CLINICAL STUDY PROTOCOL

PHASE 1, TWO-PART, MULTICENTER, NON-RANDOMIZED, OPEN-LABEL, MULTIPLE DOSE FIRST-IN-HUMAN STUDY OF DS-8201A, IN SUBJECTS WITH ADVANCED SOLID MALIGNANT TUMORS

DS8201-A-J101

IND #: 127553

VERSION 12.0, 26 APR 2019

Version 1.0 (03 Jun 2015), Version 2.0 (26 Jun 2015), Version 3.0 (14 Jan 2016), Version 4.0 (29 Feb 2016), Version 5.0 (22 Jul 2016), Version 6.0 (09 Sep 2016), Version 7.0 (16 Nov 2016), Version 8.0 (07 Mar 2017), Version 9.0 (28 Apr 2017, Japan-specific), Version 10.0 (14 Sep 2017), Version 11.0 (25 Jan 2018)

DAIICHI SANKYO

INVESTIGATOR AGREEMENT

PHASE 1, TWO-PART, MULTICENTER, NON-RANDOMIZED, OPEN-LABEL, MULTIPLE DOSE FIRST-IN-HUMAN STUDY OF DS-8201A, IN SUBJECTS WITH ADVANCED SOLID MALIGNANT TUMORS

Sponsor Approval:

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

[redacted] _____
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 Conference on Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

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

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

_____ _____
Print Name **Signature**

_____ _____
Title **Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

EudraCT/IND Number:	**Eudra CT: Not obtained/ IND Number: 127553**
Protocol Number:	DS8201-A-J101
Investigational Product:	DS-8201a
Active Ingredient(s)/INN:	Investigational new drug (INN) is not determined.
Study Title:	Phase 1, Two-part, Multicenter, Non-randomized, Open-label, Multiple Dose First-in-human Study of DS-8201a, in Subjects with Advanced Solid Malignant Tumors
Study Phase:	Phase 1
Indication Under Investigation:	DS-8201a will be evaluated in subjects with advanced solid tumors.
Study Objectives:	**Part 1 (Dose Escalation)** Primary Objectives: 1. To assess the safety and tolerability of DS-8201a. 2. To determine the maximum tolerated dose (MTD) or the recommended Phase 2 dose (RP2D) of DS-8201a. Secondary Objectives: 1. To assess the pharmacokinetic (PK) profile of DS-8201a, total anti-human epidermal growth factor receptor 2 (HER2) antibody, and MAAA-1181. 2. To evaluate the efficacy of DS-8201a. 3. To assess the incidence of anti-drug antibody (ADA) against DS-8201a. Exploratory Objectives: 1. To assess the biomarkers related to DS-8201a. **Part 2 (Dose Expansion)** Primary Objectives: 1. To assess the safety and tolerability of DS-8201a at the MTD/the RP2D. 2. To evaluate the efficacy of DS-8201a at the MTD/the RP2D. Secondary Objectives: 1. To assess the PK profile of DS-8201a, total anti-HER2 antibody, and MAAA-1181. 2. To assess the incidence of ADA against DS-8201a. Exploratory Objectives: 1. To assess the biomarkers related to DS-8201a.
Study Design:	This is a Phase 1, two-part, multicenter, non-randomized, open-label, multiple dose, first in human study of DS-8201a. This 2-part study will include both a Dose Escalation part, to identify the MTD or the RP2D of DS-8201a, and a Dose Expansion part, to confirm the safety, tolerability and efficacy of DS-8201a at the MTD/RP2D. Dose escalation of DS-

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	8201a to determine the MTD/RP2D will be guided by the modified continuous reassessment method (mCRM) using a Bayesian logistic regression model (BLRM) following escalation with overdose control (EWOC) principle. **Part 1 (Dose Escalation)** Dose escalation will begin in subjects with advanced breast cancer and gastric or gastroesophageal junction adenocarcinoma. At least 18 subjects will be enrolled in Part 1. More than 16% of subjects (eg, 1 per 6 subjects) are expected to be HER2 expression (immunohistochemistry [IHC] 2+ or 3+). The proposed human starting dose of DS-8201a is 0.8 mg/kg, based on 1/12 human equivalent dose (HED) of highest non-severely toxic dose (HNSTD) in monkey (30 mg/kg). During Part 1, an initial dose of DS-8201a will be infused intravenously into each subject for approximately 90 minutes on Day 1 of Cycle 1. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. Upon completion of Cycle 1, subjects may continue to receive DS-8201a once every 3 weeks (Q3W) (1 cycle) at the discretion of the Investigators, until unacceptable toxicity, progressive disease (PD), or withdrawal of consent. If there is no infusion related reaction after initial dose, the next dose of DS-8201a will be infused intravenously into each subject for 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% of the baseline weight, the dose will be recalculated. **Dose level increment during dose escalation (Part 1) by mCRM with EWOC** – The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure. – The dose level increment should be no more than 100% even if the model suggests a higher dose than 100% for the next cohort. The escalation by mCRM with EWOC principle will be based on a BLRM. The logistic regression model for the dose-response (dose limiting toxicity [DLT] rate) relationships will include 2 parameters, the intercept, and slope. After at least 3 subjects of each cohort complete DLT evaluation during Cycle 1, the posterior distributions of DLT rate are derived for all dose levels based on the BLRM using DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The posterior probability of DLT rate in the following 4 intervals at each dose level: [0%, 16%] as

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	DLT rate interval for under-dosing, (16%, 33%] as target DLT rate interval, (33%, 60%] as DLT rate interval for excessive toxicity, and (60%, 100%] as DLT rate interval for unacceptable toxicity will then be calculated, and used for dose recommendation for the next cohort according to the EWOC principle. The EWOC principle requires that the mCRM recommended dose for the next cohort of subjects is the one with the highest posterior probability of the DLT rate in the target DLT rate interval of (16%, 33%] among all doses fulfilling the overdose control constraint: there is less than 25% of probability for DLT rate > 33% (probability for excessive or unacceptable toxicity). The dose for the next cohort will be chosen by the Sponsor based on the dose recommendation by the mCRM, clinical assessment of toxicity profiles, and PK information observed thus far. Cohorts of at least 3 DLT evaluable subjects will be enrolled and assessed for DLT during the dose escalation process. As an exception, the model will be reevaluated before enrollment of any additional subjects to the cohort if 2 DLT evaluable subjects in the cohort experience DLT before the enrollment of the third subject. Enrollment of subjects to a new cohort requires completion of DLT evaluation of at least 3 subjects treated in the current cohort. Subjects who have neither completed DLT evaluation nor experienced DLT will be censored and not included in the BLRM update. In the event when subjects in the previous cohort experience DLT after enrollment of subjects to a new cohort has begun, dose level assignment of the next subject in the new cohort will be based on an updated BLRM using DLT outcome data from all assessed doses. The RP2D will be decided based on considerations of the respective MTD estimated by the mCRM, and on an overall assessment of safety data from subsequent cycles and efficacy/PK information collected at all different doses tested. For dose determination, the following stopping rules will be implemented for the dose escalation phase: (a) at least 6 evaluable subjects have been enrolled at the MTD/RP2D level with at least 18 evaluable subjects in total enrolled in the dose escalation part, or (b) at least 9 evaluable subjects have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) the initial dose level (0.8 mg/kg) is too toxic. Cohorts may be expanded at any dose level or at the MTD for further elaboration of safety, or PK parameters as required. **Part 2 (Dose Expansion)**

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	Upon completion of dose escalation (Part 1) with determination of MTD/RP2D, the dose expansion part will begin. Part 2 will consist of multiple cohorts: in subjects with trastuzumab emtansine (T-DM1)-treated HER2 overexpressing breast cancer (Part 2a); trastuzumab-treated HER2 overexpressing gastric or gastroesophageal junction adenocarcinoma (Part 2b); HER2 low expressing breast cancer (Part 2c), HER2 expressing other solid malignant tumor or any tumor with HER2 mutation (Part 2d); and HER2 expressing breast cancer (Part 2e). Approximately 100 subjects will be enrolled in Part 2a, approximately 40 subjects will be enrolled in Part 2b, approximately 20 to 40 subjects will be enrolled in Part 2c, approximately 60 subjects will be enrolled in Part 2d, and approximately 20 subjects will be enrolled in Part 2e, respectively. Subjects will receive DS-8201a on Day 1 of a 21-day cycle. The initial dose of DS-8201a will be infused intravenously into each subject for approximately 90 minutes on Day 1 of Cycle 1. If there is no infusion related reaction after initial dose, the next dose of DS-8201a will be infused intravenously into each subject for 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% of the baseline weight, the dose will be recalculated. **Dose Limiting Toxicity Definition** A DLT is defined as any treatment-emergent adverse event (TEAE) not attributable to disease or disease-related processes that occurs during the DLT evaluation period (Day 1 to Day 21 in Cycle 1 of Part 1) and is grade 3 or above according to National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.0, with the exceptions as defined below: <u>For hematological toxicities, a DLT is defined as follows:</u> • Grade 4 neutrophil count decreased lasting > 7 days • Grade ≥ 3 febrile neutropenia • Grade 4 anemia • Grade 4 platelet count decreased • Grade ≥ 3 platelet count decreased lasting > 7 days • Grade ≥ 3 platelet count decreased with clinically significant hemorrhage • Grade 4 lymphocyte count decreased lasting ≥14 days <u>For hepatic organ toxicities, a DLT is defined as follows:</u> • Grade 4 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increased

