

# **CLINICAL STUDY PROTOCOL**

## **PHASE 1, MULTICENTER, OPEN-LABEL STUDY OF DS-8201a TO ASSESS SAFETY AND PHARMACOKINETICS IN SUBJECTS WITH HER2-POSITIVE ADVANCED AND/OR REFRACTORY GASTRIC, GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA, OR BREAST CANCER**

**DS8201-A-A103**

**VERSION 5.0, 03 JUL 2020**

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**DAIICHI SANKYO**

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## INVESTIGATOR AGREEMENT

### PHASE 1, MULTICENTER, OPEN-LABEL STUDY OF DS-8201a TO ASSESS SAFETY AND PHARMACOKINETICS IN SUBJECTS WITH HER2-POSITIVE ADVANCED AND/OR REFRACTORY GASTRIC, GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA, OR 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 Lead

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

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EudraCT:	Not applicable
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IND Number:	Not applicable
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Protocol Number:	DS8201-A-A103
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Investigational Product:	DS-8201a
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Active Ingredient(s)/ INN:	DS-8201a consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component, MAAA-1181a.
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Study Title:	Phase 1, Multicenter, Open-label Study of DS-8201a to Assess Safety and Pharmacokinetics in Subjects With HER2-Positive Advanced and/or Refractory Gastric, Gastroesophageal Junction Adenocarcinoma, or Breast Cancer
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Study Phase:	Phase 1
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Indication Under Investigation:	DS-8201a will be evaluated in subjects with human epidermal growth factor receptor 2 (HER2) positive advanced and/or refractory gastric, gastroesophageal junction (GEJ) adenocarcinoma, or breast cancer.
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Study Objectives:	<p><u>Primary Objective:</u></p> <ol style="list-style-type: none"><li>1. To assess the safety and tolerability of DS-8201a</li></ol> <p><u>Secondary Objectives:</u></p> <ol style="list-style-type: none"><li>1. To assess the pharmacokinetic (PK) profiles of DS-8201a, total anti-HER2 antibody, and MAAA-1181a</li><li>2. To investigate the anti-tumor activity of DS-8201a</li><li>3. To assess the incidence of anti-drug antibodies (ADA) against DS-8201a</li></ol>
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Study Design:	<p>This is a Phase 1, multicenter, open-label study to evaluate the safety and tolerability of DS-8201a in Chinese subjects with HER2-positive advanced and/or refractory gastric, GEJ adenocarcinoma, or breast cancer.</p> <p>Approximately 12 eligible subjects will be enrolled at study sites in Taiwan. The primary analysis will be conducted after all subjects have either discontinued the study or completed at least 4 cycles of the study drug.</p>
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Study Duration:	The expected time from the first subject's enrollment until the last subject's enrollment is approximately 8 months. The
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screening period is 28 days and each cycle of treatment is 21 days.

The number of treatment cycles is not fixed in this study. Subjects who continue to derive clinical benefit from the study drug in the absence of withdrawal of consent, progressive disease (PD), or unacceptable toxicity may continue the study drug.

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Study Sites and Location: This study will be conducted at study sites in Taiwan, Republic of China.

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Subject Eligibility Criteria: **Inclusion Criteria**

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

1. Chinese patients aged  $\geq 20$  years
2. Pathologically documented HER2-positive advanced/unresectable or metastatic gastric, GEJ adenocarcinoma or breast cancer, with both:
  - a. HER2-positive disease documented as: immunohistochemistry (IHC) 3+ positive, and/or fluorescence in situ hybridization (ISH)  $\geq 2.0$  that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. For subject with gastric or GEJ adenocarcinoma cancers, it is preferable to determine HER2 status after completing the last HER2-targeting treatment.
  - b. Documented disease progression (by investigator's assessment) after at least one regimen of trastuzumab therapy in metastatic or unresectable locally advanced/recurrent setting.
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 to 1.
4. Left ventricular ejection fraction (LVEF)  $\geq 50\%$  by either echocardiography (ECHO) or multiple-gated acquisition (MUGA) scan within 28 days before registration.
5. Adequate organ function within 7 days before registration defined as:

Item	Laboratory value
Platelet count	$\geq 100,000/\text{mm}^3$ (platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin (Hb)	$\geq 9$ g/dL (red blood cell transfusion is

	not allowed within 1 week prior to screening assessment)
Absolute neutrophil count (ANC)	$\geq 1500/\text{mm}^3$ (granulocyte colony-stimulating factor administration is not allowed within 1 week prior to screening assessment)
Creatinine	$\leq 1.5 \times$ upper limit of normal (ULN), or creatinine clearance $\geq 60$ mL/min as calculated using the Cockcroft-Gault equation
Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)	$\leq 3 \times$ ULN (if liver metastases are present, $\leq 5 \times$ ULN)
Total bilirubin (TBL)	$\leq 1.5 \times$ ULN or $< 3 \times$ ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline
Prothrombin time and activated partial thromboplastin time	$\leq 1.5 \times$ ULN

6. Adequate treatment washout period before registration, defined as:

Treatment	Washout period
Major surgery	$\geq 4$ weeks
Radiation therapy	$\geq 4$ weeks (if palliative stereotactic radiation therapy excludes abdomen, $\geq 2$ weeks)
Autologous transplantation	$\geq 3$ months
Hormonal therapy	$\geq 2$ weeks
Chemotherapy (including antibody drug therapy and retinoid therapy)	$\geq 3$ 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, and/or weekly paclitaxel. $\geq 6$ weeks for nitrosoureas or mitomycin C)
Immunotherapy	$\geq 4$ weeks

Cytochrome P450 (CYP) 3A4 strong inhibitor and inducer	$\geq 3 \times$ elimination half-lives of the inhibitor
Organic anion transporting polypeptide (OATP1B1) inhibitor	$\geq 3 \times$ elimination half-lives of the inhibitor

7. Life expectancy of at least 3 months.
8. Subjects should be able to provide written informed consent. Subjects 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 informed consent form (ICF) before performance of any study-specific procedures or examinations.
9. Subjects should be willing to provide pre-existing diagnosis of HER2 status.
10. 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 4.5 months for males after the last dose of study drug. Methods considered as highly effective methods of contraception include:
  - a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - i. Oral
    - ii. Intravaginal
    - iii. Transdermal
  - b. Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - i. Oral
    - ii. Injectable
    - iii. Implantable
  - c. Intrauterine device
  - d. Intrauterine hormone-releasing system
  - e. Bilateral tubal occlusion
  - f. Vasectomized partner
  - g. 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 4.5 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-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone >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 the 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 the HRT. Following confirmation of their post-menopausal status, they can resume use of the HRT during the study without use of a contraceptive method.

11. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4.5 months after the final study drug administration. Preservation of sperm should be considered prior to enrolment in this study.
12. 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.

### **Exclusion Criteria**

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

1. Medical history of myocardial infarction within 6 months before enrollment, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV), troponin levels consistent with myocardial infarction as defined according to the manufacturer 28 days prior to randomization.
  2. Corrected QT interval (QTcF) prolongation to >450 ms in males and >470 ms in females based on 12-lead electrocardiograms (ECGs) performed in triplicate.
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3. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
  4. Has any evidence of severe or uncontrolled systemic diseases (including uncontrolled hypertension, and active bleeding diatheses or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV), psychiatric illness/social situations, substance abuse, or other factors which in the Investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.
  5. Have clinically significant corneal disease in the opinion of the investigator.
  6. Subjects who are pregnant (as confirmed by pregnancy tests performed within 7 days before registration) or breastfeeding, or planning to become pregnant.
  7. Have spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids 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 study enrollment.
  8. Has a history of severe hypersensitivity reactions to other monoclonal antibodies and/or to either the drug substances or inactive ingredients in the drug product.
  9. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, Grade  $\leq 1$  at baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator after consultation with the Sponsor medical monitor or designee (eg, Grade 2 chemotherapy-induced neuropathy).
  10. Presence of other primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors, or contralateral breast cancer.
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Dosage Form, Dose and Route of Administration:	<ul style="list-style-type: none"><li>• DS-8201a for injection 100mg will be provided as a sterile lyophilized powder containing 100 mg of DS-8201a in a glass vial (Lyo-DP).</li><li>• DS-8201a will be administered with 5% Dextrose as an intravenous (IV) infusion. Subjects will receive 6.4 mg/kg of DS-8201a on Day 1 of each cycle, once every 3 weeks [Q3w].</li></ul>
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Study Endpoints:

**Safety Endpoints**

- Primary safety endpoints will include serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), and adverse events (AEs) and adverse events of special interest (AESIs) leading to discontinuation.
- Other safety endpoints will include physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO or MUGA findings, and ophthalmologic findings. TEAEs will be graded according to the NCI-CTCAE version 4.03.
- ADA against DS-8201a will be assessed as a secondary safety endpoint.

**Pharmacokinetic Endpoints**

- Serum concentrations and PK parameters of DS-8201a, total anti-HER2 antibody, and MAAA-1181a.

**Efficacy Endpoints**

- Objective response rate (ORR)
- Disease control rate (DCR)
- Duration of response (DoR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Best percentage change in the sum of diameter(s) of target lesion(s)

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Planned Sample Size:	Approximately 12 subjects will be allocated to the selected dose level. The sample size of 12 subjects will provide the safety and tolerability data in Chinese subjects.
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Statistical Analyses:	The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or completed at least 4 cycles of the study drug.
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**Safety Analysis**

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All safety analyses and analysis of ADA will be performed on safety analysis set (which includes all subjects who have received at least 1 dose of DS-8201a).

Safety endpoints will include AEs, SAEs, TEAEs, AEs and AESIs leading to discontinuation, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO or MUGA findings and ophthalmologic assessments. TEAEs 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 appropriate summary statistics.

ADA assessment data will be listed and summarized as appropriate.

### **Pharmacokinetic Analyses**

The PK analyses will be performed on the PK analysis set using actual sample times and noncompartmental methods.

Cycle 1 is considered the single dose and Cycle 3 the multiple dose. PK parameters will be estimated for both cycles. The PK parameters of DS-8201a, total anti-HER2 antibody, and MAAA-1181a (AUClast, AUC<sub>0-21d</sub>, C<sub>max</sub>, T<sub>max</sub>, C<sub>trough</sub>, and if applicable, AUC<sub>inf</sub>, K<sub>el</sub>, T<sub>1/2</sub>, CL, V<sub>z</sub>, and V<sub>ss</sub>) will be listed and summarized using descriptive statistics. Descriptive statistics will also be provided for all serum concentration data.

### **Efficacy Analyses**

The efficacy analyses will be performed on the efficacy analysis set (all subjects who have received at least 1 dose of DS-8201a and had both pre- and post-treatment efficacy assessment data).

Efficacy endpoints will include ORR (the proportion of subjects who achieve a best overall response of complete response [CR] or partial response [PR]) and DCR (the proportion of subjects who achieve a best overall response of CR or PR or stable disease [SD]), DoR, PFS based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, OS, and best percentage change in the sum of diameter of target lesion(s). The point estimate of ORR and its two-sided corresponding 95% exact binomial confidence interval (CI) will be provided. The analysis of the DCR will be performed in the same manner as the ORR analysis. DoR, PFS, and OS will be summarized using the Kaplan-Meier method with median event time and two-sided 95% CI for the median. Descriptive statistics for the best percentage change in the sum of diameter(s) of target lesion(s) will be provided. A waterfall plot of the best percentage change from Screening in the sum of longest dimensions (SLD) for each subject will be presented.

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## LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BI	before infusion
BSEP	bile salt export pump
CDISC	Clinical Data Interchange Standards Consortium
CHF	congestive heart failure
CHO	Chinese hamster ovary
CI	confidence interval
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DLCO	diffusing capacity of the lungs for carbon monoxide
DoR	duration of response
ECG	electrocardiogram
ECHO	echocardiography
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
F/U	follow-up

<b>ABBREVIATION</b>	<b>DEFINITION</b>
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GPP3	Good Publication Practice for Communicating Company Sponsored Medical Research
Hb	hemoglobin
HER	human epidermal growth factor receptor
hERG	human ether-à-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
ICMJE	International Committee of Medical Journal Editors
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	investigational new drug
INN	international non-proprietary name
IRB	institutional review board
ISMPP	International Society for Medical Publication Professionals
IV	intravenous(ly)
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	inevaluable
OAT	organic anion transporting
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
ORR	objective response rate

<b>ABBREVIATION</b>	<b>DEFINITION</b>
OS	overall survival
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PR	partial response
PT	Preferred Term
Q3w	once every 3 weeks
QTc	corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
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
SD	stable disease
SLD	sum of longest dimensions
SOC	System Organ Class
SOP	standard operating procedure
SpO <sub>2</sub>	peripheral oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV	ultraviolet

#### List of Pharmacokinetic Parameters

<b>ABBREVIATION</b>	<b>DEFINITION</b>
AUC	area under the plasma/serum concentration-time curve
AUC <sub>inf</sub>	area under the plasma/serum concentration-time curve up to infinity
AUC <sub>last</sub>	area under the plasma/serum concentration-time curve up to the last quantifiable concentration
AUC <sub>tau</sub>	area under the plasma/serum concentration-time curve during dosing interval

ABBREVIATION	DEFINITION
AUC <sub>0-21d</sub>	area under the s plasma/erum concentration-time curve from time zero to 21 days.
CL	total body clearance
C <sub>max</sub>	maximum plasma/serum concentration
CrCl	creatinine clearance rate
C <sub>trough</sub>	trough plasma/serum concentration
IC <sub>50</sub>	50% inhibitory concentration
K <sub>el</sub>	elimination rate constant associated with the terminal phase
T <sub>max</sub>	time to reach maximum plasma/serum concentration
T <sub>1/2</sub>	terminal elimination half-life
V <sub>ss</sub>	volume of distribution at steady state
V <sub>z</sub>	volume of distribution based on the terminal phase

### List of Terminology

TERM	DEFINITION
DS1	drug substance manufactured using MAAL-9001 produced in CHO <span style="background-color: black; color: red;">CCI</span>
DS2	drug substance manufactured using MAAL-9001 produced in CHO <span style="background-color: black; color: red;">CCI</span>
Lyo-DP	sterile lyophilized powder containing 100 mg of DS-8201a in a glass vial
MAAA-1162a	drug-linker, the complex of MAAA-1181a and a maleimide tetrapeptide linker
MAAA-1181a	the drug component of DS-8201a – a derivative of exatecan, a topoisomerase I inhibitor
MAAL-9001	the antibody component of DS-8201a – a recombinant humanized anti-HER2 IgG1 monoclonal antibody produced in-house with reference to the same amino acid sequence of trastuzumab
MAb1	MAAL-9001 produced by CHO <span style="background-color: black; color: red;">CCI</span>
MAb2	MAAL-9001 produced by CHO <span style="background-color: black; color: red;">CCI</span>

## 1. INTRODUCTION

### 1.1. Background

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1.67 million new cases diagnosed in 2012 (25% of all cancers).<sup>1</sup> Almost 1 million new cases of stomach cancer were estimated to have occurred in 2012 (952,000 cases, 6.8% of the total), making it the fifth most common malignancy in the world, after cancers of the lung, breast, colorectum and prostate.<sup>1</sup> Human epidermal growth factor receptor 2 (HER2) is involved in the pathogenesis and poor outcomes of several types of cancer, including advanced gastric and gastroesophageal junction (GEJ) cancer.<sup>2</sup> HER2 is a member of the HER superfamily, and initiates signal transduction via the phosphoinositide 3-kinase (PI3K)/AKT and RAS/mitogen-activated protein kinase (MAPK) pathways.<sup>3,4</sup> 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,<sup>5</sup> gastric cancer,<sup>6,7</sup> pancreatic cancer,<sup>8</sup> lung cancer,<sup>9</sup> colorectal cancer,<sup>10</sup> and ovarian cancer.<sup>11</sup>

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 GEJ adenocarcinoma,<sup>12</sup> in Europe for HER2-positive metastatic breast cancer and HER2-positive metastatic adenocarcinoma of the stomach or GEJ,<sup>13</sup> and in Japan for HER2-overexpressing breast cancer and HER2-overexpressing unresectable or advanced/recurrent gastric or GEJ adenocarcinoma.<sup>14</sup>

DS-8201a is also an antibody-drug conjugate (ADC) targeting HER2, containing MAAA-1181a that inhibits topoisomerase I activity.

