Sampling

Slides of tumor tissue sections which are obtained before the first study drug administration for Biomarker (eg, HER2 by IHC and FISH) will be submitted to a central laboratory for exploratory assessment of the biomarker. If a subject has HER2 status data confirmed by a central laboratory in another DS-8201a clinical study, there is no need to collect and submit tumor samples.

Archived tumor samples including tissue samples from surgery, endoscopy or needle biopsy already collected and formalin-fixed paraffin-embedded will be used. If the both of surgery and biopsy samples are available for one patient, it is recommended to submit the most recent samples to the central laboratory.

If the size of archived tissue sample is too small, tumor tissue newly collected by needle biopsy or endoscopy should be submitted.

Paraffin-embedded tissue blocks of formalin-fixed tissue specimens will be prepared by the standard procedure at the study center and the unstained slides with tissue sections will be submitted to the courier assigned by the Sponsor.

The detail instructions for the handling of tumor samples and shipping of tumor samples are included in a separate document (eg, laboratory manual).

8.3. Pharmacokinetic (PK) Assessment(s)

Serum PK parameters (AUCtau, Cmax, Tmax and Ctrough) of DS-8201a for each subject will be estimated using standard noncompartmental methods. For total anti-HER2 antibody and MAAA-1181a, all parameters listed above will be estimated.

Blood samples of approximately 4 mL for PKs analyses will be collected at the time points specified in Table 8.1 and Table 8.2. The actual time of study drug administration and the exact time of blood sampling must be recorded in source document and the eCRF.

Table 8.1: Pharmacokinetic Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	BI (Within 10 minutes after completing ECG measurement) EOI (Within 10 minutes after EOI)

Cycle	Day	Sampling Time Point (Acceptable Range)
		2 hours after the start of administration (Within 10 minutes after completing ECG measurement) 4 hours after the start of administration (Within 10 minutes after completing ECG measurement) 7 hours after the start of administration (Within 10 minutes after completing ECG measurement)
	Day 2	24 hours after the start of administration (± 2 hours)
	Day 4	72 hours after the start of administration (± 2 hours)
	Day 8	7 days after the start of administration (± 1 day) (Within 10 minutes after completing ECG measurement)
	Day 15	14 days after the start of administration (± 1 day) (Within 10 minutes after completing ECG measurement)
	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 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 if possible. EOI: Within 30 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 administration (± 2 days)
Cycle 3	Day 1	BI (Within 10 minutes after completing ECG measurement) EOI (Within 10 minutes after completing ECG measurement) 2 hours after the start of administration (Within 10 minutes after completing ECG measurement) 4 hours after the start of administration (Within 10 minutes after completing ECG measurement) 7 hours after the start of administration (Within 10 minutes after completing ECG measurement)
	Day 2	24 hours after the start of administration (± 2 hours)
	Day 4	72 hours after the start of administration (± 2 hours)
	Day 8	7 days after the start of administration (± 1 day) (Within 10 minutes after completing ECG measurement)
	Day 15	14 days after the start of administration (± 1 day) (Within 10 minutes after completing ECG measurement)

Cycle	Day	Sampling Time Point (Acceptable Range)
	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 administration (± 2 days)
Cycle 4, 6, 8	Day 1	BI (– 8 hours) If blood sample is collected on Day 22 of Cycle 3, 5 and/or 7, the blood sample will be collected at BI on Day 1 of next Cycle if possible. EOI: Within 30 minutes after EOI

BI = before infusion, ECG = electrocardiogram, EOI = end of infusion

In case of chloroquine or hydroxychloroquine administration for SARS-CoV-2 infection, additional PK serum samples should be collected at the time points specified in Table 8.2.

Table 8.2: Schedule of PK Sample Collection for Subjects Administered Chloroquine or Hydroxychloroquine

Day of CQ or HCQ Administration	Sampling Time Point (Acceptable Ranges)
Day 1	Prior to CQ/HCQ dose
Day 3 or Day 4	Prior to CQ/HCQ dose (within 4 hrs)
End of CQ or HCQ treatment	Prior to CQ/HCQ dose (within 4 hrs)
Prior to resumption of DS-8201a (after CQ/HCQ wash-out period)[a]	Before infusion of study treament (within 8 hrs)

CQ = chloroquine; HCQ = hydroxychloroquine.
a Washout period of ≥14 days is required before restarting study treatment.

8.4. Pharmacodynamic (PD) Assessment(s)

Not applicable.

8.5. Biomarker Assessment(s)

8.5.1. HER2 Status Assessed by Central Laboratory

HER2 status in pre-treatment tumor sample will be assessed by central laboratory. The status will be assessed by IHC and/or FISH. If a subject has HER2 status data confirmed by a central laboratory in another DS-8201a clinical study, it will be also used for the DS8201-A-J102 study and there is no need to assess HER2 status again.