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	• AST or ALT > 5 × upper limit of normal (ULN), if accompanied by grade ≥ 2 blood bilirubin increased • In subjects without liver metastases, AST or ALT > 5 × ULN lasting >3 days • In subjects with liver metastases, AST or ALT > 5 × ULN lasting >3 days, if the baseline level was ≤ 3 × ULN • In subjects with liver metastases, AST or ALT > 8 × ULN lasting >3 days, if the baseline level was > 3 × ULN For non-hematological, non-hepatic major organ toxicities, a DLT is defined as follows: • Symptomatic Congestive heart failure (CHF) • Left ventricular ejection fraction (LVEF) decline to < 40% or > 20% drop from baseline • Other grade ≥ 3 non-hematological, non-hepatic major organ toxicities The following TEAEs are NOT considered DLTs: • Grade 3 fatigue lasting < 7 days • Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to grade ≤ 2 within 3 days • Isolated laboratory findings not associated with signs or symptoms including grade 3/4 alkaline phosphatase (ALP) increased, hyperuricemia, serum amylase increased, and lipase increased, and grade 3 hyponatremia lasting < 72 hours developed from grade 1 at baseline • Grade 3 lymphocyte count decreased If any of the above toxicities is observed during the DLT evaluation period, whether or not the toxicity is regarded as DLT will be determined based on consultation between the Investigator and Sponsor. In addition, with regard to other toxicities that hinder the conduct of the scheduled study treatment or anemia with blood transfusion, whether or not they are regarded as DLT will be determined based on consultation between the Investigator and Sponsor.
Study Duration:	Part 1 is expected to last approximately one and a half years from the time the first subject is enrolled to the time the last subject is off the DLT evaluation period. Part 2 is expected to last approximately one and a half years from the time the first subject is enrolled to the time the last subject is off the study. The number of treatment cycles is not fixed in this study. Subjects who continue to derive clinical benefit from the study

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	treatment in the absence of withdrawal of consent, PD or unacceptable toxicity may continue the study treatment.
Study Sites and Location:	Study sites from Japan and the United States are planned for this study. Part 2e (Dose Expansion) will be conducted at Japanese sites only.
Planned Sample Size:	Part 1: At least 18 DLT-evaluable subjects are needed to reach an accurate estimate of the MTD. Part 2: Approximately 260 subjects (100 subjects for Part 2a, 40 subjects for Part 2b, 20 to 40 subjects for Part 2c, potentially additional 20 subjects for Part 2c, 60 subjects for Part 2d and 20 subjects for Part 2e) will be enrolled. <u>Part 2a</u> If target objective response rate (ORR) is more than 15% (null hypothesis: ORR ≤ 0.15, alternative hypothesis: ORR > 0.15), then the probability of less than 9 responders out of 100 subjects will be less than 5%. The probability that more than 21 responders out of 100 subjects (ORR > 21%) are observed will be less than 5% under the null hypothesis with ORR ≤ 0.15 but more than 90% under alternative hypothesis with ORR = 0.35. <u>Part 2b</u> If target ORR is more than 10% (null hypothesis: ORR ≤ 0.10, alternative hypothesis: ORR > 0.10), then the probability of no response out of 40 subjects will be less than 5%. The probability that more than 7 responders out of 40 subjects (ORR > 17.5%) are observed will be less than 5% under the null hypothesis with ORR ≤ 0.10 but more than 80% under alternative hypothesis with ORR = 0.25. <u>Part 2c and Part 2e</u> If target ORR is more than 15% (null hypothesis: ORR ≤ 0.15, alternative hypothesis: ORR > 0.15), then the probability of no response out of 20 subjects will be less than 5%. The probability that more than 4 responders out of 20 subjects (ORR > 20%) are observed will be less than 20% under the null hypothesis with ORR ≤ 0.15 but more than 75% under alternative hypothesis with ORR = 0.30. <u>Part 2d</u> If target ORR is more than 15% (null hypothesis: ORR ≤ 0.15, alternative hypothesis: ORR > 0.15), then the probability of less than 5 responders out of 60 subjects will be less than 5%. The probability that more than 14 responders out of 60 subjects (ORR > 23.3%) are observed will be less than 5%

<table>
<tr><td>EudraCT/IND Number:</td><td>Eudra CT: Not obtained/ IND Number: 127553</td></tr>
<tr><td></td><td>under the null hypothesis with ORR ≤ 0.15 but more than 80% under alternative hypothesis with ORR = 0.30.
The probability values for the sample size are derived based on binomial distribution using SAS® version 9.2.</td></tr>
<tr><td>Subject Eligibility Criteria:</td><td><u>Inclusion Criteria</u>
Subjects must satisfy all of the following criteria to be included in the study:
Common Inclusion Criteria (Part 1 and Part 2):
1. Age ≥ 20 years in Japan, ≥ 18 years in the United States.
2. Has an Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1.
3. Has LVEF ≥ 50% by either echocardiography (ECHO) or multiple-gated acquisition (MUGA) within 28 days before registration.
4. Has adequate organ function within 7 days before registration, defined as:
<table>
<tr><th>Item</th><th>Laboratory value</th></tr>
<tr><td>Platelet count</td><td>≥ 100 000/mm^3</td></tr>
<tr><td>Hemoglobin (Hb)</td><td>≥ 8.5 g/dL</td></tr>
<tr><td>Absolute neutrophil count (ANC)</td><td>≥ 1500/mm^3</td></tr>
<tr><td>Creatinine</td><td>≤ 1.5 × ULN, or creatinine clearance ≥ 60 mL/min as calculated using the modification Cockcroft-Gault equation</td></tr>
<tr><td>AST/ALT</td><td>≤ 3 × ULN (if liver metastases are present, ≤ 5 × ULN)</td></tr>
<tr><td>Total bilirubin</td><td>≤ 1.5 × ULN or < 3 × ULN in the presence of documented Gilbert's Syndrome or liver metastases at baseline</td></tr>
<tr><td>Prothrombin time and activated partial thromboplastin time</td><td>≤ 1.5 × ULN</td></tr>
</table>
5. Has adequate treatment washout period before registration, defined as:
<table>
<tr><th>Treatment</th><th>Washout period</th></tr>
<tr><td>Major surgery</td><td>≥ 4 weeks</td></tr>
<tr><td>Radiation therapy</td><td>≥ 4 weeks (if palliative stereotactic radiation therapy without abdominal, ≥ 2 weeks)</td></tr>
<tr><td>Autologous transplantation</td><td>≥ 3 months</td></tr>
<tr><td>Hormonal therapy</td><td>≥ 3 weeks</td></tr>
<tr><td>Chemotherapy</td><td>≥ 3 weeks (≥ 2 weeks for 5-</td></tr>
</table>
</td></tr>
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(including antibody drug therapy)	fluorouracil-based agents, folinate agents and/or weekly Paclitaxel. ≥ 6 weeks for nitrosoureas or mitomycin C, >1 week for TKIs approved for the treatment of NSCLC - baseline CT scan must be completed after discontinuation of TKI)
Immunotherapy	≥ 4 weeks
Cytochrome P450 (CYP) 3A4 strong inhibitor	≥ 3 elimination half-lives of the inhibitor
Organic anion transporting polypeptide inhibitor	≥ 3 elimination half-lives of the inhibitor

6. Is able to provide written informed consent. Subject must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible toxicities) and must sign and date an Institutional Review Board (IRB) approved informed consent form (ICF) (including Health Insurance Portability and Accountability Act [HIPAA] authorization, if applicable) before performance of any study-specific procedures or examinations.
7. Is willing to provide pre-existing diagnostic or resected tumor samples.
8. Has a life expectancy of ≥ 3 months.

Additional Inclusion Criteria for Part 1 (Dose Escalation)

9. Has a pathologically documented advanced/unresectable or metastatic breast cancer or gastric or gastroesophageal junction adenocarcinoma that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.