Preliminary results from a Phase 1 study (DS8201-A-J101; NCT02564900) with DS-8201a in patients with HER2-positive solid tumors have demonstrated anti-tumor activity and a manageable safety profile. This study is being conducted to evaluate the safety and tolerability profile of DS-8201a in a Chinese population.

### 1.2. Data Summary

#### 1.2.1. Physical, Chemical, Pharmaceutical Properties and Formulation

DS-8201a is an ADC comprised of a recombinant humanized anti-HER2 immunoglobulin G1 (IgG1) monoclonal antibody produced in-house with reference to the same amino acid sequence of trastuzumab, MAAL-9001, covalently conjugated to a drug-linker, MAAA-1162a. The released drug, MAAA-1181a, inhibits topoisomerase I and leads to apoptosis of the target cells.

MAAL-9001 is expressed in Chinese hamster ovary (CHO) cells. Two kinds of CHO cells are used for manufacturing MAAL-9001, and accordingly 2 kinds of drug substance are used for the development of DS-8201a. MAAL-9001 produced by the CHO<sup>CCI</sup> is referred to as Mab1, and the DS-8201a drug substance manufactured using Mab1 is referred to as DS1. MAAL-9001 produced by CHO<sup>CCI</sup> is referred to as Mab2 and the DS-8201a drug substance manufactured using Mab2 is referred to as DS2. The development of DS-8201a was initiated with DS1. However, to support further clinical development as well as commercialization, a transition to DS2 has been made.<sup>15</sup>

## 1.2.2. Nonclinical Studies

### 1.2.2.1. Pharmacology

DS-8201a binds specifically to the HER2 extracellular domain and does not bind to other HER family proteins has been confirmed by enzyme-linked immunosorbent assay using recombinant proteins. DS-8201a is hypothesized to exhibit antitumor activity through MAAA-1181a induced apoptosis<sup>CCI</sup>

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 HER2-expressing tumors.

### 1.2.2.2. Pharmacokinetics Properties

In monkeys, the  $V_{ss}$  of DS-8201a was close to the plasma volume. The CL was much lower than hepatic flow and decreased as the dose increased, indicating non-linear process. DS-8201a administered intravenously (IV) mostly circulates in plasma while remaining in its intact form. 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 DS-8201a is largely stable in plasma. The protein binding ratio of MAAA-1181a (10 ng/mL) was 98.0% in human plasma. In monkeys, the highest radioactivity of IV administration of  $^{14}\text{C}$ -DS-8201a was observed in the blood and in monkeys, excretion of radioactivity from administered  $^{14}\text{C}$ -DS-8201a into feces was predominant. In rats, excretion of radioactivity from administered  $^{14}\text{C}$ -MAAA-1181a into feces via bile was predominant. Cytochrome P450 (CYP) 3A4 is the primary CYP enzyme in the metabolism of MAAA-1181a in vitro. No human-specific metabolites were detected in vitro. MAAA-1181a did not exhibit any inhibitory potential to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (ie, with 50% inhibitory concentration [ $\text{IC}_{50}$ ] >50  $\mu\text{mol/L}$ ). MAAA-1181a did not show any induction potential to CYP3A4, CYP1A2, and CYP2B6 up to 30  $\mu\text{mol/L}$ . MAAA-1181a did not inhibit organic anion transporting 3 (OAT3), organic cation transporter 1 (OCT1), OCT2, organic anion transporting polypeptide 1B3 (OATP 1B3), multidrug and toxin extrusion 1 (MATE1), MATE2-K, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and bile salt export pump (BSEP) ( $\text{IC}_{50}$  >30  $\mu\text{mol/L}$ ). MAAA-1181a inhibited OAT1 and OATP1B1 with the  $\text{IC}_{50}$  values of 12.7 and 14.4  $\mu\text{mol/L}$ , respectively, although the values were much higher than the  $\text{C}_{\text{max}}$  of MAAA-1181a in humans (9.25 ng/mL [0.019  $\mu\text{mol/L}$ ] at 8.0 mg/kg of DS-8201a, Table 1.1). In addition, OATPs were appeared to contribute to the human hepatic uptake of MAAA-1181a.

### 1.2.2.3. Nonclinical Safety data

In a study of intermittent IV dosing of DS-8201a in rats (once every 3 week [Q3w] dosing for 6 weeks), no dead or moribund animals were found at dose levels of 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, incisor tooth, and renal toxicity at dose levels of 60 mg/kg and greater. In an intermittent IV dose toxicity study of DS-8201a in cynomolgus monkeys (Q3w, 6 weeks), one moribund female was found at 78.8 mg/kg, the highest dose level.

The major toxicity findings in this moribund animal were intestinal toxicity, hematopoietic system toxicity, skin toxicity, and renal toxicity. This animal exhibited decreased body weight and food intake. The major findings of toxicity in the surviving animals were intestinal toxicity at dose levels of 10 mg/kg and greater, and pulmonary, testicular, and skin toxicity at dose levels of 30 mg/kg and greater. In addition, hematopoietic system, and renal toxicity, as well as electrocardiogram (ECG) abnormalities (PR interval shortened and corrected QT interval [QTc] prolongation) were found at 78.8 mg/kg.

Thus, as described above, the severely toxic dose in 10% of the animals in a rat intermittent IV dose toxicity study with DS-8201a was found to be greater than 197 mg/kg. In an intermittent IV dose toxicity study in cynomolgus monkeys, because moribundity caused by a severe worsening of the animal's condition was found at 78.8 mg/kg in one animal and evidence of critical pulmonary toxicity (eg, interstitial inflammation and/or alveolar edema) were found even in the surviving animals, it was concluded that the highest non-severely toxic dose was 30 mg/kg.

In an intermittent IV dose toxicity study with MAAA-1181a (once a week dosing for 4 weeks), although lymphatic/hematopoietic system toxicity, intestinal toxicity, and corneal toxicity were observed at 3 mg/kg and greater in rats, no deaths occurred at dose levels of 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, in cynomolgus monkeys, 1 female died and 1 male was found moribund at 12 mg/kg. Although effects on the heart (focal myocardial cell degeneration/necrosis) were found in the moribund male in addition to other these toxicities, there were no such cardiomyopathies in the dead female even though both animals exhibited similar worsening clinical conditions which were associated with sustained decreases in food consumption, and with bone marrow and intestinal toxicity. Therefore these changes were considered the cause of the death and moribundity. Intestinal toxicity and lymphatic/hematopoietic system toxicity were commonly observed in studies of DS-8201a or MAAA-1181a.

In safety pharmacology studies, when male cynomolgus monkeys equipped with a telemetry device received single IV doses of DS-8201a, no effects on the cardiovascular system, respiratory system, or central nervous system were found at dose levels of up to 78.8 mg/kg. In addition, in human ether-à-go-go-related gene (hERG) studies of MAAA-1181a, the monohydrate of the drug component, MAAA-1181a did not inhibit the hERG channel current.

In an in vitro 3T3 neutral red uptake phototoxicity study, MAAA-1181a was found to be phototoxic to Balb/c 3T3 mouse fibroblasts. However, in a single dose phototoxicity study of MAAA-1181a in pigmented rats, no phototoxic reaction was noted.

For further details of nonclinical studies, please see the current Investigator's Brochure (IB) for DS-8201a.<sup>15</sup>

### **1.2.3. Clinical Experience**

The ongoing study DS8201-A-J101 (NCT02564900) is a Phase 1, two-part, multicenter, non-randomized, open-label, multiple dose, first-in-human study of DS-8201a.

This two-part study includes both a Dose Escalation part (Part 1), to identify the maximum tolerated dose (MTD) or the recommended Phase 2 dose (RP2D) of DS-8201a, and a Dose Expansion part (Part 2), to confirm the safety, tolerability and efficacy of DS-8201a at the MTD/RP2D.

As of 8 June 2017, 148 subjects received DS-8201a in this study. In Part 1, a total of 24 patients received DS-8201a: 3 in 0.8 mg/kg cohort, 3 in 1.6 mg/kg cohort, 3 in 3.2 mg/kg cohort, 6 in 5.4 mg/kg cohort, 6 in 6.4 mg/kg cohort and 3 in 8.0 mg/kg cohort. Seventeen breast cancer patients, 6 gastric cancer patients and 1 GEJ cancer patient have been enrolled. No dose limiting toxicities (defined as occurring during Cycle 1) were reported in any patient. Two doses, 5.4 mg/kg and 6.4 mg/kg were chosen for expansion in Part 2. In Part 2, a total of 124 patients, 48 in Part 2a, 41 in Part 2b, 10 in Part 2c, and 25 in Part 2d, received DS-8201a. Of these, a total 47 patients (30 patients in Part 2a and 17 patients in Part 2b) received 5.4 mg/kg and the other 77 patients received 6.4 mg/kg of DS-8201a. In Part 2d, 11 colorectal cancer patients, 6 non-small cell lung cancer patients, 4 parotid/submandibular gland cancer patients, 2 Paget's disease patients, 1 cholangiocarcinoma patient and 1 esophageal cancer patient have been enrolled.

The most common adverse events (AEs) in 148 patients who have received DS-8201a in this study (AEs >20% of any grades) were nausea (65%), decreased appetite (53%), vomiting (34%), decreased platelet count (31%), anemia (28%), alopecia (26%), diarrhea (24%), constipation (24%), decreased neutrophil count (24%), decreased white blood cell count (24%), and malaise (22%). The majority of the AEs were of Grade 1 or 2 severity; 52 of 148 patients (35.1%) experienced Grade 3 AEs and 10 patients (6.8%) experienced Grade 4 AEs as the worst grade experienced.

Adverse events of special interest (AESIs) detailed in the Phase 1 protocol included infusion reactions, cardiac events, and interstitial lung disease (ILD). Periodic cardiac assessments are performed including echocardiography (ECHO) or multiple-gated acquisition (MUGA) scan performed at every 2 cycles (42 days) and 12-lead triplicate ECGs performed at least every cycle (21 days). A total of 13 (8.7%) patients experienced treatment-emergent adverse events (TEAEs) relating to cardiotoxicity in the on-going study. Of these 13 patients, 9 experienced QT prolongation (7 Grade 1 and 2 Grade 2, all non-serious), all considered related to the study therapy. Two patients experienced ejection fraction decreased (Grade 2, non-serious, related), 1 patient experienced Grade 2 tachycardia and 1 patient experienced decreased heart rate (related). No action was taken regarding the study drug and no patients discontinued study therapy. Pulmonary assessments are performed at the time of imaging for tumor assessments as well as evaluation of peripheral oxygen saturation (SpO<sub>2</sub>) on Day 1 of every cycle and at end of treatment (EOT). In the event of suspicion of drug induced lung disease, recommendations include consultation with a pulmonologist and interruption of DS-8201a treatment pending final diagnosis. As of 8 June 2017, there were 3 patients (where 1 received 8.0 mg/kg and the other 2 received 6.4 mg/kg) who had experienced 1 serious and 2 non-serious pneumonitis (1 was Grade 1 and the other was Grade 2). There were also 2 patients who experienced ILD (1 serious and Grade 3 in severity, and the other non-serious Grade 1 in severity).

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%. Patients receiving higher dose levels of DS-8201a ( $\geq$ 5.4 mg/kg, 15 patients) 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%.

Preliminary pharmacokinetic (PK) data are available from the 24 patients in the 0.8 mg/kg to 8.0 mg/kg cohorts in Part 1 of DS8201-A-J101. The PK parameters of MAAA-1181a, DS-8201a and total anti-HER2 antibody are shown in [Table 1.1](#), [Table 1.2](#) and [Table 1.3](#). Systemic exposure (C<sub>max</sub> and AUC<sub>last</sub>) to DS-8201a over 3.2 mg/kg exposures increased approximately dose proportionally. Following a single IV administration of DS-8201a at 6.4 mg/kg, C<sub>max</sub> of DS-8201a was achieved with a median time of maximum observed serum concentration (T<sub>max</sub>) of 2.16 h and mean T<sub>1/2</sub> of 7.33 days.

The total antibody profile was 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 T<sub>max</sub> (6 hours to 7 hours, median T<sub>max</sub>) compared to those for DS-8201a. The systemic exposure (C<sub>max</sub> 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.