8.5.2. Troponin-T Assessed

Blood samples for troponin-T testing will be collected at the time points specified in Table 8.3. Troponin (preferably high-sensitive troponin-T) testing will be conducted also by study site at the time points specified in Table 8.3.

Table 8.3: Troponin Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Screening	-	Within 7 days before enrollment
Cycle 1-3	Day 1	2 to 3 hours after EOI ▪ If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines. ▪ 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), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn. 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. ▪ If troponin level at 3 hours (6 hours post-infusion): Significantly increases per institutional guidelines, then perform a 12-lead ECG in triplicate, repeat troponin testing at 6 hours (± 1 hour) and follow institutional guidelines. ▪ Otherwise, repeat troponin testing at 6 hours (± 1 hour) or at 24 hours (± 2 hours) after initial troponin test.
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days).

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

Instructions for the handling and shipping of serum samples are included in a separate document (eg, laboratory manual).

8.6. Immunogenicity (Anti-drug antibody)

Blood samples for ADA of approximately 4 mL analyses will be collected at the time points specified in Table 8.4. 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 serum samples are included in a separate document (eg, laboratory manual).

Table 8.4: ADA Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	BI (– 8 hours)
	Day 8	± 1 day
Cycle 2	Day 1	BI (– 8 hours)
Every 2 cycles from Cycle 4 (eg, Cycle 4, 6, 8, 10, 12...)	Day 1	BI (– 8 hours)
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days).
40-Day F/U*	-	40 days (+ 7 days) after the last study drug administration or until starting new anticancer treatment, whichever comes first.

BI = before infusion, EOT = end of treatment, F/U = follow-up.
For subjects with positive ADA at 40-Day F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.

8.7. SARS-CoV-2 Serum samples collection

Portion of ADA blood sample will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 7.0 is applied for a subject. Samples will be sent to the central laboratory and stored until the tests will become available.

8.8. Pharmacogenomic Analysis

Not applicable.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

Safety endpoints will include SAEs, TEAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic assessments. TEAEs will be graded according to the NCI-CTCAE version 4.03.

9.2. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.4.1 for definitions) occurring after the subject signs the Informed Consent Form and up to the 40-Day F/U visit (+7 days), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event CRF page. 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 and SAEs are to be reported according to the procedures in Section 9.5.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal 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 Informed Consent Form) 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. Progression of an underlying disease (tumor) will be handled as follows:

- Disease progression (enlargement of measurable/non-measurable lesions, appearance of new lesions) will not be handled as an AE. However when a subject dies and no proximal cause of death other than disease progression can be determined, "disease progression" should be reported as an SAE with a fatal outcome. If a fatal event is identified due to disease progression, the event should be captured.
- An increase in the value of a tumor marker will not be regarded as an AE/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.

9.3. Adverse Events of Special Interest

For the DS-8201a clinical program, based on the available pre-clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, Interstitial lung disease and LVEF decreases are considered to be adverse events of special interest (AESI).

Additional relevant information regarding the AESIs for the DS-8201a clinical program regardless of seriousness is to be collected through the targeted questionnaires built within the eCRF in the clinical study database. In the event that eCRF is unavailable, report AESIs on a paper form. Once eCRF becomes available, please enter AESIs reported on the paper form into eCRF as soon as possible.

For broad surveillance of LVEF decrease, relevant AEs under the MedDRA SMQs of Cardiac Failure is included for enhanced data collection; additional data for these AEs are collected via TQs of heart failure.

For broad surveillance of ILD/pneumonitis, selected 42 Preferred Terms (PT) [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure are included for enhanced data collections.

9.3.1. Interstitial Lung Disease/Pneumonitis

Clinical Summary:

As of 13 Dec 2017, three 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 two studies, ILD/pneumonitis data has been summarized from the DS8201-A-J101 study.

ILD/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 Adjudication Committee (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.

Management Guidance:

ILD/pneumonitis should be ruled out if a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. 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.

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 (infectious disease consultation as clinically indicated), blood culture and CBC (other blood tests could be considered as needed), bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered, pulmonary function tests and pulse oximetry (SpO_2), arterial blood gases if clinically indicated, and one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed.

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

9.3.1.1. Interstitial Lung Disease Adjudication Committee

An independent ILD AC 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 collection will cover a more in-depth relevant medical history (eg, smoking, radiation, COPD and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for adverse events reported using selected 42 PTs [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure.

9.3.2. LVEF Decrease

Clinical Summary:

LVEF decrease 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. Refer to the current IB for a summary of preliminary clinical trial data.

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 EOT 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.

9.4. 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 (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 SAE is any untoward medical occurrence that at any dose:

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

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

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

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the Informed Consent Form) 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 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 vs. Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness of an event is based upon a universal and global Regulatory definition for reporting SAEs to regulatory agencies. For example, the NCI-CTCAE grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria. 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 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 adverse event itself is still present and observable.
- Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.

- Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- Unknown

9.5. Serious Adverse Events Reporting–Procedure For Investigators

All AEs, SAEs, AEs of special interest and medication errors including overdose will be reported in the CRF.

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)
- All potential ILD/pneumonitis cases should be reported within 24 hours; including both serious and non-serious potential ILD/pneumonitis cases (potential ILD/pneumonitis is defined by the Event Adjudication Site Manual List of PTs).
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥ 3 x ULN and an elevated TBL > 2 x ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is built as an eCRF to collect relevant additional information for these potential cases.
- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either a serious adverse event, a non-serious adverse event, or no adverse event occurs and is considered by the Investigator as clinically relevant, i.e. poses an actual or potential risk to the subject.
  - Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including trastuzumab deruxtecan dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the CRF within EDC.

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 site and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. F/U information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each F/U.

In the event that eCRF is unavailable, report SAEs on a Serious Adverse Event Report (SAVER) form. All completed SAVER forms must be signed by the Investigator, and e-mailed or faxed to the CRO using the provided fax transmittal form 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.

See Section 15.10.3 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/Ethics Committees (IRBs/ECs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study sites or other studies of the study drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

9.7. Exposure In Utero During Clinical Studies

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

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject 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 or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The following items will be measured. For clinical laboratory parameters, the reference range of the institution that performs the measurements will be used.

Information will be entered in the case report form (CRF) on whether measured, date of measurement, and measurement results for the following items.

Laboratory tests	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	Total protein, albumin, ALP, ALT, AST, TBL, blood urea nitrogen, Ca, Cl, serum creatinine, lactate dehydrogenase, K, Na, Mg

Creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation.

In addition, the following parameters will be analyzed at the visits indicated in Section 17.7 .

- Urinalysis test including protein, glucose, blood, microscopy assessments (if indicated), and specific gravity must be performed during the Screening Period.
- Prothrombin time and activated partial thromboplastin time must be performed during the Screening Period.
- 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.
- HIV antibody test must be performed during the Screening Period.
- Troponin (preferably high-sensitive troponin-T) test must be performed at the visits indicated in Table 8.3. Same assay should be used for the subject throughout their study participation.

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 and pulse rate and body temperature. Additionally, SpO_2 will be measured before administration on Day 1 of each cycle and EOT.

9.10. Electrocardiograms

Standard ECG parameters including RR, PR, QT intervals, and QRS duration will be measured using identical equipment with standardized procedures, both of which were provided by a third-party ECG central laboratory. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. All ECG data will be transmitted to the central laboratory, and a hard copy of each ECG should be printed locally and retained at the site with the source documentation.

The triplicate 12-lead safety ECGs will be performed at the time points specified in Table 9.1 in close succession, no more than approximately 2 min apart, and after at least 10 min of quiet rest in the supine position.

Note: Any study procedures such as blood sampling are not allowed during quiet rest and prior to ECG measurement. Before electrodes are removed, the electrode position is to be marked on the skin with indelible ink and the same electrode position used for all subsequent ECGs during confinement for each subject.

Table 9.1: ECG Measurement Time Points

Cycle	Day	Measurement Time Point (Acceptable Range of ECG measurement start time)
Screening	-	Within 7 days before enrollment
Cycle 1	Day 0 (within 3 days before Day 0)	15 minutes before the planned start time of administration on Cycle 1, Day 1 (± 10 minutes) 30 minutes after the planned start time of administration on Cycle 1, Day 1 (± 10 minutes) 2 hours after the planned start time of administration on Cycle 1, Day 1 (± 10 minutes) 4 hours after the planned start time of administration on Cycle 1, Day 1 (± 10 minutes) 7 hours after the planned start time of administration on Cycle 1, Day 1 (± 10 minutes)
	Day 1	15 minutes BI (± 10 minutes) 2 hours after the start of administration (± 10 minutes) 4 hours after the start of administration (± 10 minutes) 7 hours after the start of administration (± 10 minutes)
	Day 8	7 days after the start of administration (± 1 day)

Cycle	Day	Measurement Time Point (Acceptable Range of ECG measurement start time)
	Day 15	14 days after the start of administration (± 1 day)
Cycle 2	Day 1	BI (within 3 days before administration)
Cycle 3	Day 1	15 minutes BI (± 10 minutes) EOI (within 15 minutes) 2 hours after the start of administration (± 10 minutes) 4 hours after the start of administration (± 10 minutes) 7 hours after the start of administration (± 10 minutes)
	Day 8	7 days after the start of administration (± 1 day)
	Day 15	14 days after the start of administration (± 1 day)
After Cycle 4	Day 1	BI (within 3 days before administration)
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days).

BI = before infusion, EOT = end of treatment.