Additional Inclusion Criteria for Part 2a (Dose Expansion)

10. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER2 overexpression (IHC 3+ or in situ hybridization [ISH*] +) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.
    * ISH: fluorescence in situ hybridization (FISH) or dual color in situ hybridization (DISH)
11. Treated with T-DM1.
12. Has measurable disease based on Response

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	Evaluation Criteria in Solid Tumors (RECIST) version 1.1. **Additional Inclusion Criteria for Part 2b (Dose Expansion)** 13. Has a pathologically documented advanced/unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma with HER2 overexpression (IHC 3+ or IHC 2+/ISH* +) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. It is recommended to obtain HER2 status after completing the last HER2-targeting treatment. * ISH: FISH or DISH 14. Treated with trastuzumab. 15. Has measurable disease based on RECIST version 1.1. **Additional Inclusion Criteria for Part 2c (Dose Expansion)** 16. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER2 low expression (IHC 2+/ISH* –, IHC 1+/ISH* –, or IHC 1+/ISH* untested) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. Subjects with HER2 low expression metastatic breast cancer who have exhausted treatments that can confer any clinically meaningful benefit (eg, other therapies such as hormonal therapy for patients who are hormone receptor positive) are also eligible. * ISH: FISH or DISH 17. Has measurable disease based on RECIST version 1.1. **Additional Inclusion Criteria for Part 2d (Dose Expansion)** 18. Satisfy at least one of the following criteria. • Has a pathologically documented advanced/unresectable or metastatic solid malignant tumor with HER2 expression (determined by IHC, FISH, Next Generation Sequencing, or other analysis techniques as appropriate) other than breast cancer and gastric or gastroesophageal junction adenocarcinoma that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. • Has a pathologically documented advanced/unresectable or metastatic solid malignant tumor with HER2 mutation (determined by Next Generation Sequencing or other analysis techniques as appropriate) that is

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	refractory to or intolerable with standard treatment, or for which no standard treatment is available. 23. Is able to provide fresh tumor biopsy specimen. 19. Has measurable disease based on RECIST version 1.1. **Additional Inclusion Criteria for Part 2e (Dose Expansion)** 20. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER2 expression (IHC 1+, IHC 2+, IHC 3+ and/or ISH*+) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. 21. Treated with T-DM1 (patients with HER2 overexpression only). 22. Has measurable disease based on RECIST version 1.1. **<u>Exclusion Criteria</u>** Subjects who meet any of the following criteria will be disqualified from entering the study: 1. Has a medical history of symptomatic CHF (New York Heart Association [NYHA] classes II-IV) or serious cardiac arrhythmia requiring treatment. 2. Has a medical history of myocardial infarction or unstable angina within 6 months before registration or troponin levels consistent with myocardial infarction as defined according to manufacturer. 3. Has a QTc prolongation to > 450 millisecond (ms) in males and > 470 ms in females based on a 12-lead electrocardiogram (ECG) in triplicate. 4. Has a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening. 5. Has an uncontrolled infection requiring intravenous injection (IV) of antibiotics, antivirals, or antifungals. 6. Known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. 7. Is a lactating mother (Women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days before registration. 8. Male and female subjects who are unwilling to use adequate contraceptive methods (eg, concomitant use of a spermatocidal agent and barrier contraceptive, intrauterine contraceptive, which are approved or certificated in Japan [for Japanese subjects] and US

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	[for US subjects]) during the study and for at least 7 months after the last dose of DS-8201a. 9. Has clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. 10. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE version 4.0, grade ≤ 1 or baseline. Subjects with chronic grade 2 toxicities may be eligible per the discretion of the Investigator. 11. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator. 12. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product. 14. Has a history of severe hypersensitivity reactions to other monoclonal antibodies. **Additional Exclusion Criteria for Part 2 (Dose Expansion)** 13. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated, or contralateral breast cancer.
Dosage Form, Dose and Route of Administration:	Two types of DS-8201a drug product, DS-8201a for Injection [redacted] (FL-DP1) and DS-8201a for Injection [redacted] (FL-DP2), will be supplied in this study. FL-DP1 material will be used for Part 1, Part 2a, 2b, 2c and 2d. FL-DP2 material will be used for Part 2e. DS-8201a will be administered as an IV solution. Subjects with solid malignant tumors will treat with DS-8201a on Day 1 of Q3W. An alternative drug administration schedule for dose expansion may be considered after establishing the MTD and/or RP2D of DS-8201a using the above schedule, and upon review of the human safety, and PK parameters by the Investigators and Sponsor. <u>RP2D</u> Determined RP2D of DS-8201a is 6.4 mg/kg Q3W or 5.4 mg/kg Q3W. In Part 2a, approximately 50 subjects will receive 6.4 mg/kg of DS-8201a Q3W and another approximately 50 subjects will receive 5.4 mg/kg of DS-8201a Q3W. In Part 2b, approximately 20 subjects will receive 6.4

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	mg/kg of DS-8201a Q3W and another approximately 20 subjects will receive 5.4 mg/kg of DS-8201a Q3W. In Part 2c, first approximately 20 subjects will receive 6.4 mg/kg of DS-8201a Q3W but additional approximately 20 subjects may receive another dose level of DS-8201a Q3W. In Part 2d and Part 2e, all subjects will receive 6.4 mg/kg of DS-8201a Q3W.
Study Endpoints:	Safety endpoints: Safety endpoints will include DLTs, serious adverse events (SAEs), TEAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings. TEAEs will be graded according to the NCI-CTCAE version 4.0. Pharmacokinetic endpoints: Serum PK parameters (area under the concentration-versus-time curve, from time 0 to the last measurable concentration as calculated by the linear-up log-down trapezoidal method [AUClast], AUC during dosing interval [AUCtau], maximum (peak) observed concentration [Cmax], time of maximum observed concentration [Tmax] and trough serum concentrations [Ctrough]) of DS-8201a for each subject will be estimated using standard noncompartmental methods. For total anti-HER2 antibody and MAAA-1181, all parameters listed above will be estimated. Descriptive statistics will be provided for all serum concentration data and PK parameter values, with a breakdown by dose level/cohort within each Part and study day as appropriate. Efficacy endpoints: Tumor response will be evaluated using RECIST version 1.1. ORR (the sum of complete response [CR] rate and partial response [PR] rate), disease control rate (DCR, the sum of CR rate, PR rate, and stable disease [SD] rate), response duration, duration of SD, time to response (TTR), and progression free survival (PFS), overall survival (OS), percent change in target lesion, time on therapy of the most recent prior regimen the subject received and that of DS-8201a. The Efficacy Variable(s) will be also evaluated at 18 weeks after Day 1 of Cycle 1.
Statistical Analyses:	The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or the last subject enrolled in Part 2 of the study has completed at least 6 months of study drug treatment. After the primary analysis, the main study will be closed and the data will be followed until completion. Descriptive statistics will be provided for selected demographic, safety, and PK data by dose level/cohort within

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	each Part and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges (as well as geometric means and geometric coefficient of variation for Cmax and AUC PK parameters), while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented. Safety Analyses: The safety profile will be based on adverse events (AEs), physical examination findings, vital sign measurements, clinical laboratory measurements, ECG recordings, ECHO/MUGA findings, and ophthalmologic findings. AEs will be graded according to the NCI-CTCAE version 4.0. In the Dose Escalation part, the incidence of DLTs will also be evaluated. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the Dose Escalation part, the number of DLTs identified among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized for each cohort of DS-8201a. Efficacy Analyses: Efficacy variables will include ORR (the sum of CR and PR rates); DCR (the sum of CR rate, PR rate, and SD rate for a minimum of 5 weeks from the first dosing date), response duration, duration of SD, TTR, and PFS, using RECIST 1.1. The efficacy variables will be listed and summarized. For ORR and DCR, point estimates and 95% exact binomial confidence intervals will be provided. Time to event variables including PFS, OS, TTR, response duration, and duration of SD will be summarized descriptively using the Kaplan-Meier method. PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic PD or death due to any cause. Censoring rules for the PFS analysis will be specified in the statistical analysis plan (SAP). The growth modulation indices (the intrasubject ratio of PFS post-study treatment versus PFS post the most recent prior therapeutic regimen) will be summarized. Descriptive statistics for the best percent change in the sum of longest dimensions (SLD) of measurable tumors will be provided. A waterfall plot of the best percent change from screening in the SLD for each subject will be presented for subjects with advanced solid malignancies. Pharmacokinetic Analyses:

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	PK analyses will be performed on the PK analysis set. Serum concentration-time data for DS-8201a, total anti-HER2 antibody and MAAA-1181 will be listed, plotted, and summarized using descriptive statistics by dose level/cohort within each Part at each point and in study period (Part 1 and Part 2). PK parameters will be listed and summarized using descriptive statistics by dose level/cohort within each Part. <u>Biomarker and Exploratory Analyses:</u> Explorative analyses for biomarkers will be listed and summarized using descriptive statistics.