**Table 1.1: Pharmacokinetic Parameters of DS-8201a Following the First Dose**

Dosage (N)	C <sub>max</sub> <sup>a</sup> (ng/mL)	T <sub>max</sub> <sup>b</sup> (h)	AUC <sub>last</sub> (µg·d/mL)	AUC <sub>inf</sub> (µg·d/mL)	T <sub>1/2</sub> (day)	CL (mL/d/kg)	V <sub>ss</sub> (mL/kg)
0.8 mg/kg (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 (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 (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 (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 (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 (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)

h = hour; N = Total number of observations;

<sup>a</sup> Mean (standard deviation)

<sup>b</sup> T<sub>max</sub> reported as median (min, max)

**Table 1.2: Pharmacokinetic Parameters of Total Anti-HER2 Antibody Following the First Dose**

Dosage (N)	Cmax <sup>a</sup> (ng/mL)	Tmax <sup>b</sup> (h)	AUClast (µg·d/mL)	AUCinf (µg·d/mL)	T <sub>1/2</sub> (day)
0.8 mg/kg (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 (3)	41.2 (12.7)	1.92 (1.68, 4.08)	200 (191)	227 (225)	4.35 (2.77)
3.2 mg/kg (3)	67.5 (13.8)	4.08 (4.08, 6.96)	302 (97.8)	313 (102)	3.93 (0.863)
5.4 mg/kg (6)	116 (13.9)	1.92 (1.92, 6.96)	609 (151)	682 (172)	6.78 (2.39)
6.4 mg/kg (6)	146 (18.9)	3.84 (2.16, 6.96)	878 (97.1)	1050 (149)	8.25 (2.16)
8.0 mg/kg (3)	178 (18.5)	2.16 (1.92, 6.72)	1090 (213)	1270 (296)	7.35 (0.417)

h = hour; N = Total number of observations;

<sup>a</sup> Mean (standard deviation)

<sup>b</sup> Tmax reported as median (min, max)

**Table 1.3: Pharmacokinetic Parameters of MAAA-1181a Following the First Dose**

Dosage (N)	Cmax <sup>a</sup> (ng/mL)	Tmax <sup>b</sup> (h)	AUClast <sup>a</sup> (ng d/mL)	AUCinf <sup>a</sup> (ng d/mL)	T <sub>1/2</sub> <sup>a</sup> (day)
0.8 mg/kg (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 (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 (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 (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 (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 (3)	9.25 (3.18)	6.72 (6.72, 6.96)	39.4 (6.43)	43.4 (9.16)	6.36 (1.53)

h = hour; N = Total number of observations;

<sup>a</sup> Mean (standard deviation)

<sup>b</sup> Tmax reported as median (min, max)

For further details on clinical studies, please see the current IB for DS-8201a.<sup>15</sup>

### **1.3. Study Rationale**

The results from the Phase 1 study DS8201-A-J101 (NCT02564900) have shown antitumor activity and a manageable safety profile. As of 7 June 2017, there have been no reported dose limiting toxicities, and MTD was not reached in the 0.8 mg/kg to 8.0 mg/kg Q3w cohorts. Although 8.0 mg/kg was shown to be tolerable, dose reductions were required in 2 out of 3 patients, and subsequent exposure response analysis showed that 5.4 mg/kg and 6.4 mg/kg were appropriate assessment doses in the expansion cohort of this Phase 1 study. On the basis of efficacy, tolerability, and PK profile established in the Phase 1 study and pre-clinical studies, the dose of 6.4mg/kg will be used in this trial.

### **1.4. Risks and Benefits for Study Subjects**

Based on the clinical observations in the Phase 1 study (DS8201-A-J101), DS-8201a demonstrated antitumor activity in HER2-overexpressing patients (see Section 1.2.3). Overall, the reported AEs were consistent with the safety profile of DS-8201a and as expected based on the nonclinical toxicology data. The following TEAEs were considered as identified risk: nausea, decreased appetite, vomiting, decreased platelet count, anemia, alopecia, diarrhea, decreased neutrophil count, and decreased white blood cell count. The majority of the TEAEs were of Grade 1 and Grade 2 severity. Patients 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 are discussed below.

In nonclinical toxicology studies, intestinal, hematopoietic, pulmonary (interstitial inflammation and/or alveolar edema), testicular, skin and renal toxicities were found in association with the administration of DS-8201a. Ophthalmologic safety monitoring, which includes visual acuity, slit lamp exam, and fundoscopy will also be part of the overall evaluation. These assessments will be performed at baseline and at specific intervals described in the protocol and at the EOT, when an additional exam will also be performed. Moreover, at the discretion of the Investigator, ophthalmologic testing can be performed at any time during the study. In addition to these toxicities, as with other products of the same class, the possibility of cardiotoxicity, related 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 or MUGAs, will be evaluated by the Investigator or delegated physician to monitor cardiac function and troponin will be evaluated to assess cardiac function. Pulmonary toxicity was observed in association with the administration of DS-8201a in both preclinical and clinical studies. Interstitial lung disease/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the DS8201-A-J101 clinical study as well as the results of potential interstitial lung disease (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.

Additional safety assessments should be conducted as needed, at the Investigator's discretion. It can also not be denied that hepatotoxicity, embryo-fetal toxicity, visual disturbances/corneal toxicity, or phototoxicity may occur in patients receiving DS-

8201a. As with any therapeutic antibodies, there is a possibility of infusion-related reactions, and immune responses causing allergic or anaphylactic reactions of DS-8201a. Based on the efficacy and safety data observed in the nonclinical studies, the current clinical experience of the Phase 1 study, and the information from other products of the same class, the benefit-risk balance supports clinical development of DS-8201a in this patient population.

Please refer to the current IB for additional information.<sup>15</sup>

## **2. STUDY OBJECTIVES AND HYPOTHESIS**

### **2.1. Study Objectives**

#### **2.1.1. Primary Objectives**

1. To assess the safety and tolerability of DS-8201a

#### **2.1.2. Secondary Objectives**

1. To assess the PK profiles of DS-8201a, total anti-HER2 antibody, and MAAA-1181a
2. To investigate the anti-tumor activity of DS-8201a
3. To assess the incidence of anti-drug antibodies (ADA) against DS-8201a

#### **2.1.3. Exploratory Objectives**

Not applicable.

### **2.2. Study Hypotheses**

The safety and tolerability profile of DS-8201a in Chinese patients.

### **2.3. Study Endpoints**

#### **2.3.1. Primary Endpoints**

Safety endpoints:

- Safety endpoints will include serious adverse events (SAEs), TEAEs, AEs and AESIs leading to discontinuation.
- Other safety endpoints will include physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS]), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO or MUGA findings, and ophthalmologic findings. TEAEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

#### **2.3.2. Key Secondary Endpoints**

PK endpoints:

- Serum concentration data at each time point and PK parameters of DS-8201a, total anti-HER2 antibody, and MAAA-1181a will be presented.

#### **2.3.3. Other Secondary Endpoints**

- Assessment of ADA

#### **2.3.4. Exploratory Endpoints**

Efficacy endpoints:

Tumor response will be evaluated by the Investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1:

- ORR
- DCR
- Duration of response (DoR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Best percentage change in the sum of diameter(s) of target lesion(s)

### **3. STUDY DESIGN**

#### **3.1. Overall Design**

In this Phase 1, multicenter, open-label study, the safety and tolerability of DS-8201a in subjects with HER2-positive advanced and/or refractory gastric, GEJ adenocarcinoma, or breast cancer will be evaluated.

Approximately 12 eligible subjects will be enrolled at study sites in Taiwan, Republic of China.

DS-8201a at a dose of 6.4 mg/kg will be infused IV for approximately 90 minutes on Day 1 of Cycle 1. If there are no infusion-related reactions after the initial dose in Cycle 1, dosing in subsequent cycles will be infused for approximately 30 minutes. Subjects will continue to receive DS-8201a Q3w (Day 1 of each cycle), until unacceptable toxicity, progressive disease (PD), or withdrawal of consent. The subject's weight at Screening (Baseline) will be used to calculate the initial dose. If the subject's weight changes by 10% of the baseline weight, the dose will be recalculated.

#### **3.2. Discussion of Study Design**

This is an open-label study and the main objective is to assess the safety and tolerability profile of DS-8201a in Chinese subjects.

On the basis of efficacy, tolerability, and PK profiles established in the DS-8201-A-J101 study and preclinical studies, the dose of 6.4 mg/kg will be used in this study and subjects will continue to receive DS-8201a Q3w (Day 1 of each cycle) at the discretion of the investigators, until unacceptable toxicity, PD, or withdrawal of consent.

All subjects are required to have an adequate washout period from their previous oncology treatment before registration in this study (see inclusion criterion 6). Approximately 12 subjects will be enrolled in this study and the sample size of 12 will provide the safety and tolerability data in Chinese subjects.

##### **3.2.1. Duration of the Study**

The expected time from the first subject's enrollment until the last subject's enrollment is approximately 8 months. The screening period is 28 days and each cycle of treatment is 21 days.

The date of registration will be the date that the subject is successfully enrolled as eligible in the study, confirmed by the Sponsor. The date of discontinuation of treatment (EOT) will be the date the Investigator decides to discontinue treatment.

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

##### **3.2.2. 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 is not fixed in this study. Subjects who continue to derive clinical benefit from the study drug in the absence of withdrawal of consent, PD, or unacceptable toxicity may continue the study drug. If the study drug is delayed more

than 28 days from the planned date of administration, the subject will be withdrawn from the study (See sections 5.4.1 and 5.4.2).

### **3.2.3. Study Endpoints**

See Section 2.3 for the study endpoints.

The safety endpoints used in this study are standard in Phase 1 oncology studies. To assess the safety profile of DS8201a, the SAEs, TEAEs, AEs and AESIs leading to discontinuation, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO or MUGA findings, and ophthalmologic findings will be assessed.

Secondary PK endpoints for Cycle 1 and Cycle 3 will assess single and multiple dose kinetics of DS-8201a.

RECIST is a standard measure of efficacy in oncology studies. To investigate the anti-tumor activity of DS-8201a, ORR, DCR, DOR, PFS, and OS will be analyzed appropriately.

ADA data will also be analyzed to serve as a supportive indication of the safety profile.

### **3.2.4. Selection of Doses**

In this study, all enrolled subjects will receive 6.4 mg/kg of DS-8201a IV on Day 1 of each 21-day cycle.

In the Phase 1 study, DS8201-A-J101, although 8.0 mg/kg was shown to be tolerable, dose reductions were required in 2 out of 3 subjects, and subsequent exposure-response analysis showed that 5.4 mg/kg and 6.4 mg/kg were appropriate assessment doses in the expansion cohort of Phase 1 study.

Two dose reductions will be permitted in this study. The adjustment for reduced dosing of DS-8201a will be as follows:

6.4 mg/kg → 5.4 mg/kg → 4.4 mg/kg

After two reductions, further reduction is not allowed. Once the dose of DS-8201a is reduced, no escalation is permitted.

### **3.2.5. Management of Subjects with 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, ILD and LVEF decreases are considered to be AESIs.

#### **3.2.5.1. Cardiac-Related Events including Decreased Ejection Fraction (Cardiotoxicity)**

Clinical Summary:

Cardiotoxicity in association with DS-8201a is considered to be an important potential risk based on the available pre-clinical data, literature and available safety information for drugs of similar class. Refer to the current IB for a summary of preliminary clinical trial data.<sup>15</sup>

Management Guidance:

LVEF will be measured by either ECHO or MUGA scan. All ECHOs or MUGAs will be evaluated by the Investigator or delegated physician for monitoring cardiac function. Troponin will be measured at Screening and after each infusion and as needed based on subject-reported cardiac symptoms. Triplicate ECGs will be performed and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by the Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter are to be recorded in the electronic case report form (eCRF).

Subjects with confirmed symptomatic cardiac dysfunction will be discontinued from the study. A symptomatic decline in LVEF will be managed according to the algorithm shown in [Table 3.1](#).

**Table 3.1: Actions Taken for Cardiac Toxicity**

<b>Worst toxicity NCI-CTCAE version 4.03 Grade (unless otherwise specified)</b>	<b>Management Guidelines for DS-8201a</b>
<b>Cardiac Toxicity</b>	
Symptomatic congestive heart failure (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
<b>Electrocardiogram QT prolonged</b>	
Grade 3 (QTc ≥ 501 ms on at least 2 separate ECGs)	Delay dose until resolved to ≤ Grade 1 (corrected QT ≤ 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 ≥ 501 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

CHF = congestive heart failure; LVEF = left ventricular ejection fraction

**3.2.5.2. Interstitial Lung Disease/Pneumonitis**

Clinical Summary

Interstitial lung disease/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the clinical development program as well as the results of potential interstitial lung disease (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:

Please refer to [Table 3.2](#).

**Table 3.2: Actions Taken for Pulmonary Toxicity**

<b>Worst toxicity NCI-CTCAE version 4.03 Grade (unless otherwise specified)</b>	<b>Management Guidelines for DS-8201a</b>
<b>Pulmonary Toxicity</b>	
	<p>If a subject develops radiographic changes potentially consistent with ILD 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.</p> <p>If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include:</p> <ul style="list-style-type: none"> <li>• High resolution CT</li> <li>• Pulmonologist consultation (infectious disease consultation as clinically indicated)</li> <li>• blood culture and CBC (other blood tests could be considered as needed)</li> <li>• bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered</li> <li>• Pulmonary function tests and pulse oximetry (SpO<sub>2</sub>).</li> <li>• Arterial blood gases if clinically indicated</li> <li>• One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.</li> </ul> <p>Other tests could be considered, as needed.</p> <p>If the AE is confirmed to be ILD/pneumonitis, follow the ILD management guidance as outlined below. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.</p>

Grade 1	<p>The administration of trastuzumab deruxtecan must be interrupted for any ILD events regardless of grade.</p> <ul style="list-style-type: none"> <li>• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry</li> <li>• Consider follow-up imaging in 1-2 weeks (or as clinically indicated).</li> <li>• 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.</li> <li>• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.*</li> </ul> <p>For Grade 1 events, trastuzumab deruxtecan 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 &gt; 28 days from day of onset, reduce dose 1 level          However, if the event grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued.          * If patient is asymptomatic, then patient should still be considered as Grade 1 even if steroid treatment is given</p>
Grade 2	<p>Permanently discontinue subject from study treatment</p> <ul style="list-style-type: none"> <li>• Promptly start and treat with systemic steroids (e.g., at least 1mg/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.</li> <li>• Monitor symptoms closely.</li> <li>• Re-image as clinically indicated.</li> <li>• If worsening or no improvement in clinical or diagnostic observations in 5 days,             <ul style="list-style-type: none"> <li>• Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone).</li> <li>• Re-consider additional work-up for alternative etiologies as described above.</li> <li>• Escalate care as clinically indicated.</li> </ul> </li> </ul>
Grade 3 and 4	<p>Permanently discontinue subject from study treatment.</p> <ul style="list-style-type: none"> <li>• Hospitalization required.</li> <li>• Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 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.</li> <li>• Re-image as clinically indicated.</li> <li>• If still no improvement within 3 to 5 days,</li> </ul>

	<ul style="list-style-type: none"><li>- Re-consider additional work-up for alternative etiologies as described above.</li></ul> Consider other immuno-suppressants and/or treat per local practice.
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## 4. STUDY POPULATION

All subjects must sign and date the informed consent form (ICF) provided by the study site before any study-specific qualification procedures are conducted.