9.10.1. Central review

In addition to evaluation by Investigator, ECGs at Screening, Cycle 1, Cycle 2 and Cycle 3 will be reviewed by a suitably-qualified cardiologist in the central laboratory. In the review, information such as demographics and time point will be blinded.

The detail procedures for the review are included in a separate document.

9.11. Physical Examinations

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

9.12. Other Examinations

Either ECHO or MUGA, and ophthalmologic assessments will be performed as described in the schedule of events. LVEF will be measured by either ECHO or MUGA. Ophthalmologic assessments will include visual acuity testing, slit lamp examination, and fundoscopy. All ECHOs/MUGAs, and the ophthalmologic assessments must be evaluated by the Investigator or delegated physician. Additional safety assessments should be conducted as needed, at the Investigator's discretion.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or completed at least 3 cycles, whichever comes first. After the primary analysis, the main study will be closed and the data will be followed until completion.

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

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

Safety analyses will be performed based on the safety analysis set. ECG analyses will be performed based on the cardiac safety analysis set. Analysis of PK parameters will be based on the PK analysis sets and biomarker analyses will be based on the biomarker analysis sets. Efficacy endpoints will be analyzed based on the efficacy analysis set.

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

11.2. Analysis Sets

11.2.1. Enrolled Analysis Set

The enrolled analysis set will include all subjects who signed an ICF and were enrolled in the study.

11.2.2. Efficacy Analysis Set

The efficacy analysis set will include all subjects enrolled in the study who received at least one dose of DS-8201a and who had pre- and post-treatment efficacy data.

11.2.3. Safety Analysis Set

The safety analysis set will include all subjects enrolled in the study who received at least one dose of DS-8201a.

11.2.4. Cardiac Safety Analysis Set

The cardiac safety analysis set will include all subjects enrolled in the study who received at least one dose of DS-8201a, had time-matched baseline and post-treatment ECG data and didn't receive QTc prolongation drugs.

11.2.5. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the enrolled analysis set who received at least one dose of DS-8201a and had measurable serum concentrations of DS-8201a.

11.2.6. Biomarker Analysis Set

The biomarker analysis set will include all subjects in the enrolled analysis set who received at least one dose of DS-8201a and who had the baseline assessment and where applicable, at least one post-baseline assessment for biomarkers.

11.3. Study Population Data

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

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

11.4. Statistical Analysis

11.4.1. Primary Analyses

The primary endpoints include baseline-adjusted QTcF interval, serum concentration and PK parameters of DS-8201a, total anti-HER2 antibody, and MAAA-1181a.

11.4.1.1. QTc Prolongation Analyses

The QT intervals will be corrected for heart rate by Fridericia's formula ($QTcF = QT/[RR]^{1/3}$). The baseline QTcF interval for each subject will be subtracted from QTcF interval to create a baseline-adjusted QTcF interval for each subject at each time point (Cycle 1 to 3). The primary analysis for the baseline-adjusted QTcF will be performed based on the cardiac safety analysis set.

The baseline-adjusted QTcF will be averaged across subjects at each time point and a pointwise two-sided 90% confidence interval (CI) will also be calculated. If the upper limit of the one-side 95% CI for the calculated mean baseline-adjusted average QTcF interval <10 ms at each time point, the effect on QTc interval will be considered clinically insignificant. The subjects with ADA's will be included for this analysis.

The descriptive statistics will be provided for ECG parameters (eg. HR, PR, QRS and RR) and changes from time-matched baseline by scheduled time of evaluation, including the EOT visit and the maximum post-treatment value. In addition, the number and

percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc ≤ 450 ms, > 450 to ≤ 480 ms, > 480 ms to ≤ 500 ms, and > 500 ms).

Relationship between drug concentrations and QTcF will also be explored.

11.4.1.2. Pharmacokinetic Analyses

The primary analysis for serum concentration and PK parameters of DS-8201a, total anti-HER2 antibody, and MAAA-1181a, will be performed based on the PK analysis set. Serum concentration-time data for DS-8201a, total anti-HER2 antibody and MAAA-1181a will be listed, plotted, and summarized using descriptive statistics at each time point.

PK parameters of DS-8201a, total anti-HER2 antibody and MAAA-1181a will be listed and summarized using descriptive statistics.

The pop-PK models which were constructed using PK data from the Phase 1 study (DS8201-A-J101) will be updated to evaluate the effect of intrinsic and extrinsic factors on PK of DS-8201a and MAAA-1181a. After establishment of the pop-PK model, a exposure-response model will be updated to evaluate the relationship between exposure and efficacy and toxicity. The results of population PK analyses will be reported separately (ie, not in the Clinical Study Report).

11.4.2. Safety Analyses

Safety endpoints will be based on AEs, physical examination findings, vital sign measurements, clinical laboratory measurements, ECG recordings, ADA, ECHO/MUGA findings, and ophthalmologic findings. AEs will be graded according to the NCI-CTCAE version 4.03.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

11.4.2.1. Adverse Event Analyses

A TEAE is defined as an AE that emerges during the treatment period (from first dose date until 40-Day F/U visit), having been absent at pre-treatment; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pre-treatment state, when the AE is continuous.