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ABBREVIATION	DEFINITION
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BI	before infusion
BLRM	Bayesian logistic regression model
cfDNA	cell free DNA
CFR	Code of Federal Regulations
CHF	congestive heart failure
CR	complete response
CRF	case report form
CRO	contract research organization
CSF	colony stimulating factor
CSPV	Clinical Safety and Pharmacovigilance
CT	computed tomography
cTnI	cardiac troponin I
CYP	cytochrome P450
DAR	drug-to-antibody ratio
DCR	disease control rate
DISH	dual color in situ hybridization
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
ECD	extracellular domain
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOI	end of infusion
EOT	end of treatment
EWOC	escalation with overdose control
F/U	follow-up
FISH	fluorescent in situ hybridization
GCP	Good Clinical Practice
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2

ABBREVIATION	DEFINITION
hERG	human ether-a-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	investigational new drug
INN	International Non-proprietary Name
IRB	institutional review board
IRT	interactive response technology
ISH	in situ hybridization
IV	intravenous injection
IVRS	interactive voice response systems
IWRS	interactive web response system
LVEF	left ventricular ejection fraction
mCRM	modified continuous reassessment method
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
NE	inevaluable
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival
OTC	over the counter
PAD	pharmacologically active dose
PD	progressive disease
PDy	pharmacodynamic(s)
PFS	progression free survival
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
Q3W	once every 3 weeks

ABBREVIATION	DEFINITION
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SAVER	serious adverse event report
SCR	screening
SD	stable disease
SLD	sum of longest dimensions
SOC	System Organ Class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse event reaction
T-DM1	trastuzumab emtansine
TEAE	treatment emergent adverse event
TTR	time to response
ULN	upper limit of normal

List of Pharmacokinetic Parameters

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

List of Definitions of Terms

ABBREVIATION	DEFINITION
FL-DP1	[redacted]
FL-DP2	[redacted]
MAAA-1181	The drug component of DS-8201a – a derivative of exatecan, a topoisomerase I inhibitor
MAAL-9001	The antibody component of DS-8201a – a humanized IgG1 monoclonal antibody produced in-house with reference to the same amino acid sequence of trastuzumab

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Data Summary

1.1.1. Investigational Product(s)

1.1.1.1. Name

DS-8201a

1.1.1.2. Description

DS-8201a is an antibody-drug conjugate (ADC) that targets HER2. DS-8201a consists of an antibody component ("MAAL-9001" hereafter), which is a humanized immunoglobulin G1 (IgG1) monoclonal antibody produced in house with reference to the amino acid sequence of trastuzumab, that is bound via a maleimide tetrapeptide linker to a drug component, which is an exatecan derivative that is a topoisomerase I inhibitor ("MAAA-1181" hereafter).

Two types of DS-8201a drug product, DS-8201a for Injection [redacted] (FL-DP1 hereafter) and DS-8201a for Injection [redacted] (FL-DP2 hereafter), will be supplied in this study. FL-DP2 drug product is added to be evaluated in subjects enrolled in the newly added cohort of Part 2e.

1.1.1.3. Intended Use Under Investigation

DS-8201a will be evaluated in subjects with advanced solid tumors

1.1.1.4. Nonclinical Studies

1.1.1.4.1. Pharmacology

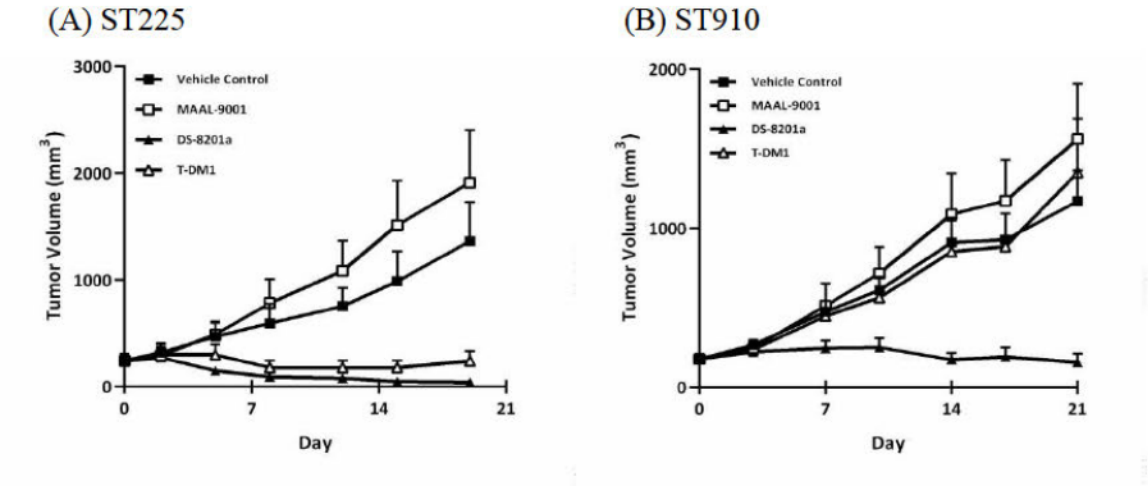
The fact that DS-8201a binds specifically to the HER2 extracellular domain (ECD) and does not bind to other HER family proteins has been confirmed by enzyme-linked immunosorbent assay (ELISA) using recombinant proteins. In addition, since the binding affinity of DS-8201a to HER2 was comparable to that of MAAL-9001, the antibody component of DS-8201a – a humanized IgG1 monoclonal antibody produced in-house with reference to the same amino acid sequence of trastuzumab, it is not considered that the conjugation of MAAA-1181 with MAAL-9001 has any effect on the binding affinity of MAAL-9001.

The results of in vitro cell growth inhibition studies conducted using several cancer cell lines have shown that DS-8201a has a more potent growth inhibition against HER2-positive cells than MAAL-9001, suggesting that the conjugation of MAAA-1181 enhances the growth inhibition of DS-8201a. Moreover, no growth inhibition was confirmed in HER2-negative cells, thus confirming the HER2 specificity of DS-8201a.

Similarly, when the in vivo antitumor activity of DS-8201a in a tumor-bearing mouse model of a HER2-positive gastric cancer cell line was studied, it was confirmed that DS-8201a exhibited potent, dose-dependent antitumor activity with tumor regression, and that this activity was even stronger than that of MAAL-9001.

In studies conducted in a tumor-bearing mouse model utilizing grafted tumor tissue obtained from breast cancer patients, DS-8201a exhibited antitumor activity both in an HER2 high-expressing model with an IHC score of 2+ and also in an HER2 low-expressing model with an IHC score of +1, in which T-DM1 was insensitive. Therefore, in the clinical setting, DS-8201a is expected to be effective against HER2 low-expressing tumors for which T-DM1 does not have an indication. (**Figure 1.1**)

Figure 1.1: Anti-tumor Effect of DS-8201a, MAAL-9001, and T-DM1 against ST225 and ST910 Patient-Derived Breast Cancer Xenograft Model



Data represent the mean + standard error of the mean (n = 5).
Mice were subcutaneously implanted with ST225 and ST910 patient-derived xenografts.
DS-8201a, MAAL-9001, or T-DM1 at the dose of 10 mg/kg were administered on Day 0.
The tumor volume of each mouse was calculated according to the following equation:

Tumor volume (mm^3) = 0.52 × length × $width^2$

HER2 expressing levels; ST225 model was IHC 2+ and FISH positive, and ST910 model was IHC 1+ and FISH negative.

In studies on the mechanism of action of DS-8201a, DS-8201a [redacted] has also been confirmed to cause deoxyribonucleic acid damage and induce apoptosis, effects that are assumed to be the result of MAAA-1181, which has topoisomerase I inhibitory activity.

Therefore, DS-8201a is considered to exhibit HER2-specific cell growth inhibition and antitumor activity via a novel mechanism of action that combined the pharmacological activities of MAAL-9001, the antibody component, with those of MAAA-1181, the drug component.

1.1.1.4.2. Safety Pharmacology

In telemetered male cynomolgus monkeys treated with single intravenous doses of DS-8201a, no effects on the cardiovascular system, the respiratory system, or the central nervous system were observed at dose levels up to 78.8 mg/kg. In addition, in human ether-a-go-go-related gene (hERG) studies of MAAA-1181, the drug component, MAAA-1181 did not inhibit the hERG channel current at concentrations of up to 10 µmol/L (approximately 5000 ng/mL).

1.1.1.4.3. Pharmacokinetics and Drug Metabolism

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

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

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

No major differences were found among the metabolite profiles of DS-8201a in rat, monkey, and human hepatocytes. MAAA-1181 was metabolized by CYP enzymes; CYP3A4 was the primary CYP enzyme in the metabolism, CYP3A5 and CYP2D6 were also involved in the metabolism.