### 4.1. Inclusion Criteria

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

1. Chinese patients aged  $\geq 20$  years
2. Pathologically documented HER2-positive advanced/unresectable or metastatic gastric, GEJ adenocarcinoma, or breast cancer, with both:
  - a. HER2-positive disease documented as: immunohistochemistry (IHC) 3+ positive, and/or fluorescence in situ hybridization (ISH)  $\geq 2.0$  that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. For subject with gastric or GEJ adenocarcinoma cancers, it is preferable to determine HER2 status after completing the last HER2-targeting treatment.
  - b. Documented disease progression (by the Investigator's assessment) after at least one regimen of trastuzumab therapy in metastatic or unresectable locally advanced/recurrent setting.
3. ECOG PS 0 to 1.
4. LVEF  $\geq 50\%$  by either ECHO or MUGA scan within 28 days before registration.
5. Adequate organ function within 7 days before registration defined as:

Item	Laboratory value
Platelet count	$\geq 100,000/\text{mm}^3$ (platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin (Hb)	$\geq 9$ g/dL (red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count (ANC)	$\geq 1500/\text{mm}^3$ (granulocyte colony-stimulating factor administration is not allowed within 1 week prior to screening assessment)
Creatinine	$\leq 1.5 \times$ upper limit of normal (ULN), or creatinine clearance $\geq 60$ mL/min as calculated using the Cockcroft-Gault equation
Aspartate aminotransferase (AST)/alanine aminotransferase (ALT)	$\leq 3 \times$ ULN (if liver metastases are present, $\leq 5 \times$ ULN)

Total bilirubin (TBL)	$\leq 1.5 \times \text{ULN}$ or $< 3 \times \text{ULN}$ in the presence of documented Gilbert's Syndrome or liver metastases at baseline
Prothrombin time and activated partial thromboplastin time	$\leq 1.5 \times \text{ULN}$

6. Adequate treatment washout period before registration, defined as:

<b>Treatment</b>	<b>Washout period</b>
Major surgery	$\geq 4$ weeks
Radiation therapy	$\geq 4$ weeks (if palliative stereotactic radiation therapy excludes abdomen, $\geq 2$ weeks)
Autologous transplantation	$\geq 3$ months
Hormonal therapy	$\geq 2$ weeks
Chemotherapy (including antibody drug therapy and, retinoid therapy)	$\geq 3$ 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, and/or weekly paclitaxel. $\geq 6$ weeks for nitrosoureas or mitomycin C)
Immunotherapy	$\geq 4$ weeks
CYP3A4 strong inhibitor and inducer	$\geq 3 \times$ elimination half-lives of the inhibitor
OATP1B1 inhibitor	$\geq 3 \times$ elimination half-lives of the inhibitor

7. Life expectancy of at least 3 months.
8. Subjects should be 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.
9. Subjects should be willing to provide pre-existing diagnosis of HER2 status.
10. 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 4.5 months for males after the last dose of study drug. Methods considered as highly effective methods of contraception include:
  - a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - i. Oral
    - ii. Intravaginal
    - iii. Transdermal

- b. Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - i. Oral
  - ii. Injectable
  - iii. Implantable
- c. Intrauterine device
- d. Intrauterine hormone-releasing system
- e. Bilateral tubal occlusion
- f. Vasectomized partner
- g. 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 4.5 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-childbearing potential is 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 the 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 the HRT. Following confirmation of their post-menopausal status, they can resume use of the HRT during the study without use of a contraceptive method.

- 11. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4.5 months after the final study drug administration. Preservation of sperm should be considered prior to enrolment in this study.
- 12. 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:

- 1. Medical history of myocardial infarction within 6 months before enrollment, symptomatic CHF (New York Heart Association Class II to IV), troponin levels consistent with myocardial infarction as defined according to the manufacturer 28 days prior to randomization.

2. QTcF prolongation of >450 ms in males and >470 ms in females based on 12-lead ECG performed in triplicate.
3. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
4. Has any evidence of severe or uncontrolled systemic diseases (including uncontrolled hypertension, and active bleeding diatheses or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV), psychiatric illness/social situations, substance abuse, or other factors which in the Investigator's opinion makes it undesirable for the subject to participate in the study or which would jeopardize compliance with the protocol. Screening for chronic conditions is not required.
5. Have clinically significant corneal disease in the opinion of the Investigator.
6. Subjects who are pregnant (as confirmed by pregnancy tests performed within 7 days before registration) or breastfeeding, or planning to become pregnant.
7. Have spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids 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 study enrollment.
8. Has a history of severe hypersensitivity reactions to other monoclonal antibodies and/or to either the drug substances or inactive ingredients in the drug product.
9. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE version 4.03, Grade  $\leq$ 1 at baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator after consultation with the Sponsor medical monitor or designee (eg, Grade 2 chemotherapy-induced neuropathy).
10. Presence of other primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors, or contralateral breast cancer.

### **4.3. Subject Replacement**

Subject replacement is not allowed in this study.

### **4.4. Subject Re-screening Procedures**

The study will allow re-screening for any subject who failed to meet eligibility criteria upon initial screening. Re-screening will be allowed only once and requires an approval from the Sponsor. The subject number must remain the same at the time of re-screening. The initial screening information and the reason why the subject was ineligible for the initial evaluation will be recorded on the screening log.

## **5. STUDY TREATMENT**

### **5.1. Assigning Subjects to Treatment Group/Sequences and Blinding**

#### **5.1.1. Treatment Group/Sequences**

There is a single treatment group in this study. The study drug, dosage, and study procedures are the same for all subjects enrolled in this study.

#### **5.1.2. Method of Treatment Group/Sequences Allocation**

This is an open-label, non-randomized study.

#### **5.1.3. Enrollment**

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (initials, age, sex) date and outcome of screening process (eg, enrolled 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. The unique Subject Number for all subjects who provide written informed consent will be assigned by the Sponsor.

The date of registration is defined as the date that subject is successfully enrolled as eligible, confirmed by the Sponsor. The date of screen failure is defined as the date that subject is considered as ineligible. Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects, allocated Subject Numbers on enrolling in the study, allows the Investigator to reveal the identity of any subject when necessary.

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.

After assigning subject number to each subject at Screening at each site, Investigators will assess the eligibility of a subject based on the inclusion and exclusion criteria after obtaining written informed consent from the subject.

Data for all study visits will be recorded on the eCRF for subjects who receive study drug. Only minimal data will be recorded on the eCRF for subjects who do not meet the eligibility criteria and/or do not receive study drug (screen failures). Further data, such as AEs, will not be collected from subjects once they are considered screen failures or have decided to withdraw prior to receiving study drug.

#### **5.1.4. Blinding**

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

#### **5.1.5. Emergency Unblinding Procedure**

Not applicable.

## **5.2. Study Drug**

The Investigators must ensure that the study drug will be used only in accordance with the protocol.

### **5.2.1. Description**

DS-8201a for injection 100mg will be provided as a sterile lyophilized powder containing 100 mg of DS-8201a in a glass vial (Lyo-DP). Each glass vial should be reconstituted with 5 mL water for Injection to a concentration of 20 mg/mL (ie, 100mg/5mL). DS-8201a will be administered with 5% Dextrose as an IV infusion. 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 for injection 100mg will be supplied by Daiichi Sankyo. This will be labeled and packaged in compliance with regulatory requirements. The packaging will clearly display the name of the study drug, the study drug manufacturing code, the drug number, storage conditions, and other required information in accordance with local regulations.

### **5.2.3. Preparation**

The drug solution for IV infusion is prepared by dilution of the required volume of the study drug calculated based on the subject's body weight. Prepared medicinal solutions should be used immediately. The preparation will be conducted in accordance with the pharmacy manual provided by Daiichi Sankyo. 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 6.4 mg/kg Q3w. The initial dose of DS-8201a will be infused IV into each subject for approximately 90 minutes on Day 1 of Cycle 1. If there is no infusion-related reaction after the initial dose, the second and subsequent doses of DS-8201a will be infused over approximately 30 minutes. The subject's weight at Screening (Baseline) will be used to calculate the initial dose. If the subject's weight changes by 10% or more from the baseline weight, the dose will be recalculated.

### **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 the 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 the 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 drug received, subject's (identification number and/or initials or supply number as applicable), for whom the study drug was dispensed, the date and quantity of study drug dispensed and remaining, if from individual subject drug units as well as the initials/seal of the dispenser.

At the end of the study, or as directed, all unused DS-8201a will be returned to a designee as instructed by the Sponsor. The 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. Unused drug supplies may be destroyed by the supervisor of study drugs when approved in writing by Sponsor and Sponsor has received copies of the site's drug handling and disposition SOPs.

All study drug inventory forms must be made available for inspection by a sponsor authorized representative or designee and regulatory agency inspectors. The Investigators or designees will be responsible for the accountability of all used and unused study supplies at the site.

### **5.3. Control Treatment**

Not applicable.

### **5.4. Dose Interruptions and Reductions**

All confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection events must be recorded in the eCRF. Please refer to Section 17.7 for additional information on dose modification.

#### **5.4.1. Dose Interruptions**

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 the 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 AEs 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 Daiichi Sankyo's Medical Monitor or designee.

#### 5.4.2. Dose Reductions

Note: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified in [Table 5.2](#) and Section 3.2.5.

Two dose reductions are permitted in this study. The adjustment for reduced dosing of DS-8201a will be as shown in [Table 5.1](#).

**Table 5.1 Reference Scheme of Dose Reduction**

Dose level before dose interruption		Dose level after first dose reduction		Dose level after second dose reduction
6.4 mg/kg	→	5.4 mg/kg	→	4.4 mg/kg

The Investigator may consider dose reductions or discontinuation of the study drug according to the condition of the subject and after discussion with the Sponsor.

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

#### Dose Interruption and Modification/Toxicity Management Guidelines:

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

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

All confirmed or suspected COVID-19 infection events must be recorded in the eCRF. Please refer to Section 17.7 for additional information on dose modification. The dose modification schedule is presented in [Table 5.2](#).

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

<b>Worst toxicity NCI-CTCAE version 4.03 Grade (unless otherwise specified)</b>	<b>Management Guidelines for DS-8201a</b>
<b>No toxicity</b>	Maintain dose and schedule
<b>Infusion-Related Reaction</b>	
See Section 3.2.5.1 for management of infusion-related reactions	
<b>Hematologic Toxicity</b>	
<b>Neutrophil Count Decreased</b>	
Grade 3 (<math>1.0 \times 10^9/L</math> to <math>0.5 \times 10^9/L</math>)	Delay dose until resolved to $\leq$ Grade 2, then maintain dose
Grade 4 (<math><0.5 \times 10^9/L</math>)	Delay dose until resolved to $\leq$ Grade 2, Reduce dose by 1 level
Febrile neutropenia (ANC <math><1 \times 10^9/L</math>, fever >38.3°C or a sustained temperature of $\geq 38^\circ\text{C}$ for more than 1 hour)	Delay dose until resolved, Reduce dose by 1 level
<b>Lymphocyte Count Decreased<sup>a</sup></b>	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (<math><0.2 \times 10^9/L</math>)	Delay dose until resolved to $\leq$ Grade 2: <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 14</math> days from day of onset, maintain dose</li> <li>• If resolved in &gt;14 days from day of onset, reduce dose 1 level</li> </ul>
<b>Anaemia</b>	
Grade 3 (Hb <math><8.0</math> g/dL); transfusion indicated	Delay dose until resolved to $\leq$ Grade 2, then maintain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose until resolved to $\leq$ Grade 2, then reduce dose 1 level
<b>Platelet Count Decreased</b>	
Grade 3 (platelets <math><50 \times 10^9/L</math> to <math>25 \times 10^9/L</math>)	Delay dose until resolved to $\leq$ Grade 1: <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in &gt;7 days from day of onset, reduce dose 1 level</li> </ul>
Grade 4 (platelets <math><25 \times 10^9/L</math>)	Delay dose until resolved to $\leq$ Grade 1, then reduce dose 1 level
<b>Cardiac Toxicity</b>	
See Section 3.2.5.1 for management of cardiac toxicities	
<b>Ocular</b>	
Grade 3	Delay dose until resolved to $\leq$ Grade 1: <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in &gt;7 days from day of onset, reduce dose 1 level</li> </ul>
Grade 4	Discontinue subject from study treatment
<b>Pulmonary Toxicity</b>	
Please see Section 3.2.5.2 for management of pulmonary toxicity	
<b>Blood creatinine increased</b>	
Grade 3 (>3.0 to <math>6.0 \times \text{ULN}</math>)	Delay dose until resolved to $\leq$ Grade 2 or Baseline, then reduce dose 1 level
Grade 4 (>6.0 $\times$ ULN)	Discontinue subject from study treatment