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

Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs/SAEs considered related to DS-8201a.

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

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from DS-8201a, will be listed.

11.4.2.2. Clinical Laboratory Evaluation Analyses

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

Abnormal laboratory results will be graded according to NCI-CTCAE version 4.03, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

11.4.2.3. Vital Sign Analyses

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

11.4.2.4. Anti-drug Antibodies Analyses

A shift table, presenting the 2-way frequency tabulation for baseline and each schedules time, including the EOT Visit, will be provided for incidence of ADA.

11.4.2.5. Other Safety Analyses

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

11.4.3. Efficacy Analyses

Efficacy endpoints will include ORR (the sum of CR and PR rates); DCR (the sum of CR rate, PR rate, and SD rate for a minimum of 5 weeks from the first dosing date), CBR (the proportion of subjects who achieved a best overall response of CR or PR or more than 6 months SD), DoR, duration of SD, TTR, PFS, OS, and percent change in target lesion using RECIST 1.1.

The efficacy endpoints will be listed and summarized. For ORR, DCR and CBR, point estimates and 95% exact binomial CIs will be provided. Time to event variables including duration of response, duration of SD TTR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method.

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 objective documentation of radiographic PD. Duration of response will be measured for responding subjects (CR or PR) only. Duration of SD is defined for subjects whose best response is SD as the time from the date of the first dose to the date of the first documentation of PD. TTR is defined as the time from the date of the first dose to the date of the first documentation of objective response (CR or PR). Detailed censoring rules for DoR, duration of SD, and TTR will be specified in the SAP.

PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic PD or death due to any cause. Censoring rules for the PFS analysis will be specified in the SAP. The growth modulation indices (the intrasubject ratio of PFS post-study treatment versus PFS post the most recent prior therapeutic regimen) will be summarized.

OS is defined as the time from the date of the first dose 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.

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

11.4.4. Pharmacodynamic/Biomarker Analyses

11.4.4.1. Pharmacodynamic Analyses

Not applicable.

11.4.4.2. Biomarker Analyses

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

11.4.4.3. Pharmacogenomic Analyses

Not applicable.

11.5. Interim Analyses

No formal interim analysis is planned.

11.6. Sample Size Determination

The sample size of 50 subjects was chosen to secure enough probability of observing the upper bound of the two-sided 90% CI for the baseline-adjusted QTcF interval < 10 ms. From the results of the T-DM1 phase 2 study (TDM4688g), SD of the baseline-adjusted QTcF interval was estimated as approximately 15 ms. Assuming that the expected baseline-adjusted QTcF interval is 0 ms and the SD is 15 ms, the sample size of 50 subjects provides 99.9% probability that the upper bound of the two-sided 90% CI for the baseline-adjusted QTcF interval < 10 ms. Thus, the probability of observing the upper bound of the two-sided 90% CI for the baseline-adjusted QTcF interval < 10 ms for all time points (total of 14 time points) is more than 90%.

The probability values for the sample size are derived based on binomial distribution using SAS® version 9.3.

11.7. Statistical Analysis Process

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

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

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

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

12. DATA INTEGRITY AND QUALITY ASSURANCE

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, CRFs, source data, and other pertinent documents).

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

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

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

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

12.2. Data Collection

Daiichi Sankyo or a designee will supply eCRFs. An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the EDC software's "audit trail."

Completion of the eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. All information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. The eCRF will be completed, reviewed and signed off or e-signed by the Investigator. 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.

12.3. Electronic Data Capture System

The EDC system used for completing eCRF in this study is shown below.

Name of EDC system	**Medidata Rave®**
EDC system developer	Medidata Solutions Inc.
Entry method	Web-based data entry
Input terminal	Desktop/laptop computer at the study site
Incompatible operating systems	None
Recommended browsers	The Medidata Rave® supports any browser which is HTML 5 and CSS2 compliant. Browsers must have JavaScript enabled.
Screen Resolution	The minimum screen resolution required to properly display Medidata Rave applications is 1024 x 764.
Connection Speed	128kbps is the minimum connection speed recommended for using Medidata Rave.
Other	Adobe Flash Player : ver. 10 or above is required

12.4. 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 sites, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor or CRO. Data will be vetted both electronically and manually for CRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies. CRFs queries will be raised and resolved within the EDC application.

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

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

All Adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All concomitant medications and prior cancer therapies will be coded using World Health Organization Drug Reference (WHODRUG) List.

12.5. Study Documentation and Storage

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

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

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

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

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

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.6. 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 contained in the Trial Master File 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 site, 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.

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

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

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

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. 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 Council for 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, Labour and Welfare (MHLW) Ordinance No. 28 of 27 March, 1997 and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics of 25 November, 2014 and/or;
- Other applicable local regulations.