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

1.1.1.4.4. Toxicology

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

In an intermittent intravenous dosing study of DS-8201a in cynomolgus monkeys (Q3W, 6 weeks), one female was sacrificed moribund at 78.8 mg/kg, the highest dose level. The major toxicity findings in this moribund animal were observed in the intestine, hematopoietic system, skin, and kidney. The cause of the moribundity appeared to be the deteriorated condition of the animal which included decreased body weight and food consumption, as well as bone marrow toxicity and intestinal toxicity. The major findings of toxicity in the surviving animals were observed in the intestine at dose levels of 10 mg/kg and greater, and in the lung, testes, and skin at dose levels of 30 mg/kg and greater. In addition, hematopoietic system toxicity, renal toxicity,

and ECG abnormalities (shortened PR interval and QTc prolongation) were found at 78.8 mg/kg. Except for the pulmonary and skin toxicity (pigmentation), these findings tended to recover.

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

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

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

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

1.1.1.4.5. Human Starting Dose

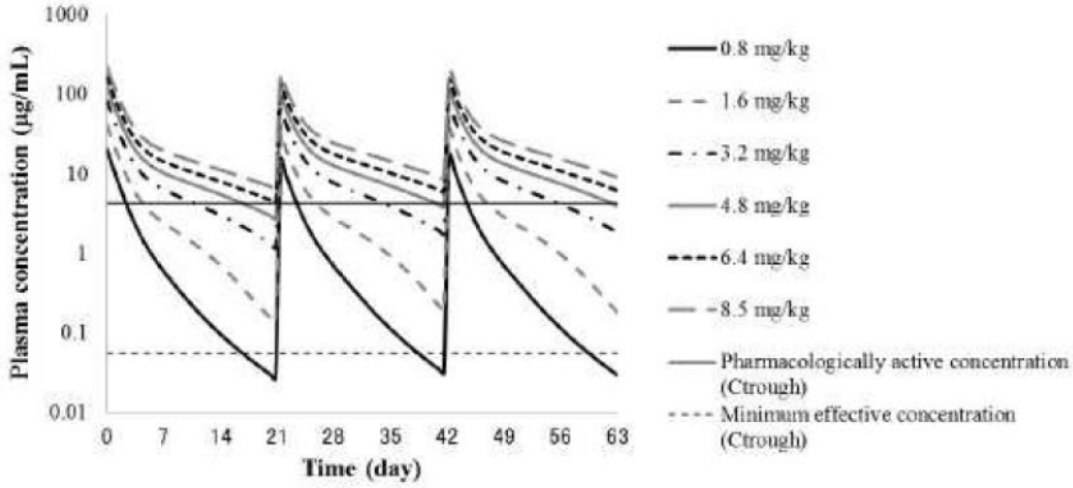
The initial human starting dose is determined by using the HNSTD in cynomolgus monkeys, which exhibit a higher level of toxicological sensitivity than rats and which exhibit a level of cross-reactivity similar to that of humans. For the HNSTD in cynomolgus monkeys, the HED is used. It was converted so that the dose per body surface area (mg/m^2) was the same in the experimental animals and in humans, in accordance with the extrapolation method that is widely used for drug products that exhibit cytotoxicity.

The HED of HNSTD was calculated to be 9.7 mg/kg by dividing the HNSTD in cynomolgus monkeys, 30 mg/kg, by the correction factor for cynomolgus monkeys of 3.1. In accordance with the Nonclinical Evaluation for Anticancer Pharmaceuticals (the ICH S9 guidelines), the estimated maximum starting dose for a Phase 1 clinical study would be 1.60 mg/kg as one-sixth of the HED of HNSTD. However, as a conservative approach, the human starting dose of 0.8

mg/kg which is one-twelfth of HED of HNSTD is selected for this study, because the results of the toxicity studies in cynomolgus monkeys suggested that the lungs might be affected.

Additionally, in the nonclinical pharmacology study, the plasma concentration-time profiles following repeated administration of DS-8201a Q3W for 3 cycles (Q3W × 3) to humans were simulated on the basis of the pharmacokinetics of DS-8201a in cynomolgus monkeys. The results are shown in Figure 1.2. Based on the Ctrough data during the treatment cycle, 0.8 and 4.8 mg/kg of the dose given Q3W would be required to achieve Ctrough close to the anticipated minimum effective concentration (0.0551 μg/mL) and pharmacologically active concentration (4.26 μg/mL). Assuming DS-8201a pharmacokinetics in humans are similar to those in cynomolgus monkeys, these results suggest that the minimum effective dose and the PAD were expected to be 0.8 and 4.8 mg/kg, respectively, with a dosage Q3W in humans.

Figure 1.2: Predicted Plasma Concentration Profiles of DS-8201a in Monkeys after Repeated Intravenous Administration Every 3 Weeks for 3 Cycles



Minimum effective concentration and pharmacologically active concentration were determined in a human gastric tumor mouse xenograft model.

1.1.1.5. Clinical Experience

This is the first-in human study of DS-8201a. No prior clinical experience of DS-8201a is available.

1.2. Study Rationale

DS-8201a is an ADC that targets HER2. A humanized IgG1 monoclonal antibody with reference to the amino acid sequence of trastuzumab is used as the antibody component and a derivative of exatecan, a topoisomerase I inhibitor, is used as the drug component. DS-8201a is expected to inhibit tumor growth on the basis of the following reasons: it exhibits [redacted] the MAAA-1181 that is released from DS-8201a after the internalization induces apoptosis by inhibiting topoisomerase I.

HER2 is a member of the HER superfamily, and initiates signal transduction via the PI3K/AKT and RAS/MAPK pathways.[1], [2] In human advanced solid tumors, expression of HER2 protein has been reported in various tumor tissues and a variety of cultured tumor cell lines including breast cancer,[3] gastric cancer,[4], [5] pancreatic cancer,[6] lung cancer,[7] colorectal cancer,[8] and ovarian cancer.[9] There are also many reports demonstrating an association between expression of HER2 protein and clinical poor prognosis. In normal human tissue, low expression of HER2 protein has been reported on cell membranes of epithelial cells in the gastro-intestinal, respiratory, reproductive, and urinary tract as well as in the skin, breast and placenta.[10]

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

In nonclinical studies, the fact that DS-8201a binds specifically to the HER2 ECD and does not bind to other HER family proteins has been confirmed. In vitro studies indicate that DS-8201a exhibits HER2 expression-dependent cell growth inhibition activity, moreover, no growth inhibition was confirmed in HER2-negative cells, thus confirming the HER2 specificity of DS-8201a. In vivo studies using a tumor-bearing mouse model suggest that administration of DS-8201a results in the regression of HER2-positive tumors. Emtansine, which has a tubulin polymerization inhibition activity, is used as the drug component in T-DM1. Since MAAA-1181 that inhibits topoisomerase I is used in DS-8201a, DS-8201a is expected to be effective even in tumors that do not respond or are resistant to T-DM1. DS-8201a exhibits anti-tumor effect with tumor regression in tumors that express low levels of HER2, against which T-DM1 has little effect, and is therefore also expected to be effective against tumors that express low levels of HER2, for which HER2 therapy including T-DM1 has not been approved. One reason for this may be that the drug-to-antibody ratio (DAR) for DS-8201a is approximately 8, compared to a DAR of average 3.5 for T-DM1,[14] meaning that DS-8201a can deliver more drugs into the cell than T-DM1.

In summary, DS-8201a has a different drug component from that of T-DM1 and is expected to show activity in the tubulin inhibitor insensitive tumors and in low HER2-expressing tumors. Thus, DS-8201a will be a benefit to a broader patient population than T-DM1. Therefore, DS-8201a is being developed as an ADC targeting HER2. This clinical trial is the first-in-human study designed to evaluate the safety, tolerability, PK, and efficacy of DS-8201a doses using FL-DP1 drug product in the dose escalation Part 1 of the trial; after the dose for expansion is selected from Part 1, the safety, tolerability, efficacy and PK, will be further evaluated in dedicated cohorts of subjects with solid tumors administered FL-DP1 drug product (Parts 2a, 2b, 2c, and 2d) and in subjects administered FL-DP2 drug product (Part 2e). The PK profile between FL-DP1 and FL-DP2 drug product will be assessed for bridging in clinical use.

1.3. Risks and Benefits for Study Subjects

Non-clinical studies have demonstrated the potent anti-tumor activity of DS-8201a in tumor-bearing mouse models. Thus, similar to other HER2-targeted products, DS-8201a is expected to demonstrate efficacy in treating HER2-expressing tumors.

In nonclinical toxicology studies, the intestinal toxicity, hematopoietic system toxicity, pulmonary toxicity, testicular toxicity, skin toxicity, and renal toxicity were found in association with the administration of DS-8201a. In addition to these toxicities, similar to other products of the same class, the possibility of cardiotoxicity, hepatotoxicity, embryo-fetal toxicity, or phototoxicity occurring in subjects receiving DS-8201a cannot be excluded. As with any therapeutic antibodies, there is a possibility of infusion related reactions, immune responses causing allergic or anaphylactic reactions of DS-8201a.