<b>Hepatic Toxicity</b>	
<b>Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) with Simultaneous total Bilirubin (TBL)</b>	
AST/ALT $\geq 3.0 \times$ ULN with simultaneous TBL $> 2.0 \times$ ULN	<p>Delay study medication until drug-induced liver injury can be ruled out.</p> <p>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 the Sponsor.</p> <p>If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment.</p> <p>Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.</p>
<b>Aspartate Aminotransferase (AST) or alanine Aminotransferase (ALT)</b>	
Grade 2 ( $>3.0$ to $5.0 \times$ ULN )	No action for Grade 2 AST/ALT
Grade 3 : $>5.0$ to $20.0 \times$ ULN. In subjects without liver metastases and subjects with liver metastases and baseline level $\leq 3 \times$ ULN	<p>Repeat testing within 3 days. Delay dose until resolved to <math>\leq</math> Grade 1 if baseline <math>\leq 3 \times</math> ULN, otherwise delay dose until resolved to <math>\leq</math> baseline, then:</p> <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in <math>&gt;7</math> days from day of onset, reduce dose 1 level</li> </ul>
Grade 3: $>8.0$ to $20.0 \times$ ULN) In subjects with liver metastases, if the baseline level was $>3 \times$ ULN	<p>Repeat testing within 3 days. Delay dose until resolved to <math>\leq</math> baseline level, then:</p> <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in <math>&gt;7</math> days from day of onset, reduce dose 1 level</li> </ul>
Grade 4 ( $>20 \times$ ULN )	Discontinue subject from study treatment
<b>Total Bilirubin (TBL)</b>	
Grade 2 ( $>1.5$ to $3.0 \times$ ULN )	<p>If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to <math>\leq</math> Grade 1:</p> <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in <math>&gt;7</math> days from day of onset, reduce dose 1 level</li> </ul> <p>If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment</p>
Grade 3 ( $>3.0$ to $10.0 \times$ ULN )	<p>If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to <math>\leq</math> Grade 1:</p> <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, reduce dose 1 level</li> <li>• If resolved in <math>&gt;7</math> days from day of onset, discontinue DS-8201a</li> </ul> <p>If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to <math>\leq</math> Grade 2:</p> <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, reduce dose 1 level</li> <li>• If resolved in <math>&gt; 7</math> days from day of onset, discontinue DS-8201a</li> </ul>
Grade 4 ( $>10.0 \times$ ULN)	Discontinue subject from study treatment
<b>Blood Alkaline Phosphatase (ALP) Increased</b>	
Grade 3 or 4 ( $>5.0 \times$ ULN)	No modification unless determined by the Investigator to be clinically significant or life-threatening.
<b>Gastrointestinal</b>	
<b>Nausea</b>	
Grade 3	<p>Delay dose until resolved to <math>\leq</math> Grade 1</p> <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in <math>&gt;7</math> days from day of onset, reduce dose 1 level</li> </ul>
<b>Diarrhea/Colitis</b>	
Grade 3	Delay dose until resolved to $\leq$ Grade 1

	<ul style="list-style-type: none"> <li>• If resolved in <math>\leq 3</math> days from day of onset, maintain dose</li> <li>• If resolved in <math>&gt; 3</math> days from day of onset, reduce dose 1 level</li> </ul>
Grade 4	Discontinue subject from study treatment
<b>Other Laboratory Adverse Events</b>	
Grade 3	Delay dose until resolved to $\leq$ Grade 1 or baseline level: <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in <math>&gt; 7</math> days from day of onset, reduce dose 1 level</li> </ul>
Grade 4	Discontinue subject from study treatment
<b>Other Non-Laboratory Adverse Events</b>	
Grade 3	Delay dose until resolved to $\leq$ Grade 1 or Baseline: <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose</li> <li>• If resolved in <math>&gt; 7</math> days from day of onset, reduce dose 1 level</li> </ul>
Grade 4	Discontinue subject from study treatment
<b>Troponin</b>	
Grade 1 (Levels above the ULN and below the level of myocardial infarction as defined by the manufacturer)	<p>If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3.</p> <p>For new diagnosed grade 1, repeat troponin testing at 3 hours (<math>\pm 1</math> hour) after initial troponin test.</p> <ul style="list-style-type: none"> <li>• If levels at 3 hours (6 hours post-infusion) rises significantly per institutional guidelines, <ul style="list-style-type: none"> <li>– Perform ECG in triplicate;</li> <li>– Repeat troponin testing at 6 hours (<math>\pm 1</math> hour)</li> <li>– Follow institutional guidelines for management of detectable troponin testing.</li> </ul> </li> <li>• If levels at 3 hours (<math>\pm 1</math> hour) does not rise significantly per institutional guidelines, <ul style="list-style-type: none"> <li>– Repeat troponin testing at 6 hours (<math>\pm 1</math> hour) or at 24 hours (<math>\pm 2</math> hours) after initial troponin test.</li> <li>– Continue treatment with DS-8201a.</li> </ul> </li> </ul>
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	<p>Perform ECG in triplicate.</p> <p>Repeat troponin testing at 6 hours (<math>\pm 1</math> hour) and 12 hours (<math>\pm 1</math> hour) after initial troponin test.</p> <p>Follow institutional guidelines for management of detectable troponin testing. If AMI confirmed, discontinue subject from study therapy.</p> <p>Otherwise, delay dose until resolved to <math>\leq</math> Grade 1:</p> <ul style="list-style-type: none"> <li>• If resolved in <math>\leq 7</math> days from day of onset, maintain dose.</li> <li>• If resolved in <math>&gt; 7</math> days from day of onset, reduce dose 1 level.</li> </ul>

ALT = alanine aminotransferase, AST = aspartate aminotransferase, NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, ECG = electrocardiogram, Hb = hemoglobin, TBL = total bilirubin, ULN = upper limit of normal

a. There will be no dose modifications for Grade 1 to Grade 3 lymphopenia. All dose modifications should be based on the worst preceding toxicity.

In addition, investigators may consider dose reductions or discontinuations of the study drug according to the subject's condition and after discussion with the Daiichi Sankyo's Medical Monitor or designee.

## **5.5. Method of Assessing Treatment Compliance**

All doses of the study drug 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 drug. Start and stop date/time of injection, amount of drug administered, and reason for change or interruption (if applicable) must be recorded in medical record by clinical study personnel. These data will be recorded in the electronic case report form (eCRF).

## **5.6. Prior and Concomitant Medications**

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

### **5.6.1. 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 and products are prohibited during this study. The Sponsor must be notified if a patient receives any of these during the study.

- Other anticancer therapy, including cytotoxics, targeted agents, immunotherapy, antibody, retinoid or hormonal therapy. Concurrent use of hormones for no cancer-related conditions (e.g. insulin for diabetes and hormone replacement therapy) is acceptable.
- Other investigational 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 and 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 Section 17.7 for further details.

#### Permitted Therapies/Products

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

2. Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.
3. Prophylactic or supportive treatment of study-drug induced AEs will be otherwise as per Investigator's discretion and institutional guidelines.
4. Based on the currently available clinical safety data, it is recommended that patients receive prophylactic anti-emetic agents prior to infusion of T-DXd and on subsequent days. Antiemetics such as 5-hydroxytryptamine receptor (5-HT<sub>3</sub>) 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.

#### **5.6.2. Restricted products**

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

#### **5.6.3. Dietary and Lifestyle Restrictions**

The following food products are prohibited during this study:

- Foods containing *Hypericum perforatum* (Saint John's wort).

### **5.7. Subject Withdrawal/Discontinuation**

#### **5.7.1. Reasons for Withdrawal**

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

The date of discontinuation of treatment (EOT) is defined as the date the Investigator decides to discontinue treatment.

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

- PD (per RECIST)
- Clinical Progression (provide date)
- AE
- Death
- Withdrawal by subject
- Lost to F/U
- Protocol violation (specify)
- Physician Decision
- Pregnancy
- Study terminated by the Sponsor
- Other, specify (eg, discretion of the Investigator)

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

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

All subjects who are withdrawn from the study and received study drug should complete the protocol specified withdrawal procedures (Section [5.7.2](#)).

#### **5.7.2. Withdrawal Procedures**

Protocol-specified withdrawal procedures will involve an EOT visit and a F/U visit 40 days after the last administration of DS-8201a. Protocol-specified withdrawal procedures are the same as those to be performed at the EOT visit and the F/U visit (Sections [6.4](#) and [6.5](#)).

#### **5.7.3. Subject Replacement**

Subject replacement is not allowed in this study.

#### **5.7.4. Subject Re-screening Procedures**

Please refer to Section [4.4](#).

## 6. STUDY PROCEDURES

A study visit schedule (Schedule of Events) is provided in Section 17.6 (Table 17.3). All assessments will be performed at time points specified in the schedule of events.

### 6.1. Screening

Obtain of a signed and dated ICF before any study-related procedures or assessments are conducted. In this study, registration process will be followed as per Section 5.1.3.

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

- Check eligibility criteria

#### Before registration

- Assign a subject number.
- Record demographic (eg, birth date, sex, race, ethnicity), primary cancer history, significant medical history and prior cancer treatment history.
- Record historical HER2 status.
- Review eligibility criteria.
- Assess subjects for AEs.

#### Within 90 days before registration

- Perform a HIV antibody test (as required by local regulations or IRB/ECs).

#### Within 28 days before registration

- Perform either ECHO or MUGA to measure LVEF.
- Perform tumor assessment by CT or magnetic resonance imaging (MRI) scans of the brain, chest, abdomen, pelvis, and any other sites of disease (Section 17.4).
- Perform ophthalmologic examinations: the assessments will include visual acuity testing, slit lamp examination, and fundoscopy.

#### Within 7 days before registration

- Perform a complete physical examination and record the subject's height and weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Assess functional status using the ECOG PS scale (Section 17.3).
- Obtain blood samples for clinical laboratories (Section 8.8), prothrombin time and activated partial thromboplastin time, and troponin (preferably troponin-T) testing by study site.
- 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.

- Obtain urine samples for other urinalysis (Section 8.8).
- Perform a 12-lead ECG in triplicate.

## **6.2. Randomization**

Not applicable.

## **6.3. Treatment Period**

In consideration of the subject's safety, the subjects will be hospitalized as required during the study to allow careful safety monitoring, at the Investigator's discretion. Additional safety assessments should be conducted as needed, at the Investigator's discretion.

### **6.3.1. Tumor Assessment**

The same imaging tumor assessment as at Screening by CT or MRI scans will be performed every 6 weeks ( $\pm 7$  days) in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks ( $\pm 7$  days) regardless of a delay in dosing. The assessment will be conducted before Day 1 of each Cycle if possible. CT or MRI (spiral CT or MRI with  $\leq 5$  mm cuts) of the brain, chest, abdomen, and pelvis and other areas of disease should be used for tumor assessments unless another modality of disease assessment is necessary for the lesions at Screening. Every effort should be made to use the same assessment modality for all assessments for each subject, and confirmatory scan are required for responding patients. However, if there is no brain metastasis at 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 (Section 17.4).

Detailed instructions for the handling of images are included in a separate document.

### **6.3.2. Cycle 1, Day 1**

#### **6.3.2.1. Before Infusion**

The following procedures will be completed at predose on Day 1;

- Assess subjects for AEs.
- Record concomitant medications.

#### Within 3 days before the first dose of the study drug

- Perform a 12-lead ECG in triplicate. ECGs will be taken in close succession, a few minutes apart, after being in a supine/semi-recumbent position for 5 minutes.

#### Within 8 hours before administration

- Obtain PK blood sampling (Section 7.1.1).

- Obtain blood sampling for ADA (Section 7.4.1).

Latest data within 3 days before administration: If assessments at Screening are performed within this period, they can be considered to be Day 1 data and there is no need to repeat them:

- Perform a complete physical examination and record the subject's weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate, body temperature and SpO<sub>2</sub>).
- Assess functional status using the ECOG PS scale (Section 17.3).
- Obtain blood samples for clinical laboratories (Section 8.8).

#### 6.3.2.2. Administration and After Infusion

- Administer DS-8201a as per Section 5.2.4.

The following procedures will be completed postdose on Day 1:

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Perform a 12-lead ECG in triplicate within 30 minutes after end of infusion (EOI), and 2 hours to 4 hours after the start of administration.
- Obtain PK blood samples at the following time points: within 15 minutes after EOI, 2 hours, 4 hours, and 7 hours ( $\pm$  15 minutes) after the start of administration (Section 7.1.1).
- Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2 hours to 3 hours after EOI.
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (NCI-CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 hours ( $\pm$  1 hour) and 12 hours ( $\pm$  1 hour) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the ULN and below the level of myocardial infarction as defined by the manufacturer (NCI-CTCAE Grade 1), repeat troponin testing at 3 hours ( $\pm$  1 hour) after initial troponin test was drawn. If troponin level at 3 hours (6 hours post-infusion):
    - Significantly increases per institutional guidelines, then repeat troponin testing at 6 hours ( $\pm$  1 hour) and follow institutional guidelines.
    - Otherwise, repeat troponin testing at 6 hours ( $\pm$  1 hour) or at 24 hours ( $\pm$  2 hours) after initial troponin test.
  - If troponin levels are above the ULN 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.
- Record concomitant medications.

- Assess subjects for AEs.

### **6.3.3. 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, respiratory rate and body temperature).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Obtain PK blood samples at the 24 hours ( $\pm$  2 hours) after the start of Day 1 administration (Section 7.1.1).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for AEs.

### **6.3.4. 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, respiratory rate and body temperature).
- Obtain PK blood samples at the 72 hours ( $\pm$  2 hours) after the start of Day 1 administration (Section 7.1.1).
- Record concomitant medications.
- Assess subjects for AEs.

### **6.3.5. Cycle 1, Day 8**

The following procedures will be performed on Day 8 ( $\pm$  1 day):

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Obtain PK blood samples (Section 7.1.1).
- Obtain a blood samples for ADA (Section 7.4.1).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for AEs.

### **6.3.6. Cycle 1, Day 15**

The following procedures will be performed on Day 15 ( $\pm$  1 day):

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Obtain PK blood samples (Section 7.1.1).

- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for AEs.

#### **6.3.7. Cycle 1, Day 22**

If Day 1 of the next cycle is delayed for 3 days or more, or if the subject cannot continue into the next cycle, the following procedures will be performed on Day 22 ( $\pm 2$  days):

- Obtain PK blood samples (Section 7.1.1)
- Record concomitant medications.
- Assess subjects for AEs.

#### **6.3.8. Cycle 2, Day 1**

##### **6.3.8.1. Before Infusion**

The following procedures will be completed at predose on Day 1:

- Record concomitant medications.
- Assess subjects for AEs.

##### Within 8 hours before administration

- Obtain PK blood samples (Section 7.1.1). If blood sample is collected on Day 22 of Cycle 1, the blood sample will be collected before infusion (BI) on Day 1 of Cycle 2, if possible.
- Obtain a blood samples for ADA (Section 7.4.1).

##### 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 the subject's weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate, body temperature and SpO<sub>2</sub>).
- Assess functional status using the ECOG PS scale (Section 17.3).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Perform either ECHO or MUGA to measure 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.
- Perform a 12-lead ECG in triplicate.

### 6.3.8.2. Administration and After Infusion

- Administer DS-8201a per Section 5.2.4.