Additional information for Japanese study sites

This study will be conducted in compliance with the standards stipulated in Article 14-3 and Article 80-2 of the Pharmaceutical and Medical Device Act and by the "Ordinance Regarding Good Clinical Practice" (MHLW Ordinance No. 28, dated 27 Mar 1997). In compliance with the ethical principles of the Declaration of Helsinki, the human rights, welfare, and safety of the subjects will be the first considerations in the conducting of this study.

15.2. Subject Confidentiality

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

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject 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(s), and the IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific 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.

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

15.4. 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 Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing and approving the Final Clinical Study Report and testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those Investigators who have enrolled and treated at least one subject. However, where an Investigator has special knowledge of the field or of the trial, the Coordinating Investigator can be chosen prior to enrolment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

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 site 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. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory authorities and implementation of these changes happen only after approval by the relevant regulatory bodies, as required.

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

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

15.5. Protocol Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the 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 or 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 Independent Ethics Committee (IEC)/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 sites 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 site(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 the study termination may also be requested by (a) competent authority/ies.

15.9. Data and Safety Monitoring Board

Not applicable.

15.10. Address List

A list of key study personnel (including personnel at the sponsor, CRO, laboratories, and other vendors) and their contact information (address, telephone, fax, email) will be kept on file and regularly updated as necessary.

15.10.1. Sponsor's Responsible Medical Officer

PPD

Shonan Tobu Sougou Hospital
500 Nishikubo, Chigasaki, Kanagawa 253-0083, Japan
PPD (representative)
PPD (representative)

15.10.2. Sponsor's Clinical Study Leader

PPD

3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan
PPD
PPD
PPD

15.10.3. Sponsor's Safety Contacts

PPD

3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426, Japan
PPD
PPD
PPD

PPD

3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426, Japan
PPD
PPD
PPD

15.10.4. ARO

Not applicable.

15.10.5. CROs

CMIC Co., Ltd.
1-1-1, Shibaura, Minato-ku, Tokyo, 105-0023, Japan
PPD
PPD

15.10.6. IXRS Vendor

Almac
25 Fretz Road Souderton, PA 18964
PPD
PPD

15.10.7. EDC Vendor

Medidata Solutions, Inc.
350 Hudson Street, 9th Floor, New York, New York 10014, USA
PPD
PPD

15.10.8. EDC System Support

Fujitsu Limited
Shinagawa season terrace 1-2-70 Konan, Minato-ku, Tokyo 108-0075 Japan
PPD
PPD

15.10.9. Central Laboratory

Covance Inc.
8211 SciCor Drive
Indianapolis, IN 46214
PPD
PPD

15.10.10. Bioanalytical Laboratory (PK and ADA)

PPD
2244 Dabney Road, Richmond, VA 23230, USA
PPD
PPD

15.10.11. ECG Central Laboratory

Bioclinica Inc.
211 Carnegie Center, Princeton, NJ 08540, USA
PPD
PPD

15.10.12. Sponsor's Biostatistician

PPD
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
PPD
PPD
PPD

15.10.13. Data Safety Monitoring Board

Not applicable.

15.10.14. SARS-CoV-2 Assessment (RT-PCR test)

Covance Inc.
8211 SciCor Drive
Indianapolis, IN 46214
PPD
PPD

16. REFERENCES

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17. APPENDICES

17.1. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCL; mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight in kilograms (1 kilogram = 2.2 pounds):

Conventional – serum creatinine in mg/dL:

Male:

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

Female:

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

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

Male:

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

Female:

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

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

17.2. Eastern Cooperative Oncology Group Performance Status Scale

GRADE	DESCRIPTION
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work

GRADE	DESCRIPTION
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, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):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 and in F/U, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

17.3.1.1.2. 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 of the first dose of study drug administration.

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 F/U. Imaging based evaluation

should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

17.3.2. 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.

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 $\geq$ 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 $\geq$ 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 characterise 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 quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease: The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment

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

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

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

17.3.2.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the EOT. No 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 17.1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, Table 17.2 is to be used.

Table 17.1: Overall Response: Subjects with Target (+/–Non-target) Disease

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

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

Table 17.2: Overall Response: Subjects with Non-target Disease Only

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

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

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

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

17.3.2.4.4. 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.

17.3.2.5. Frequency of Tumor Re-evaluation

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

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

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

The radiographic evaluation must include CT or MRI scanning of the brain, chest, abdomen, and pelvis at screening period. Any additional suspected sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. However, if there is no brain metastasis at the time

of screening, CT or MRI should only be done when symptoms associated with brain metastasis occur during study period. If no clinical symptoms are observed, brain CT or MRI is not mandatory during study period. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

17.4. 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. Supplement List

Supplements are prepared separately from protocol, and their versions are independent from protocol.