Based on the efficacy and safety data observed in the nonclinical studies and the information from other products of the same class, the benefit-risk balance supports clinical development of DS-8201a.

1.4. Population, Route, Dosage, Dosage Regimen, Treatment Period

DS-8201a will be administered as an IV solution. Subjects with solid malignant tumors will receive DS-8201a on Day 1 of Q3W. An alternative drug administration schedule for dose escalation may be considered after establishing the MTD and/or RP2D of DS-8201a using the above schedule, and upon review of the human safety, and PK parameters by the Investigators and Sponsor (Refer to Section 3 and 4 for details.).

Subjects enrolled in Part 1, Part 2a, Part 2b, Part 2c and Part 2d will receive FL-DP1 drug product, and those enrolled in Part 2e will receive FL-DP2 drug product.

1.5. Compliance Statement, Ethics and Regulatory Compliance

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

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

1.5.1. Subject Confidentiality

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

The Investigator must ensure that the subject's anonymity is maintained. On the Electronic Case Report Forms (eCRF) or other documents submitted to Sponsor and/or its contract research organization (CRO), subjects should be identified by a unique Subject Number as designated by the Sponsor. Documents that are not for submission to Sponsor or 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 Independent Ethics Committee (IEC) or Institutional Review Board (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.

1.5.2. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. The written ICF should be prepared in the local language(s) of the potential subject population.

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

The subject's written informed consent should be obtained prior to his/her participation in the study, and 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 that informed consent was given should be recorded on the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has orally 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 in the United States, an additional consent is required for the HIPAA.

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

The consent form should be signed and personally dated by the subject or legally acceptable representative prior to his/her participation in the study.

1.5.3. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator brochure, any 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 must submit and, where necessary, obtain approval from the IRB and/ or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB of deviations from the protocol or SAEs occurring at the site and other AE reports received from Sponsor 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 insure 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.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

2.1.1.1. Part 1 (Dose Escalation)

The primary objectives are as follows:

1. To assess the safety and tolerability of DS-8201a.
2. To determine the MTD or the RP2D of DS-8201a.

2.1.1.2. Part 2 (Dose Expansion)

The primary objectives are as follows:

1. To assess the safety and tolerability of DS-8201a at the MTD/the RP2D.
2. To evaluate the efficacy of DS-8201a at the MTD/the RP2D.

2.1.2. Secondary Objectives

2.1.2.1. Part 1 (Dose Escalation)

The secondary objectives are as follows:

1. To assess the PK profile of DS-8201a, total anti-HER2 antibody, and MAAA-1181.
2. To evaluate the efficacy of DS-8201a.
3. To assess the incidence of anti-drug antibody (ADA) against DS-8201a.

2.1.2.2. Part 2 (Dose Expansion)

The secondary objectives are as follows:

1. To assess the PK profile of DS-8201a, total anti-HER2 antibody, and MAAA-1181.
2. To assess the incidence of ADA against DS-8201a.

2.1.3. Exploratory Objectives: Part 1 (Dose Escalation) and Part 2 (Dose Expansion)

The exploratory objectives are as follows:

1. To assess the biomarkers related to DS-8201a.

2.2. Study Hypothesis

DS-8201a will be safe and well-tolerated and exhibit acceptable PK properties in subjects with advanced solid malignant tumors. See Section 11.10 for sample size determination.

3. STUDY DESIGN

3.1. Overall Plan

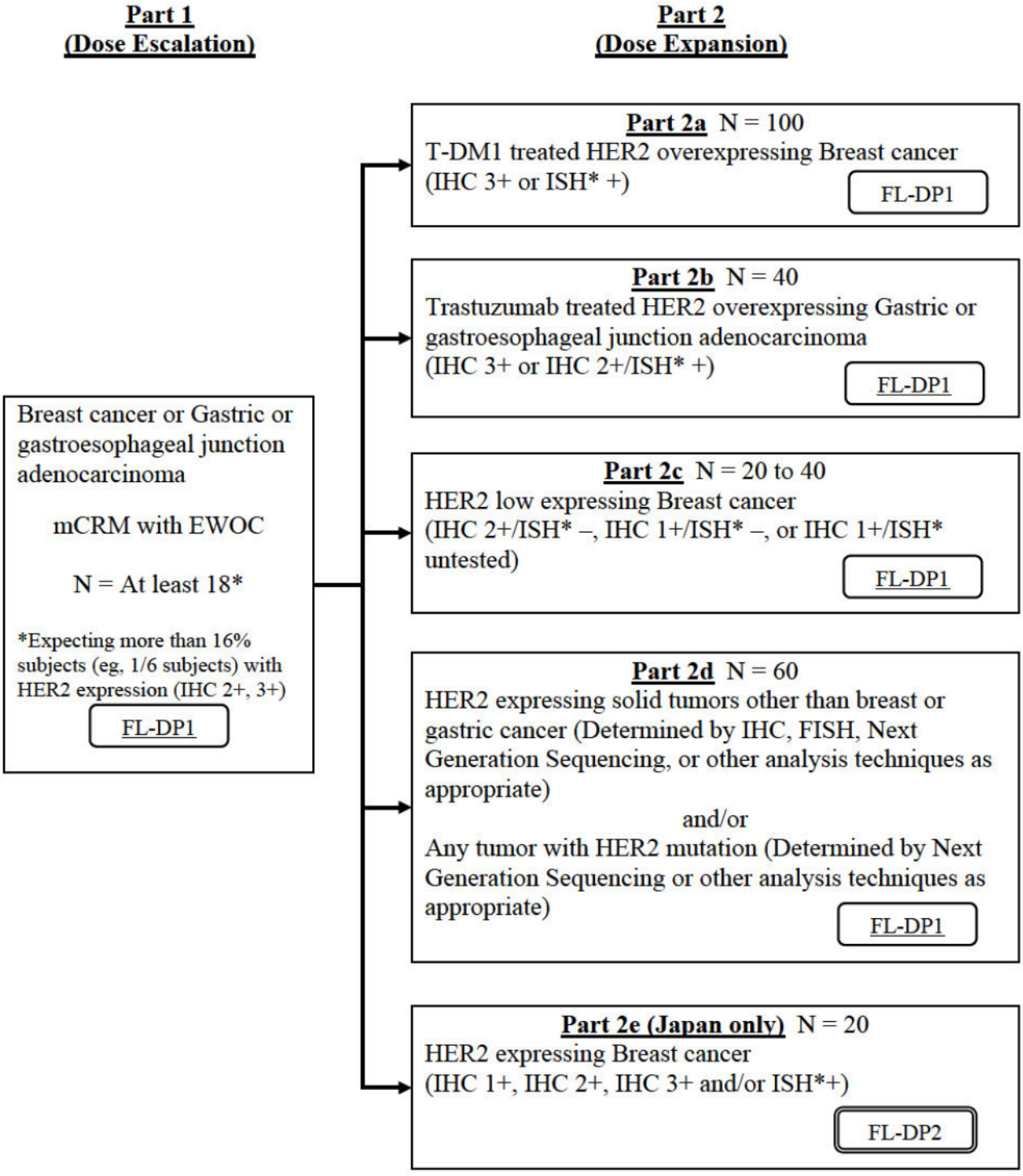
3.1.1. Study Type

This is a Phase 1, two-part, multicenter, non-randomized, open-label, multiple dose, first in human study of DS-8201a. Study sites from Japan and the United States are planned for this study. Part 2e (Dose Expansion) will be conducted at Japanese sites only.

3.1.2. Treatment Groups

This 2-part study will include both a Dose Escalation part, to identify the MTD or the RP2D of DS-8201a, and a Dose Expansion part, to confirm the safety, tolerability and efficacy of DS-8201a at the MTD/RP2D. In Part 1, more than 16% of subjects (eg, 1 per 6 subjects) are expected to be HER2 expression (IHC 2+ or 3+). In Part 2, subjects with HER2 expression, including HER2 low, will be enrolled. In order to assess the safety, efficacy and PK profile of FL-DP1 and FL-DP2 drug products in each cohort, at least 20 subjects will be enrolled in each Part. The Study Design Schema is as shown below:

Figure 3.1: Study Design Schema of DS8201-A-J101



* ISH: FISH or DISH

3.1.3. Study Endpoints

The endpoints for the study include the following:

- Safety endpoints:

Safety endpoints will include DLTs, SAEs, TEAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings. TEAEs will be graded according to the NCI-CTCAE version 4.0.

- Pharmacokinetic endpoints:

Serum PK endpoints (area under the concentration-versus-time curve, from time 0 to the last measurable concentration as calculated by the linear-up log-down trapezoidal method [AUClast], AUC during dosing interval [AUCtau], maximum (peak) observed concentration [Cmax], time of maximum observed concentration [Tmax] and trough serum concentrations [Ctrough]) of DS-8201a for each subject will be estimated using standard noncompartmental methods. For total anti-HER2 antibody and MAAA-1181, all parameters listed above will be estimated.