The following procedures will be completed postdose on Day 1:

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Obtain PK blood samples within 15 minutes after EOI (Section 7.1.1).
- Perform a 12-lead ECG in triplicate.
- Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2 hours to 3 hours after EOI.
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (NCI-CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 hours ( $\pm 1$  hour) and 12 hours ( $\pm 1$  hour) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the ULN and below the level of myocardial infarction as defined by the manufacturer (NCI-CTCAE Grade 1), repeat troponin testing at 3 hours ( $\pm 1$  hour) after initial troponin test was drawn. If troponin level at 3 hours (6 hours post-infusion):
    - Significantly increases per institutional guidelines, then repeat troponin testing at 6 hours ( $\pm 1$  hour) and follow institutional guidelines.
    - Otherwise, repeat troponin testing at 6 hours ( $\pm 1$  hour) or at 24 hours ( $\pm 2$  hours) after initial troponin test.
  - If troponin levels are above the ULN 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.
- Record concomitant medications.
- Assess subjects for AEs.

### 6.3.9. Cycle 2, Day 8 and Day 15

The following procedures will be performed on Day 8 ( $\pm 2$  days) and Day 15 ( $\pm 2$  days):

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Record concomitant medications.
- Assess subjects for AEs.

### **6.3.10. Cycle 2, Day 22**

If Day 1 of the next cycle is delayed for 3 days or more, or if the subject cannot continue into the next cycle, the following procedures will be performed on Day 22 ( $\pm 2$  days):

- Obtain PK blood samples (Section 7.1.1).
- Record concomitant medications.
- Assess subjects for AEs.

### **6.3.11. Cycle 3, Day 1**

#### **6.3.11.1. Before Infusion**

The following procedures will be completed predose on Day 1:

- Record concomitant medications.
- Assess subjects for AEs.

##### Within 8 hours before administration

- Obtain PK blood samples (Section 7.1.1). 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.

##### Within 3 days before administration

- Perform a complete physical examination and record the subject's weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate, body temperature and SpO<sub>2</sub>).
- Assess functional status using the ECOG PS scale (Section 17.3).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Perform either ECHO or MUGA to measure 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.
- Perform a 12-lead ECG in triplicate.

#### **6.3.11.2. Administration and After Infusion**

- Administer DS-8201a per Section 5.2.4.

The following procedures will be completed postdose on Day 1:

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Obtain PK blood samples at the following time points: within 15 minutes after EOI, 2 hours, 4 hours and 7 hours ( $\pm 15$  minutes) after the start of administration (Section 7.1.1).
- Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2 hours to 3 hours after EOI.

- If troponin levels are consistent with myocardial infarction as defined according to manufacturer (NCI-CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 hours ( $\pm$  1 hour) and 12 hours ( $\pm$  1 hour) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the ULN and below the level of myocardial infarction as defined by the manufacturer (NCI-CTCAE Grade 1), repeat troponin testing at 3 hours ( $\pm$  1 hour) after initial troponin test was drawn. If troponin level at 3 hours (6 hours post-infusion):
    - o Significantly increases per institutional guidelines, then repeat troponin testing at 6 hours ( $\pm$  1 hour) and follow institutional guidelines.
    - o Otherwise, repeat troponin testing at 6 hours ( $\pm$  1 hour) or at 24 hours ( $\pm$  2 hours) after initial troponin test.
  - If troponin levels are above the ULN 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.
- Record concomitant medications.
  - Assess subjects for AEs.

#### **6.3.12. Cycle 3, Day 2 and Day 4**

The following procedures will be performed on Day 2 and Day 4.

- Obtain PK blood samples (Section 7.1.1).
- Record concomitant medications.
- Assess subjects for AEs.

#### **6.3.13. Cycle 3, Day 8 and Day 15**

The following procedures will be performed on Day 8 ( $\pm$  2 days) and Day 15 ( $\pm$  2 days):

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Obtain PK blood samples (Section 7.1.1).
- Record concomitant medications.
- Assess subjects for AEs.

#### **6.3.14. Cycle 3, Day 22**

If Day 1 of the next cycle is delayed for 3 days or more, or if the subject cannot continue into the next cycle, the following procedures will be performed on Day 22 ( $\pm$  2 days):

- Obtain PK blood samples (Section 7.1.1).

- Record concomitant medications.
- Assess subjects for AEs.

### **6.3.15. Cycle 4 and All Subsequent Cycles, Day 1**

#### **6.3.15.1. Before Infusion**

The following procedures will be completed predose on Day 1:

- Record concomitant medications.
- Assess subjects for AEs.
- 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.

#### Within 8 hours before administration

##### On Day 1 in Cycle 4, 6, and 8

- Obtain PK blood samples (Section 7.1.1). If blood sample is collected on Day 22 of Cycle 3, the blood sample will be collected at BI on Day 1 of Cycle 4 if possible.

##### On Day 1 every 2 cycles from Cycle 4 to the EOT (eg, Day 1 in Cycle 4, 6, 8, 10, and so on)

- Obtain a blood samples for ADA (Section 7.4.1). A portion of ADA blood sample from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 5.0 is applied for a subject. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 4 (Cycle 4, Cycle 8 etc.).

#### Within 3 days before administration

- Perform a complete physical examination and record the subject's weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate, body temperature and SpO<sub>2</sub>).
- Assess functional status using the ECOG PS scale (Section 17.3).
- Obtain blood samples for clinical laboratories (Section 8.8).
- Perform a 12-lead ECG in triplicate.

##### On Day 1 every 2 cycles from Cycle 3 to the EOT (eg, Day 1 in Cycle 3, 5, 7, 9, 11, and so on)

- Perform either ECHO or MUGA to measure 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.

On Day 1 every 4 cycles from Cycle 2 to the EOT (eg, Day 1 in Cycle 2, 6, 10, 14, and so on)

#### **6.3.15.2. Administration and After Infusion**

- Administer DS-8201a per Section 5.2.4.

The following procedures will be completed postdose on Day 1:

- Record concomitant medications.
- Assess subjects for AEs.

After Cycle 4 at every 2 cycles until Cycle 8 at the maximum (ie, Day 1 of cycle 4, 6, and 8)

- Obtain PK blood samples within 15 minutes after EOI (Section 7.1.1).

#### **6.4. End of Treatment**

The date of discontinuation of treatment (EOT) is defined as the date the Investigator decides to discontinue treatment. The following assessments will be performed at the EOT visit (within 7 days after the date of discontinuation).

- Ophthalmologic assessments: the assessments will include visual acuity testing, slit lamp examination, and fundoscopy.
- Perform a complete physical examination and record the subject's weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate, body temperature and SpO<sub>2</sub>).
- Assess functional status using the ECOG PS scale (Section 17.3).
  - Obtain blood samples for clinical laboratories (Section 8.8) and ADA (Section 7.4.1). A portion of ADA blood sample from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 5.0 is applied for a subject. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 4 (Cycle 4, Cycle 8 etc.).
- 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 a 12-lead ECG in triplicate.
- Perform either ECHO or MUGA to measure LVEF.

- Perform same imaging tumor assessment as at Screening by CT or MRI scans. CT or MRI (spiral CT or MRI with  $\leq 5$  mm cuts) of the brain, chest, abdomen, and pelvis should be used for tumor assessments unless another modality of disease assessment is necessary for the lesions at Screening. 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 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 (Section 17.4). 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. Follow-up

The F/U visit should occur 40 days (+ 7 days) days after the last administration of DS-8201a. If the subject begins another anticancer therapy before the end of the 40 days (+ 7 days), every effort will be made to complete all the F/U assessments prior to commencing the new therapy. In case of unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant. If assessments at EOT or treatment period are performed within this period, they can be considered to be the F/U data and there is no need to repeat them. If discontinuation of treatment is decided later than 40 days after the last administration of DS-8201a, there is no need to perform the F/U assessments.

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, respiratory rate and body temperature).
- Perform a complete physical examination and record the subject's weight.
- Assess functional status using the ECOG PS scale (Section 17.3).
- Obtain blood samples for clinical laboratories (Section 8.8) and ADA (Section 7.4.1). For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months ( $\pm 1$  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 from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 5.0 is applied for a subject. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 4 (Cycle 4, Cycle 8 etc.).
- 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.

- Obtain SpO<sub>2</sub>.
- Record concomitant medications.
- Assess subjects for AEs.

#### **6.6. New Cancer Treatment and Survival Follow-up**

Not Applicable.

## 7. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

### 7.1. Pharmacokinetic Assessments

The PK sampling will be performed at time points indicated in Section 7.1.1.

Detailed instructions on collection, processing, handling, storage, and sample shipment are described in the separate Laboratory Manual.

#### 7.1.1. Serum Sampling

Blood samples for PK 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.

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

Blood samples of approximately 7 mL for PK analyses will be collected at the time points specified in Section 17.6 and tabulated in Table 7.1.

The actual time of study drug administration (start and EOI) and the exact time of blood sampling must be recorded in source document and the eCRF. Any delays or interruptions in the infusion of dose should also be recorded.

**Table 7.1: Pharmacokinetic Sampling Time Points**

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1 and Cycle 3	Day 1	Predose (within 8 hours of BI) EOI (within 15 minutes after dose administration) 2 hours after start of administration ( $\pm$ 15 minutes) 4 hours after start of administration ( $\pm$ 15 minutes) 7 hours after start of administration ( $\pm$ 15 minutes)
	Day 2	24 hours after start of administration ( $\pm$ 2 hours)
	Day 4	72 hours after start of administration ( $\pm$ 2 hours)
	Day 8	168 hours after start of administration ( $\pm$ 1 day)
	Day 15	336 hours after start of administration ( $\pm$ 1 day)
	Day 22	504 hours after start of administration ( $\pm$ 2 days), collect only if the next cycle is delayed by 3 or more days, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of administration
Cycle 2, Cycle 4, Cycle 6, and Cycle 8	Day 1	Predose (within 8 hours of BI) EOI (within 15 minutes after EOI)
	Day 22	504 hours after start of administration ( $\pm$ 2 days), collect only if the next cycle is delayed by 3 or more days, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of administration

BI = before infusion; 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 7.2.

**Table 7.2: 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) <sup>a</sup>	Before infusion of study treatment (within 8 hrs)

CQ = chloroquine; HCQ = hydroxychloroquine.

<sup>a</sup> Washout period of no less than 14 days is required before resumption of DS-8201a.

## 7.2. Pharmacodynamic Assessment(s)

Not applicable.

## 7.3. Biomarker and Exploratory Assessment(s)

Not applicable.

## 7.4. Immunogenicity

### 7.4.1. Anti-Drug Antibodies

Blood samples for ADA analyses of approximately 4 mL will be collected at the time points specified in [Table 7.3](#). Serum concentrations of DS-8201a and/or total anti-HER2 antibody may be measured using the same ADA samples for the purpose of ADA assessment.

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

**Table 7.3: ADA Sampling Time Points**

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	BI (within 8 hours before administration)
	Day 8	± 1 day
Cycle 2	Day 1	BI (within 8 hours before administration)
After Cycle 4 at every 2 cycles (eg, Cycle 4, 6, 8, 10, 12, and so on)	Day 1	BI (within 8 hours before administration)
EOT	-	The date investigator decides the discontinuation of the study drug (+ 7 days).
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; ADA = anti-drug antibodies;

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

#### **7.4.2. SARS-CoV-2 Serum samples collection**

Portion of ADA blood sample from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 5.0 is applied for a subject. Samples will be sent to the central laboratory and stored until the tests will become available.

#### **7.5. Pharmacogenomic Analysis**

Not applicable.

## **8. SAFETY EVALUATION AND REPORTING**

### **8.1. Assessment of Safety Endpoint Event(s)**

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

### **8.2. Adverse Event Collection and Reporting**

All clinical AEs occurring after the subject signs the ICF and up to the F/U visit after the last dose of study drug (ie, the F/U period) defined as 40 + 7 days, whether observed by the Investigator or reported by the subject, will be recorded on the AE Case Report Form (CRF) page. Medical conditions (including clinical laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

All AEs and SAEs are to be reported according to the procedures in Section 8.5.

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

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

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

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

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

PD is a study endpoint and consequently, should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, “Progressive disease” should be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to the study drug should also be reported and managed as an SAE. The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal clinical laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

### **8.3. Adverse Events of Special Interest**

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, ILD and LVEF decreases are considered to be 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 applicable eCRFs in the clinical study database.

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

Please refer to Section 3.2.5 for management of AESIs in this study.

#### **8.3.1. Interstitial Lung Disease Adjudication Committee**

An independent ILD Adjudication Committee for the DS-8201a program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. These additional data 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 Preferred Terms [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure.

### **8.4. Adverse Event**

#### **8.4.1. Definition of Adverse Event**

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

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

#### **8.4.2. Serious Adverse Event**

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

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

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

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

Note:

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

#### **8.4.3. Severity Assessment**

All AEs will be graded (1 to 5; see below) according to the NCI-CTCAE version 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). This is not the same as "seriousness," which is based on

patient/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

#### **8.4.4. Causality Assessment**

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

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

or

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

#### **8.4.5. Action Taken Regarding Study Drug(s)**

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

#### **8.4.6. Other Action Taken for Event**

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or OTC medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.

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

#### **8.4.7. Adverse Event Outcome**

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

#### **8.5. Serious Adverse Events Reporting-Procedure for Investigators**

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

Serious events that are also efficacy endpoints (eg, PD) and/or safety endpoints will be exempted from SAE processing and expedited reporting. Disease progression should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, “disease progression” should be reported as an SAE and captured on designated eCRF. These events are clinically anticipated events in the target treatment population, and will be periodically reviewed by the Daiichi Sankyo safety teams to ensure prompt identification of any clinically concerning safety issues.

The following types of events should be reported by the Investigator in electronic data capture (EDC) within 24 hours of awareness. A treatment-emergent adverse event (TEAE) is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after the initiating the study drug until 47 days after last dose of the study drug. SAEs with an onset or worsening 48 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs.

- SAEs (see Section 8.4.2 for definition)
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD 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)  $\geq 3 \times$  ULN and an elevated TBL  $> 2 \times$  ULN that may occur either at different time points or simultaneously during the study conduct. A targeted questionnaire is in-built within the 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. Disease progression/worsening of primary cancer (gastric, gastroesophageal junction [GEJ] adenocarcinoma, or breast cancer) will not be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression may be recorded as AEs.

Death due to disease progression should be recorded on the Death eCRF.