Supplement 6 is a Japan-specific document. This will be prepared in Japanese language and only submitted for Japanese site's IRB.

Supplements are listed as follow:

- Supplement 1: Serious Adverse Event Report (SAVER) form
- Supplement 2: Exposure in Utero (EIU) Reporting Form
- Supplement 3: The list of QT prolongation drugs
- Supplement 4: The list of CYP3A4 strong inhibitors and OATP inhibitors
- Supplement 5: Not applicable
- Supplement 6: Additional information

17.6. Instructions related to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Due to the potential impact of SARS-CoV-2, ie COVID-19, on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected SARS-CoV-2 while being treated with DS-8201a. Dose modifications will be based on the worst CTCAE grade. All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

17.6.1. Dose modification criteria for suspected or confirmed COVID-19

If SARS-CoV-2 infection is suspected, interrupt DS-8201a and rule out SARS-CoV-2 per local guidance.

- If SARS-CoV-2 is confirmed or is still suspected after evaluation follow dose modification as outlined in Table 17.3 below and manage SARS-CoV-2 per local guidance until recovery of SARS-CoV-2. SARS-CoV-2 recovery is defined as no signs/symptoms of SARS-CoV-2, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

Table 17.3: SARS-CoV-2 Dose Modification Criteria

SARS-CoV-2 Worst Toxicity NCI-CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for DS-8201a
Grade 1	Resume study drug at the same dose[a]
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved[a] Reduce by 1 dose level if chest CT findings are nearly resolved
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved Discontinue study drug if chest CT findings are **not** completely resolved
Grade 4	Discontinue study drug

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); CT = computed tomography

[a] Closely monitor signs/symptoms after resuming DS-8201a, initially with a phone call every 3 days for the first week, and then with a weekly phone call thereafter, for a total of 6 weeks.

In addition to the recommendations outlined in Table 17.3, investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 5.2).

17.6.2. Prior and Concomitant Medications

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 5.6.1).
  - If treatment is absolutely required for SARS-CoV-2, DS-8201a must be interrupted.
  - If administered, then a washout period of no less than 14 days is required before resumption of DS-8201a.

17.6.3. PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected, if chloroquine or hydroxychloroquine is administered for SARS-CoV-2 infection, at the time points specified in Table 8.2.

The chloroquine or hydroxychloroquine administration time and the exact time of blood sample collection for PK analysis must be recorded on the eCRF.

17.6.4. SARS-CoV-2 Assessment(s)

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of SARS-CoV-2, but the real-time RT-PCR test is not available at the site, a sample kit will be provided for sample collection to be tested at a central laboratory.

Serum samples will be used for SARS-CoV-2 testing from each subject who provides consent. Samples will be collected prior to the study drug infusion, shipped to a central laboratory, and stored there until the tests become available.

If subjects consent, the remaining serum samples will also be stored for future analysis.

17.6.5. Statistical Analysis - Assessment of the Impact of SARS-CoV-2

If deemed appropriate, analyses will be performed to explore the impact of SARS-CoV-2 on safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of SARS-CoV-2 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the statistical analysis plan

17.7. Schedule of Events

Table 17.4: Schedule of Events

	SCR	Cycle 1								Cycle 2					Cycle 3							Cycle 4 and subsequent cycles		Cycle 5 and subsequent cycles		EOT[a]	40D F/U[b]	NCT and SU F/U
Day [Allowance (±)]		0	1		2	4	8 [1]	15 [1]	(22) [2]	1 [2]		8 [2]	15 [2]	22 [2]	1 [2]		2	4	8 [1]	15 [1]	(22) [2]	1 [2]		1 [2]					
			BI	EOI						BI	EOI				BI	EOI						BI	EOI	BI	EOI			
Informed consent	X																											
Demographic information	X																											
Inclusion/ Exlusion Criteria	X																											
Urinalysis test	X[d]																											
HIV antibody test	X[c]																											
Pregnancy test	X[d]																								X	X		
IHC/FISH (tumor sample)	X																											
Administer DS-8201a			X							X					X							X		X				
Height	X																											
Weight, ECOG PS	X[d]		X[e]							X[e]					X[e]							X[e]		X[e]		X	X	
Vital sign	X[d]		X[e]	X	X	X	X	X		X[e]	X	X	X		X[e]	X	X	X	X	X		X[e]		X[e]		X	X	
Physical examination	X[d]		X[e]							X[e]					X[e]							X[e]		X[e]		X	X	
SpO_2			X[e]							X[e]					X[e]							X[e]		X[e]		X	X	