- Efficacy endpoints:

Tumor response will be evaluated using RECIST version 1.1. ORR (the sum of CR rate and PR rate), DCR (the sum of CR rate, PR rate, and SD rate), response duration, duration of SD, TTR, PFS, OS, percent change in target lesion, time on therapy of the most recent prior regimen the subject received and that of DS-8201a. Tumor assessment will be performed by both the investigator and independent central imaging facility. The Efficacy Variable(s) will be also evaluated at 18 weeks after Day 1 of Cycle 1.

3.1.4. Duration of the Study

Part 1 is expected to last approximately one and a half years from the time the first subject is enrolled to the time the last subject is off the DLT evaluation period. Part 2 is expected to last approximately one and a half years from the time the first subject is enrolled to the time the last subject is off the study.

3.1.5. Duration of Subject Participation

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

3.1.6. Stopping Rules

The study treatment will be continued according to the dosing criteria to derive clinical benefit in the absence of withdrawal of subject consent, PD, or unacceptable toxicity. If the study treatment is delayed more than 4 weeks from the planned date of administration, the subject will be withdrawn from the study (See sections 3.2.1.2.1, 3.2.1.2.3.1 and 4.2.1).

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

3.1.7. Dose-limiting Toxicities

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the DLT evaluation period (Day 1 to Day 21 in Cycle 1 of Part 1) and is grade 3 or above according to NCI-CTCAE version 4.0, with the exceptions as defined below:

For hematological toxicities, a DLT is defined as follows:

- Grade 4 neutrophil count decreased lasting > 7 days, neutrophil count decreased that requires standard therapies, such as colony stimulating factor (CSF)
- Grade ≥ 3 febrile neutropenia
- Grade 4 anemia
- Grade 4 platelet count decreased
- Grade ≥ 3 platelet count decreased lasting > 7 days
- Grade ≥ 3 platelet count decreased with clinically significant hemorrhage
- Grade 4 lymphocyte count decreased lasting ≥ 14 days

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

- Grade 4 AST or ALT increased
- AST or ALT > 5 × ULN (Grade 3), if accompanied by Grade ≥ 2 blood bilirubin increased
- In subjects without liver metastases, AST or ALT > 5 × ULN (Grade 3) lasting > 3 days
- In subjects with liver metastases, AST or ALT > 5 × ULN (Grade 3) lasting > 3 days, if the baseline level was ≤ 3 × ULN (Grade ≤ 1)
- In subjects with liver metastases, AST or ALT > 8 × ULN lasting > 3 days, if the baseline level was > 3 × ULN (Grade ≥ 2)

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

- Symptomatic CHF
- LVEF decline to < 40% or > 20% drop from baseline
- Other grade ≥ 3 non-hematological, non-hepatic major organ toxicities

The following TEAEs are NOT considered DLTs:

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

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

In addition, with regard to other toxicities that hinder the conduct of the scheduled study treatment or anemia with blood transfusion, whether they are regarded as DLT will be determined based on consultation between the Investigator and Sponsor.
The premedication, which is a treatment before study drug administration to avoid AE, is prohibited during the DLT evaluation period.

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

For example:

- Neutrophil count decreased: CSF administration
- Nausea, vomiting: Antiemetics

3.1.8. Maximum Tolerated Dose and Recommended Phase 2 Dose Definition

Once the dose escalation stopping criteria are met, the MTD estimated by mCRM + EWOC will be the dose with the highest posterior probability of the DLT rate in the target DLT rate interval of (16%, 33%] among all doses fulfilling the overdose control constraint: there is less than 25% probability of a DLT rate > 33% (probability for excessive or unacceptable toxicity) (Section 3.2.1.2.1). The final MTD for each dosing schedule will be decided based on considerations of the respective MTDs estimated by the mCRM and on an overall assessment of safety data from subsequent cycles and PK information collected at all different doses tested. Upon determining the final MTD of the original Q3W and/or alternative dosing schedules, dosing regimen(s) will be selected for further evaluation in Part 2 (Dose Expansion). This regimen given at the final MTD determined in Part 1 is referred to as the "RP2D." RP2D can be several dose levels depending on the risk-benefit of study drug.

3.1.9. Management of Subjects With Adverse Events of Interests

3.1.9.1. Infusion Related Reactions

If an infusion related reaction is observed during DS-8201a administration, the infusion speed should be reduced or the infusion should be interrupted or discontinued based on the symptoms. Action taken for the infusion related reaction is referred according to the following Table 3.1.

Please see Section 9.3.3 for clinical summary and further management guidance.

Table 3.1: Actions Taken for Infusion Related Reaction

NCI-CTCAE Grade	Actions
Grade 1 Mild transient reaction: ; infusion interruption not indicated ; intervention not indicated	• If infusion related reaction is observed during administration, the infusion speed should be reduced by 50% and subjects should be closely monitored. • If no other reactions appear, the subsequent infusion speed could be resumed at the initial planned speed.

Table 3.1: Actions Taken for Infusion Related Reaction (Continued)

NCI-CTCAE Grade	Actions
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	• Administration of DS-8201a should be interrupted briefly. • Symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids) • If the event resolves or improves to grade 1, infusion can be re-started at a 50% reduced infusion speed. • Subsequent administrations should be conducted at the reduced speed.
Grade 3 Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion): recurrence of symptoms following initial improvement: hospitalization indicated for clinical sequelae	• Administration of DS-8201a should be discontinued immediately and permanently. • Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, intravenous fluid therapy, oxygen inhalation etc., should be administered.
Grade 4 Life-threatening consequences: urgent intervention indicated	

3.1.9.2. Cardiac Toxicity

Taking into consideration of the results of the nonclinical toxicology studies of DS-8201a and MAAA-1181 and the nonclinical and clinical information that are available for trastuzumab and T-DM1, the Investigator will check the LVEF to monitor for cardiac toxicity.

LVEF will be monitored by either ECHO or MUGA at the screening, BI of cycle 2, 3, and every 2 cycles thereafter until the end of treatment (EOT) (eg, Day 1 in Cycle 3, 5, 7, 9, 11...). Subjects with confirmed symptomatic cardiac dysfunction will be discontinued from the study. A symptomatic decline in LVEF will be handled with the algorithm shown in Table 3.2.

Please see Section 9.3.1 for clinical summary and further management guidance.

Table 3.2: Actions Taken for Cardiac Toxicity

Symptomatic CHF	LVEF < 40% or > 20% drop from baseline	LVEF 40% to ≤ 45% and decrease is ≥ 10% from baseline	LVEF 40% to ≤ 45% and decrease is < 10% from baseline	LVEF > 45%
Discontinue DS-8201a	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF < 40% or > 20% drop from	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within	Continue treatment with DS-8201a Repeat LVEF assessment within 3 weeks.	Continue treatment with DS-8201a

Symptomatic CHF	LVEF < 40% or > 20% drop from baseline	LVEF 40% to ≤ 45% and decrease is ≥ 10% from baseline	LVEF 40% to ≤ 45% and decrease is < 10% from baseline	LVEF > 45%
	baseline is confirmed, discontinue DS-8201a.	10% from baseline, discontinue DS-8201a.		

CHF = Congestive Heart Failure; LVEF = Left Ventricular Ejection Fraction

3.1.9.3. Pulmonary Toxicity

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

If a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out interstitial lung disease (ILD) /pneumonitis.

If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modification section below.

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations.

Evaluations should include:

- high resolution CT
- pulmonologist consultation
- pulmonary function tests and pulse oximetry (SpO_2)
- arterial blood gases if clinically indicated
- one blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (Kubo K, et al 2013 for guidance). [18]

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined in Table 3.3.

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

Please see Section 9.3.2 for clinical summary and further management guidance.

Table 3.3: Actions Taken for Study Drug Induced ILD or pneumonitis

NCI-CTCAE Grade	Actions
Grade 1	The administration of DS-8201a must be interrupted for any ILD events regardless of grade. For Grade 1 events, DS-8201a can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤ 28 days from date of onset, maintain dose • If resolved in > 28 days from date of onset, reduce dose 1 level
Grade 2, 3 or 4	Permanently discontinue subject from study treatment.

3.2. Selection of Doses

3.2.1. Experimental Treatments

The study will enroll subjects into cohorts with dose escalation by mCRM with EWOC principle as outlined in Section 3.2.1.2. The starting dose will be 0.8 mg/kg (See Section 1.1.1.4.5 for justification of the human starting dose).

Upon completion of Cycle 1 of Part 1 (Dose Escalation) and determination of the MTD/RP2D, Part 2 (Dose Expansion) will begin. In Part 1, the second subject in each dosing level should start dosing at least 24 hours after the initial dosing of the first subject to check the acute toxicity such as infusion-related reaction. Subjects in Part 2 will receive DS-8201a at the MTD/RP2D defined in Section 3.2.1.2.