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.

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

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

Daiichi Sankyo and/or CRO will inform Investigators, IRBs, and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other sites as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

In Taiwan, upon receipt of the Sponsor's notification of SUSARs, it is the Investigator's responsibility to report all SUSARs to the IRB according to the reporting guideline of the IRB.

### 8.7. Exposure in Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject who becomes pregnant while receiving or within 4 months of discontinuing the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject or a partner of male subject using the Exposure in Utero (EIU) Reporting form, within 24 hours of learning of the pregnancy. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The Investigator should make every effort to follow the subject or partner until completion of the pregnancy and complete the EIU Reporting form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 8.5.

### 8.8. Clinical Laboratory Evaluations

Blood samples for laboratory evaluations will be collected according the time points indicated in the schedule of events (Table 17.3).

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

The following clinical laboratory tests will be performed:

Laboratory tests	Parameters
Hematology	Red blood cell count, Hb, 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, troponin, blood urea nitrogen, calcium, chloride, serum creatinine, lactate dehydrogenase, potassium, sodium, and magnesium
Urinalysis	Protein, blood, gravity, glucose, PH, ketone, nitrite, leukocyte esterase, urobilinogen, bilirubin, color, clarity/turbidity

In addition, the following parameters will be analyzed at the visits indicated in appendix Section 17.6.

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

All laboratory values must be assessed 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 SAE information should be reported according to the procedures (see Section 8.5). Abnormal laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or Baseline), stabilize, or are no longer clinically significant.

### **8.9. Vital Signs**

Vital sign evaluations will be performed according to the time points indicated in the schedule of events (Table 17.3).

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate and body temperature. Additionally, SpO<sub>2</sub> will be measured before administration on Day 1 of each cycle and EOT.

### **8.10. Electrocardiograms**

ECG evaluations will be performed according to the time points indicated in the schedule of events (Table 17.3).

Standard supine 12-lead ECGs in triplicate will be performed in the schedule of events (Table 17.3). Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by the Investigator or delegated physician for the presence of abnormalities.

### **8.11. Physical Examinations**

Physical examinations will be performed according to the time points indicated in the schedule of events (Table 17.3).

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

### **8.12. Other Examinations**

Other evaluations such as ECHO or MUGA, ECOG PS, and ophthalmologic assessments will be performed according to the time points indicated in the schedule of events (Table 17.3).

LVEF will be measured by either ECHO or MUGA. Ophthalmologic assessments will include visual acuity testing, slit lamp examination, funduscopy testing. All ECHOs or MUGAs, and the ophthalmologic assessments must be evaluated by the Investigator or delegated physician.

#### Pulmonary Assessments

- Pulmonary assessment will include CT or MRI of the chest, SpO<sub>2</sub> and will be performed as described in schedule of events. For more details please refer to Section 6 of the protocol.
- An ILD AC will review all cases of ILD on an ongoing basis. Description of the ILD AC is available in Section 8.3.1 .

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

## **9. EFFICACY ASSESSMENTS**

### **9.1. Assessments for Efficacy Endpoints**

Efficacy assessments will be based on tumor assessments. The same imaging tumor assessment as at Screening by CT or MRI scans will be performed every 6 weeks ( $\pm 7$  days) in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks ( $\pm 7$  days) regardless of the delay in dosing. The clinical activity of DS-8201a will be assessed by evaluating tumor response. Tumor response will be evaluated using RECIST version 1.1 (Section 17.4).

CT or MRI (spiral CT or MRI with  $\leq 5$  mm cuts) of the brain, chest, abdomen, and pelvis should be used for tumor assessments unless another modality of disease assessment is necessary for the lesions at Screening. 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 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 endpoints will be assessed. The efficacy variable(s) will be also evaluated at 18 weeks after Day 1 of Cycle 1:

- 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
- PFS
- OS
- Best percentage change in the sum of diameter(s) of target lesion(s)

### **9.2. Appropriateness of Selected Efficacy Assessments**

The anti-tumor effect of DS-8201a will be assessed by evaluating tumor response according to RECIST version 1.1 as it is generally recognized as standard tumor response criteria.

**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 4 cycles of the study drug. After the data-cutoff date for primary analysis, data of interest will be followed for subjects who are still benefiting from the study drug until study completion.

Descriptive statistics will be provided for selected demographic, safety, and PK data by dose level/cohort, if applicable.

- Continuous variables: number of nonmissing observations, mean, standard deviation, median, minimum, and maximum as well as geometric means and geometric coefficient of variation for PK parameters, if applicable.
- Categorical variables: frequencies and percentages.
- Time-to-event variables: number of nonmissing observations (N), median, minimum, and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time-to-event variables.

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

Safety analyses will be performed based on the safety analysis set. Analysis of PK parameters will be based on the PK analysis set. Efficacy endpoints will be analyzed based on the efficacy analysis set. Data will be summarized by dose level/cohort.

Data will be listed and summarized using Statistical Analysis System (SAS<sup>®</sup>) Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina) according to the Sponsor-agreed reporting standards, where applicable. Complete details of the statistical analyses will be documented in the statistical analysis plan (SAP).

PK parameters will be derived using standard noncompartmental methods using Phoenix WinNonlin<sup>®</sup> 6.4 or higher (Pharsight Corp., Certara Company, Princeton, New Jersey, United States); and/or SAS Version 9.2 or higher. Graphics may be prepared with SAS<sup>®</sup> Version 9.2, or higher; SigmaPlot<sup>®</sup> 12.5, or higher (Systat Software, Inc., San Jose, California, United States); or Phoenix WinNonlin 6.4, or higher.

### **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. Safety Analysis Set**

The safety analysis set will include all subjects who receive at least 1 dose of DS-8201a.

### **11.2.3. Pharmacokinetic Analysis Set**

The PK analysis set will include all subjects in the enrolled analysis set who received at least 1 dose of DS-8201a and had at least 1 evaluable postdose serum concentration of DS-8201a without major protocol deviations or events (eg, incomplete dosing, disallowed concomitant medications, etc.) affecting PK.

### **11.2.4. Efficacy Analysis Set**

The efficacy analysis set will include all subjects who received at least 1 dose of DS-8201a and had both pre- and post-treatment efficacy assessment data.

## **11.3. Study Population Data**

Subject disposition and reasons for treatment and study discontinuation will be summarized at each dose level and in total, if applicable, in the enrolled analysis set and safety analysis set.

Demographic and baseline characteristics such as age, sex, race, ethnicity, baseline ECOG PS, cancer stage, histology will be summarized for the enrolled analysis set, safety analysis set, and efficacy analysis set.

## **11.4. Statistical Analysis**

### **11.4.1. Efficacy Analyses**

The efficacy analyses will be performed for the efficacy analysis set. The efficacy endpoints will include ORR, DCR, and time-to-event assessments including DoR, PFS, OS, and Best percent change in the sum of diameter(s) of target lesion(s).

All efficacy endpoints will be listed and summarized.

#### ORR and DCR:

ORR is the proportion of subjects who achieved a best overall response of CR or PR. The point estimate of ORR and corresponding 95% exact binomial confidence intervals (CIs) will be provided.

DCR is the proportion of subjects who achieved a best overall response of CR, PR or SD. The analyses of DCR will be performed in the same manner as the ORR analyses.

#### DoR, PFS and OS:

DoR 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 PD. DoR will be measured for responding subjects (CR or PR) only. Detailed censoring rules for DoR will be specified in the SAP.

PFS is defined as the time interval from the date of the first dose of the study drug to the date of first objective documentation of radiographic PD or death due to any cause. Detailed censoring rules for the PFS analysis will be specified in the SAP.

OS is defined as the time interval from the date of the first dose to the date of death for any cause. Subjects will be censored at the time last known to be alive if the subjects have not been reported to have died by the time of cutoff for the primary analysis.

The time-to-event variables, including DoR, PFS and OS will be summarized descriptively using the Kaplan-Meier method to provide the median event time and the corresponding 95% CI.

Best percent change in the sum of diameter(s) of target lesion(s):

Descriptive statistics for the best percent change in the sum of diameter(s) of target lesion(s) will be provided. A waterfall plot of the best percentage change from Screening in the sum of the longest dimensions (SLD) for each subject will be presented.

#### 11.4.2. Pharmacokinetic Analyses

The PK analyses will be performed on the PK Analysis Set using actual sample times and noncompartmental methods. Serum concentration-time data for DS-8201a will be listed, and summarized using descriptive statistics by study cycle at each nominal collection time. Applicable plots will illustrate the appropriate data.

PK parameters will be estimated for both cycles. The PK parameters of DS-8201a, total anti-HER2 antibody, and MAAA-1181a (AUClast, AUC<sub>0-21d</sub>, C<sub>max</sub>, T<sub>max</sub>, and C<sub>trough</sub>) will be listed and summarized using descriptive statistics. AUC<sub>inf</sub>, Kel, T<sub>1/2</sub>, CL, Vz, and V<sub>ss</sub> will be estimated if determined to be appropriate. Descriptive statistics will be provided for all serum concentration data at each time point and PK parameters for each analyte as appropriate. Primary PK parameters are presented in [Table 11.1](#) and all other parameters are considered secondary.

**Table 11.1: Pharmacokinetics Parameters**

Cycle 1	<ol style="list-style-type: none"> <li>1. AUClast</li> <li>2. AUC<sub>0-21d</sub></li> <li>3. C<sub>max</sub></li> <li>4. T<sub>max</sub></li> </ol>
Cycle 3	<ol style="list-style-type: none"> <li>1. AUClast</li> <li>2. AUC<sub>tau</sub></li> <li>3. C<sub>max</sub></li> <li>4. T<sub>max</sub></li> </ol>

#### 11.4.3. Safety Analyses

Safety analyses will be performed on the safety analysis set. Safety endpoints will include AEs, SAEs, TEAEs, AEs and AESIs leading to discontinuation, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO or MUGA findings and ophthalmologic assessments. AEs will be graded according to the NCI-CTCAE

version 4.03. Safety analysis in general will be descriptive and will be presented in tabular format with appropriate summary statistics.

#### **11.4.3.1. Adverse Event Analyses**

A TEAE is defined as an AE that emerges during the treatment period (from first dose date until F/U visit after the last dose of study medication), 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 percentages of subjects reporting TEAEs will be tabulated by the worst NCI-CTCAE grade, System Organ Class (SOC) and Preferred Term (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.

The time interval from the date of first dose of the study drug to the first onset date of AESIs will be summarized by AESI category.

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.

#### **11.4.3.2. Clinical Laboratory Evaluation Analyses**

Descriptive statistics will be provided for selected clinical laboratory test results (hematology, coagulation, chemistry, and urinalysis and changes from Baseline by scheduled time of evaluation, including the EOT visit. In addition, the change from Baseline will be summarized for the maximum post-treatment value and minimum value.

Abnormal laboratory results for selected clinical laboratory tests will be graded according to the NCI-CTCAE version 4.03, if applicable. A shift table, presenting the 2-way frequency tabulation for Baseline and the worst value according to 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.

#### **11.4.3.3. Vital Sign Analyses**

Descriptive statistics will be provided for the vital sign measurements and changes from Baseline by scheduled time of evaluation, including the EOT visit. In addition, the change from Baseline will be summarized for the maximum and minimum value.

#### **11.4.3.4. Electrocardiogram Analyses**

A shift table, presenting the 2-way frequency tabulation for Baseline and each scheduled time, including the EOT visit according to the categories for ECG (normal and abnormal) will be provided. Other ECG data will be listed.

#### **11.4.3.5. Other Safety Analyses**

Abnormal ECHO or MUGA findings and ophthalmologic findings will be summarized.

ADA assessment data will be listed and summarized appropriately.

#### **11.5. Interim Analyses**

No interim analyses are planned for this study.

#### **11.6. Data Monitoring Committee**

Not applicable.

#### **11.7. Safety Monitoring Team**

There is a safety monitoring team established for the purpose of assessing safety and tolerability of subject. The meeting will be held regularly. The members may include medical expert/medical monitor of Daiichi Sankyo and medical advisor of Quintiles. This meeting will be held after 6 patients have completed Cycle 1 and when necessary. Detailed procedures will be specified in the medical monitoring plan and relative study plans.

#### **11.8. Sample Size Determination**

Approximately 12 subjects will be allocated to the selected dose level. The sample size of 12 subjects will provide the safety and tolerability data in Chinese subjects.

#### **11.9. Statistical Analysis Process**

The clinical study will be analyzed by QuintilesIMS followed by this protocol and the SAP will demonstrate all methodologies and displays for statistical analyses.

The SAP will provide the statistical methods and the analysis of the efficacy, safety, and PK 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.

## **12. DATA INTEGRITY AND QUALITY ASSURANCE**

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

### **12.1. Monitoring and Inspections**

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

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

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

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

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

### **12.2. Data Collection**

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

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

The Investigator will e-sign according to the study data flow.

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

### **12.3. Data Management**

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

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

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

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

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

Refer to Section 17.5 for details of the EDC system used for completing eCRF.

### **12.4. Study Documentation and Storage**

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

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

## **12.5. Record Keeping**

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

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

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

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

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

No study document should be destroyed without prior written agreement between the 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 will provide insurance for study subjects to make available compensation in case of study-related injury. Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

## **14. PUBLICATION POLICY**

Daiichi Sankyo is committed to meeting the highest standards of publication and public disclosure of information arising from clinical trials sponsored by the company. Daiichi Sankyo will comply with US, European Union, Asian, and Japanese policies for public disclosure of the clinical trial protocol and clinical trial results, and for sharing of clinical trial data. Daiichi Sankyo follows the principles set forth in “Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)” published by the International Society for Medical Publication Professionals (ISMPP), and publications will adhere to the “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” established by the International Committee of Medical Journal Editors (ICMJE).

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

## **15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION**

### **15.1. Compliance Statement, Ethics and Regulatory Compliance**

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

### **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 assigned by a unique subject number as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

In compliance with ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB 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. The consent form should be signed and personally dated by the subject or legally acceptable representative prior to his/her participation in the study.

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

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

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

For studies conducted outside the US, a separate special consent for Pharmacogenomic testing will be obtained from patients in accordance with health authorities in their particular region/country.

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

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

The Investigator and/or the Sponsor must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Sponsor or 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 of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

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 the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB.

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. The 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 drug, and had at least 1 administration of study drug, data should be collected for safety purposes.

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

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

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

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

If the subject information is revised, it must be re-approved by the IRB. 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. The Sponsor approval of local amendments will be clearly documented.