	SCR	Cycle 1								Cycle 2					Cycle 3							Cycle 4 and subsequent cycles		Cycle 5 and subsequent cycles		EOT[a]	40D F/U[b]	NCT and SU F/U
Day [Allowance (±)]		**0**	**1**		**2**	**4**	**8 [1]**	**15 [1]**	**(22) [2]**	**1 [2]**		**8 [2]**	**15 [2]**	**22 [2]**	**1 [2]**		**2**	**4**	**8 [1]**	**15 [1]**	**(22) [2]**	**1 [2]**		**1 [2]**				
			BI	**EOI**						**BI**	**EOI**				**BI**	**EOI**						**BI**	**EOI**	**BI**	**EOI**			
Ophthalmologic assessments	X[f]									X[e]																X		
Tumor assessment	X[f]	Every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1, and thereafter every 12 weeks (± 7 days)																								X		
Laboratory tests	X[d]		X[e]		X		X	X		X[e]		X	X		X[e]		X		X	X		X[e]		X[e]		X	X	
prothrombin time, activated partial thromboplastin time	X[d]																											
ADA			X[h]				X			X[h]												X[hi]				X	X	(X)[j]
Troponin	X[d]			X[k]							X[k]					X[k]										X		
12-lead ECG in triplicate	X[d]	X[l]	X[m]	X[n]			X	X		X[e]					X[m]	X[o]			X	X		X[e]		X[e]		X		
PK			X[p]	X[q]	X[r]	X[r]	X[p]	X[p]	(X)[s]	X[h]	X[t]			(X)[s]	X[p]	X[u]	X[r]	X[r]	X[p]	X[p]	(X)[s]	X[hv]	X[tv]		(X)[sy]			
ECHO or MUGA	X[f]									X[e]					X[e]									X[ew]		X		
AEs	X[z]																											
Concomitant medications	X																											
New cancer treatment and Survival																												X[x]

SCR: screening, BI: before infusion, EOI: end of infusion, EOT: end of treatment, 40D F/U: 40-Day follow-up, NCT: new cancer treatment, SU: survival

[a] The date Investigator decides the discontinuation of the study treatment (+ 7 days).

[b] 40 days (+ 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first.

[c] Latest data within 90 days before enrollment.
[d] Latest data within 7 days before enrollment.
[e] Latest data within 3 days before administration.
[f] Latest data within 28 days before enrollment.
[h] Within 8 hours BI.
[i] Every 2 cycles until the EOT (eg, Cycle 4, 6, 8, 10, 12...). A portion of ADA blood sample will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 7.0 is applied for a subject. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 4 (Cycle 4, Cycle 8 etc.).
[j] For subjects with positive ADA at 40D F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
[k] Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2-3 hours after EOI. If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines. 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), repeat troponin testing at 3 hours (± 1 hour) after initial troponin test was drawn. If troponin level at 3 hours (6 hours post-infusion):Significantly increases per institutional guidelines, then perform ECG testing, repeat troponin testing at 6 hours (± 1 hour) and follow institutional guidelines. Otherwise, repeat troponin testing at 6 hours (± 1 hour) or at 24 hours (± 2 hours) after initial troponin test. 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.
[l] 15 minutes before the planned start time of administration on Cycle 1, Day 1 (± 10 minutes), and 30 minutes, 2, 4 and 7 hours after the planned start time of administration on Cycle 1, Day 1 (± 10 minutes).
[m] 15 minutes BI (Acceptable range of ECG measurement start time: ± 10 minutes).
[n] 2, 4 and 7 hours after the start of administration (Acceptable range of ECG measurement start time: ± 10 minutes).
[o] EOI (Within 15 minutes) and 2, 4 and 7 hours after the start of administration (Acceptable range of ECG measurement start time: ± 10 minutes).
[p] Within 10 minutes after completing ECG measurement.
[q] Within 10 minutes after EOI, and 2, 4 and 7 hours after the start of administration (Within 10 minutes after completing ECG measurement).
[r] 24 and 72 hours after the start of administration (± 2 hours).
[s] 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 for PK analysis.
[t] Within 30 minutes after EOI.
[u] EOI and 2, 4 and 7 hours after the start of administration (Within 10 minutes after completing ECG measurement).
[v] Every 2 cycles until Cycle 8 (eg, Cycle 4, 6, 8). Even if blood sample is collected on Day 22 of Cycle 3, 5 and/or 7, the blood sample will be collected at BI on Day 1 of Cycle 4, 6 and/or 8 if possible.
[w] Every 2 cycles until the EOT (eg, Cycle 5, 7, 9, 11, 13...).
[x] Subjects will be assessed every 3 months (±14 days), from the date of 40-Day F/U visit, for survival and subsequent anticancer therapy until death, withdrawal of consent, lost to F/U or study closure, whichever occurs first.
[y] Cycle 5, Day 22 and Cycle 7, Day 22 only.

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

- high resolution CT
- pulmonologist consultation (infectious disease consultation as clinically indicated)
- blood culture and CBC. Other blood tests could be considered as needed
- consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- pulmonary function tests and pulse oximetry (SpO_2)
- arterial blood gases if clinically indicated
- one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.