A protocol amendment may be implemented after it has been approved by the IRB 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 competent authority/ies.

### **15.9. Data Safety Monitoring Board**

Not applicable.

### **15.10. Address List**

Refer to protocol supplement for detail. Supplements are prepared separately from protocol and their versions are independent from protocol.

#### **15.10.1. Sponsor**

Daiichi Sankyo Co., Ltd.  
3-5-1, Nihonbashi -honcho, Chuo-ku, Tokyo 103-8426, Japan

#### **15.10.2. Contract Research Organization (CRO)**

IQVIA Inc.  
IQVIA RDS Ltd.  
7F, No. 138, Sec. 3, Min Sheng East Road, Taipei, 105, Taiwan, R.O.C.  
PPD

#### **15.10.3. Electronic Data Capture (EDC) Vendor**

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

#### **15.10.4. Bioanalytical Laboratory (Pharmacokinetics and Anti-Drug Antibodies Assessment)**

PPD Development, LP  
2244 Dabney Road Richmond, VA 23230. USA  
PPD

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## 17. APPENDICES

### 17.1. Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight in kg (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 $\mu\text{mol/L}$ :

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;16:31-41.

## 17.2. New York Heart Association

The ninth edition, revised by the Criteria Committee of the American Heart Association, New York City Affiliate, was released March 14, 1994. The new classifications are summarized below for the many physicians and scientists who use them to describe the status of individual patients.

<b>Functional Capacity</b>	<b>Objective Assessment</b>
<b>Class I.</b> Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	<b>A.</b> No objective evidence of cardiovascular disease.
<b>Class II.</b> 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>B.</b> Objective evidence of minimal cardiovascular disease.
<b>Class III.</b> 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.	<b>C.</b> Objective evidence of moderately severe cardiovascular disease.
<b>Class IV.</b> 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.	<b>D.</b> Objective evidence of severe cardiovascular disease.

Source: American heart Association. 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](http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp)

### 17.3. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

**Table 17.1: 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 housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

## **17.4. Response Evaluation Criteria in Solid Tumors (Version 1.1)**

Assessment of tumor responses will be performed according to revised RECIST guidelines, version 1.1.

### **17.4.1. Measurability of Tumor at Baseline**

#### **17.4.1.1. Definitions**

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

##### **17.4.1.1.1. Measurable**

Tumor lesions: Must be accurately measured in at least one 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  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At Baseline and during F/U, only the short axis will be measured and followed. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

##### **17.4.1.1.2. Non-measurable**

All other lesions, including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  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, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

##### **17.4.1.1.3. Special Considerations Regarding Lesion Measurability**

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

Bone lesions:

- Bone scan, 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.

Lesions with prior local treatment:

- 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.

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 since the therapy.

#### **17.4.1.2. Specifications by Methods of Measurements**

##### **17.4.1.2.1. Measurement of Lesions**

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 4 weeks before the beginning of the treatment.

##### **17.4.1.2.2. Method of Assessment**

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

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

#### **17.4.2. Tumor Response Evaluation**

##### **17.4.2.1. Assessment of Overall Tumor Burden and Measurable Disease**

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

##### **17.4.2.2. Baseline Documentation of ‘Target’ and ‘Non-target’ Lesions**

When more than one measurable lesion is present at Baseline all lesions up to a total of two lesions per organ and a maximum of five 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 one or two organ sites involved a maximum of two and four 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 two 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  $\times$  30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis  $\geq 10$  mm but  $< 15$  mm) should be considered non-target lesions. Nodes that have a short axis  $< 10$  mm are considered non-pathological and should not be recorded or followed.

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

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

#### **17.4.2.3. Response Criteria**

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

#### **17.4.2.4. 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 one 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.

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

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

#### **17.4.2.5. 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 one 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 one or more new lesions is also considered progression).

#### **17.4.2.5.1. 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 one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

#### **17.4.2.6. 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 pre-existing lesions). This is particularly important when the subject’s baseline lesions show partial 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 of brain 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 that indicated its presence.

#### **17.4.2.7. 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 this study; however, this can be decided by study personnel. The subject’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

#### 17.4.2.7.1. Time Point Response

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

**Table 17.2: 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, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

#### 17.4.2.7.2. Missing Assessments and In-evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at F/U only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

#### 17.4.2.7.3. Best Overall Response: All Time Points

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

Best response determination in trials where confirmation of complete or PR is not required: Best response in these trials is defined as the best response across all time points (for example, 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, 7 weeks, in the case of scan intervals of 8 weeks or “5 weeks”, in the case of scan intervals of 6 weeks. If the minimum time is not met when SD is otherwise the best time point response, the subject’s best response depends on the subsequent assessments. For example, a subject who has a SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to F/U after the first SD assessment would be considered NE.

#### **17.4.2.7.4. 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 CRF.

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. If a radiographic tumor assessment has not been performed within 4 weeks of the time of clinical progression, then another radiographic assessment should be performed without waiting for the next regularly scheduled scan.

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

#### **17.4.2.8. Frequency of Tumor Re-evaluation**

In this study, tumor measurement will be conducted at Screening, and then at the intervals specified or sooner if clinically indicated. Tumor measurement will be performed during the EOT visit if it was not done within the previous 8 weeks <<or other number of weeks depending upon the scan interval>> or the previous assessment demonstrated disease progression.

Baseline tumor assessments must be performed within 4 weeks prior to the first dose of treatment.

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 chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-47.

## 17.5. 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

Abbreviations: eCRF = electronic case report form; EDC = electronic data capture.

## **17.6. Schedule of Events**

The schedule of events and assessments for this study is presented in [Table 17.3](#).

**Table 17.3: Schedule of Events for DS8201-A-A103 Study**

	SC R	Cycle 1						Cycle 2					Cycle 3					Cycle 4 and subseque nt cycles		EOT <sup>a</sup>	F/U <sup>b</sup>		
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)	Day 1		Day 8	Day 15	(Day 22)	Day 1		Day 2, 4	Day 8	Day 15	(Day 22)	Day 1			
		BI	EOI			(± 1 day)	(± 1 day)	(± 2 days)	BI	EOI	(± 2 days)	(± 2 days)	(± 2 days)	BI	EOI		(± 2 days)	(± 2 days)	(± 2 days)	BI	EOI	(+ 7 days)	(+ 7 days)
Informed consent	•																						
Administration DS-8201a		•						•						•						•			
Demographic information	•																						
Vital sign	• <sup>c</sup>	• <sup>d</sup>	•	•	•	•		• <sup>d</sup>	•	•	•		• <sup>d</sup>	•		•	•		• <sup>d</sup>		•	•	
Physical examination	• <sup>c</sup>	• <sup>d</sup>						• <sup>d</sup>					• <sup>d</sup>						• <sup>d</sup>		•	•	
SpO <sub>2</sub>		• <sup>d</sup>						• <sup>d</sup>					• <sup>d</sup>						• <sup>d</sup>		•	•	
Inclusion/Exclusion Criteria	•																						
Height		•																					
Weight, ECOG PS	• <sup>c</sup>	• <sup>d</sup>						• <sup>d</sup>					• <sup>d</sup>						• <sup>d</sup>		•	•	
Laboratory tests <sup>f</sup>	• <sup>c</sup>	• <sup>d</sup>		•		•	•	• <sup>d</sup>		•	•		• <sup>d</sup>			•	•		• <sup>d</sup>		•	•	
Prothrombin time, activated partial thromboplastin time	• <sup>c</sup>																						

	SC R	Cycle 1						Cycle 2					Cycle 3					Cycle 4 and subsequent cycles		EOT <sup>a</sup>	F/U <sup>b</sup>		
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)	Day 1		Day 8	Day 15	(Day 22)	Day 1		Day 2, 4	Day 8	Day 15	(Day 22)	Day 1			
		BI	EOI			(± 1 day)	(± 1 day)	(± 2 days)	BI	EOI	(± 2 days)	(± 2 days)	(± 2 days)	BI	EOI		(± 2 days)	(± 2 days)	(± 2 days)	BI	EOI	(+ 7 days)	(+ 7 days)
PK		• <sup>c</sup>	• <sup>f, g</sup>	• <sup>h</sup>	• <sup>h</sup>	•	•	• <sup>i</sup>	• <sup>c</sup>	• <sup>f</sup>			• <sup>i</sup>	• <sup>c</sup>	• <sup>f, g</sup>	• <sup>h</sup>	•	•	• <sup>i</sup>	• <sup>c</sup>	• <sup>f</sup>		
ADA <sup>v</sup>		• <sup>k</sup>				•		• <sup>k</sup>												• <sup>k</sup>		•	• <sup>q</sup>
HIV antibody test (as required by local regulations or IRB/ECs)	• <sup>l</sup>																						
Troponin <sup>n</sup>	• <sup>c</sup>		•						•						•								
ECHO or MUGA (LVFF)	• <sup>o</sup>							• <sup>d</sup>						• <sup>d, m</sup>						• <sup>d-m</sup>		•	
12-lead ECG in triplicate	• <sup>c</sup>	• <sup>d</sup>	• <sup>p</sup>	•		•	•		• <sup>d</sup>	•				• <sup>d</sup>						• <sup>d</sup>		•	
Tumor assessment	• <sup>o</sup>		Every 6 weeks (± 7 days) in the first 24 weeks after Day1 of Cycle 1, and thereafter every 12 weeks (± 7 days)																		•		
Pregnancy test	• <sup>c</sup>																					•	•
Ophthalmologic assessments	• <sup>o</sup>								• <sup>r</sup>													•	
Urinalysis	• <sup>c</sup>																						
Concomitant medications			• <sup>s</sup>																				
AEs			• <sup>u</sup>																				

ADA = anti-drug antibodies; AE = adverse event; BI = before infusion; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ECHO = echocardiography; EOI = end of infusion; EOT = end of treatment; F/U = follow-up; HIV = human immunodeficiency virus; IRB = institutional review board; MUGA = multiple-gated acquisition; PK = pharmacokinetics; SCR = screening; SpO<sub>2</sub> = peripheral oxygen saturation

- a The date investigator decides the discontinuation of the study drug (+ 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 7 days before registration
- d Latest data within 3 days before administration
- e Within 8 hours BI on Day 1 of each cycle until Cycle 4 and then every 2 cycles until Cycle 8 (ie, Cycle 1, 2, 3, 4, 6, 8)
- f Within 15 minutes at EOI on Day 1 of each cycle until Cycle 4 and then every 2 cycles until Cycle 8 (ie, Cycle 1, 2, 3, 4, 6, 8)
- g After 2, 4, 7 hours from the start of administration ( $\pm$  15 minutes)
- h 24 hours ( $\pm$  2 hours) and 72 hours ( $\pm$  2 hours) after the start of administration
- i If Day 1 of the next cycle is delayed for 3 days or more, or if the subject cannot continue into the next cycle, collect blood sample for PK analysis on Day 22 of this cycle (Cycle 1, 2, 3, 4, 6 and 8)
- j 4 hours after the start of administration ( $\pm$  15 minutes)
- k Within 8 hours BI on Day 1 in Cycle 1 and 2, and then every 2 cycles until the end (eg, Cycle 1, 2, 4, 6, 8, 10, 12, and so on)
- l Latest data within 90 days before registration.
- m Before administration at every 2 cycles from Cycle 3 (eg, Cycle 3, 5, 7, 9, and so on)
- n Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2 hours to 3 hours after EOI. If troponin levels are consistent with myocardial infarction as defined according to manufacturer (NCI-CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 hours ( $\pm$  1 hour) and 12 hours ( $\pm$  1 hour) after initial troponin test was drawn, and follow institutional guidelines. If troponin levels are above the ULN and below the level of myocardial infarction as defined by the manufacturer (NCI-CTCAE Grade 1), repeat troponin testing at 3 hours ( $\pm$  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.
- o Latest data within 28 days before registration
- p Within 30 minutes after EOI, and 2 hours to 4 hours after the start of administration
- q For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months ( $\pm$  1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than Baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first
- r Ophthalmologic assessments will be performed on Day 1 of Cycle 2 (within 3 days before administration) and every 4 cycles ( $\pm$  7 days) thereafter (eg, Day 1 of Cycle 2, 6, 10, 14, and so on) and as clinically indicated.
- s Concomitant medications used from the time the subject signs the ICF to Follow-up will be recorded.
- t Hematology tests will include red blood cell count, Hb, hematocrit, platelet count, white blood cell count, and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and clinical chemistry tests will include total protein, albumin, ALP, ALT, AST, TBL, blood urea nitrogen, calcium, chloride, serum creatinine, lactate dehydrogenase, potassium, sodium, and magnesium. At Screening, prothrombin time, either partial thromboplastin or activated partial thromboplastin time, and urinalysis (visual, microscopic, and chemical analyses: color, clarity/turbidity, pH,

specific gravity, glucose, ketones, nitrites, leukocyte esterase, bilirubin, urobilirubin, blood, protein, red blood cells, white blood cells, squamous epithelial cells, casts, crystals, bacteria, and yeast) will be performed.

- u For suspected ILD/pneumonitis, treatment with study drug should be interrupted pending 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
  - Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
  - Pulmonary function tests and pulse oximetry (SpO<sub>2</sub>)
  - Arterial blood gases if clinically indicated
  - One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.
- v A portion of ADA blood sample from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing once protocol version 5.0 is applied for a subject. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 4 (Cycle 4, Cycle 8 etc.). Other tests could be considered, as needed.

### 17.7. 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. Use CTCAE version 5.0 general grading criteria to evaluate SARS-CoV-2. All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

#### Dose Modification Criteria for Suspected or Confirmed SARS-CoV-2

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

- If SARS-CoV-2 is ruled out, follow dose modification and management guidance as outlined in [Table 17.4](#).
- If SARS-CoV-2 is confirmed or is still suspected after evaluation follow dose modification as outlined in [Table 17.4](#) 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 17.4: 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 <sup>a</sup>
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved <sup>a</sup> 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 <b>not</b> completely resolved

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

<sup>a</sup> 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 17.4](#), 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, manage per protocol ILD management guideline (Table 3.2).

### **Prior and Concomitant Medications - Prohibited Therapies/Products**

- 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.

### **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 the Schedule of Events (Table 7.3).

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

### **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. The results will be provided to the site from the 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.

Sample collection, preparation, handling, storage, and shipping instructions are provided in the Study Laboratory Manual.

### **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 the 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.