Subjects in Part 1, Part 2a, Part 2b, Part 2c and Part 2d will receive FL-DP1 drug product, and those in Part 2e will receive FL-DP2 drug product.

3.2.1.1. For the Study

See Sections 1.1.1.4.5 and 1.2.

3.2.1.2. For Individual Subjects

3.2.1.2.1. Part 1 (Dose Escalation)

Dose escalation of DS-8201a to determine the MTD/RP2D will be guided by the mCRM using a BLRM following EWOC principle. Dose escalation will begin in subjects with advanced breast cancer and gastric or gastroesophageal junction adenocarcinoma. At least 18 subjects will be enrolled in Part 1. More than 16% of subjects (eg, 1 per 6 subjects) are expected to be HER2 expression (IHC 2+ or 3+). The proposed human starting dose of DS-8201a is 0.8 mg/kg, based on 1/12 HED of HNSTD in monkey (30 mg/kg).

During Part 1, an initial dose of DS-8201a will be infused intravenously into each subject for approximately 90 minutes on Day 1 of Cycle 1. A 21-day observation period (Cycle 1) will then occur, at the end of which all relevant safety data will be reviewed. Upon completion of Cycle 1, subjects may continue to receive DS-8201a Q3W(1 cycle) at the discretion of the Investigators, until unacceptable toxicity, PD, or withdrawal of consent. If there is no infusion related reaction

after initial dose, the next dose of DS-8201a will be infused intravenously into each subject for 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% of the baseline weight, the dose will be recalculated.

Dose level increment during dose escalation (Part 1) by mCRM with EWOC

- The dose level increment should be no less than 30% in order to have distinction among dose levels considering the inter-subject variability in exposure.
- The dose level increment should be no more than 100% even if the model suggests a higher dose than 100% for the next cohort.

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

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

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

The RP2D will be decided based on considerations of the respective MTD estimated by the mCRM, and on an overall assessment of safety data from subsequent cycles and efficacy/PK information collected at all different doses tested. For dose determination, Part 1 will be stopped according to the following rules: (a) at least 6 evaluable subjects have been enrolled at the MTD/RP2D level with at least 18 evaluable subjects in total enrolled in the dose escalation part, or (b) at least 9 evaluable subjects have been enrolled at a dose level which is the model's recommendation for the next dose cohort and for which the posterior probability of targeted toxicity is at least 50%, or (c) the initial dose level is too toxic.

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

3.2.1.2.2. Part 2 (Dose Expansion)

Upon completion of dose escalation (Part 1) with determination of MTD/RP2D, the Dose expansion part will begin.

Part 2 will consist of multiple cohorts: in subjects with T-DM1-treated HER2 overexpressing breast cancer (Part 2a); trastuzumab-treated HER2 overexpressing gastric or gastroesophageal junction adenocarcinoma (Part 2b); HER2 low expressing breast cancer (Part 2c); HER2 expressing other solid malignant tumor or any tumor with HER2 mutation (Part 2d); and HER2 expressing breast cancer (Part 2e). Approximately 100 subjects will be enrolled in Part 2a, approximately 40 subjects will be enrolled in Part 2b, approximately 20 to 40 subjects will be enrolled in Part 2c, approximately 60 subjects will be enrolled in Part 2d and approximately 20 subjects will be enrolled in Part 2e, respectively.

Subjects will receive DS-8201a on Day 1 of a 21-day cycle. The initial dose of DS-8201a will be infused intravenously into each subject for approximately 90 minutes on Day 1 of Cycle 1. If there is no infusion related reaction after initial dose, the next dose of DS-8201a will be infused intravenously into each subject for 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% of the baseline weight, the dose will be recalculated.

RP2D

Determined RP2D of DS-8201a is 6.4 mg/kg Q3W or 5.4 mg/kg Q3W. In Part 2a, approximately 50 subjects will receive 6.4 mg/kg of DS-8201a Q3W and another approximately 50 subjects will receive 5.4 mg/kg of DS-8201a Q3W. In Part 2b, approximately 20 subjects will receive 6.4 mg/kg of DS-8201a Q3W and another approximately 20 subjects will receive 5.4 mg/kg of DS-8201a Q3W. In Part 2c, first approximately 20 subjects will receive 6.4 mg/kg of DS-8201a Q3W but additional approximately 20 subjects may receive another dose level of DS-8201a Q3W. In Part 2d and Part 2e, all subjects will receive 6.4 mg/kg of DS-8201a Q3W.

3.2.1.2.3. Dose Interruptions and Reductions

3.2.1.2.3.1. Dose Interruptions

Investigators should confirm whether subjects satisfy the following dose interruption criteria before administration of the study drug (latest date within 3 days before administration). If a subject satisfies the dose interruption criteria, the dosing of DS-8201a must be interrupted until the subject recovers from all toxicities, after which, the Dose Resumption Rules shown in Table 3.4 should be followed.

The dose can be interrupted for up to 4 weeks from the planned date of administration. If a subject is assessed as requiring a dose delay longer than 4 weeks, the subject will be withdrawn from the study.

Table 3.4: Dose Interruption Criteria and Dose Resumption Rules

Toxicities	Dose Interruption criteria (within 3 days before administration)	Dose Resumption Rules
Neutrophil count decreased	< 1000/mm^3	Resolved to ≥ 1000/mm^3
Platelet count decreased	< 50 000/mm^3.	Resolved to ≥ 50 000/mm^3
Cardiac Toxicity	See Section 3.1.9.2.	
Pulmonary Toxicity	See Section 3.1.9.3.	
All other non-hematological toxicities, except alopecia	NCI-CTCAE version 4.0 grade ≥ 3 and Grade ≥ 3 fatigue lasting ≥ 48 hours.	Resolved to grade ≤ 1 or baseline values.
All other laboratory abnormalities that are not DLTs	NCI-CTCAE version 4.0 grade ≥ 3; the treatment interruption and resumption with DS-8201a will be at the discretion of the Investigator.	

The Investigator may consider dose interruptions or discontinuation of the study drug based on other events not listed in Table 3.4 according to the condition of subject.

3.2.1.2.3.2. Dose Reductions

For Part 1

If the dose is interrupted due to toxicities meeting the DLT definition (See Section 3.1.7 for DLT definitions) during treatment period, dose reduction should be conducted on the next administration.

When the study treatment is resumed, the next dose should be reduced to the dose of the previous cohort.

The dose level will not be below 0.8 mg/kg. After two reductions, further reduction should not be conducted and administration should be discontinued. However, further dose reduction may be conducted based on consultation between the Investigator and Sponsor. Once the dose of DS-8201a is reduced, no escalation is permitted.

The reference scheme of dose reduction at provisional doses is shown in Table 3.5.

Table 3.5: Reference Scheme of Dose Reduction at Provisional Doses for Part 1

Dose level before dose interruption		Dose level after first dose reduction		Dose level after second dose reduction
0.8 mg/kg	->	Discontinuation	->	-
1.6 mg/kg	->	0.8 mg/kg	->	Discontinuation
3.2 mg/kg	->	1.6 mg/kg	->	0.8 mg/kg
5.0 mg/kg	->	3.2 mg/kg	->	1.6 mg/kg

Dose level before dose interruption		Dose level after first dose reduction		Dose level after second dose reduction
6.4 mg/kg	->	3.2 mg/kg	->	1.6 mg/kg
8.0 mg/kg	->	6.4 mg/kg	->	5.4 mg/kg

The Investigator may consider dose reductions or discontinuation of the study drug according to the condition of subject.

For Part 2

If the dose is interrupted due to toxicities meeting the DLT definition (See Section 3.1.7 for DLT definitions) during treatment period, dose reduction should be conducted on the next administration.

When the study treatment is resumed, the next dose should be reduced according to Table 3.6.

After two reductions, further reduction should not be conducted and administration should be discontinued. However, further dose reduction may be conducted based on consultation between the Investigator and Sponsor. Once the dose of DS-8201a is reduced, no escalation is permitted.

Table 3.6: Scheme of Dose Reduction for Part 2

Dose level before dose interruption		Dose level after first dose reduction		Dose level after second dose reduction
8.0 mg/kg	->	6.4 mg/kg	->	5.4 mg/kg
6.4 mg/kg	->	5.4 mg/kg	->	4.4 mg/kg
5.4 mg/kg	->	4.4 mg/kg	->	3.2 mg/kg

The Investigator may consider dose reductions or discontinuation of the study drug according to the condition of subject.

3.2.2. Control Treatments

Not applicable.

4. STUDY POPULATION

4.1. 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, enroll in the study, reason for ineligibility, refused to participate).

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned Subject Number. The unique Subject Number for all subjects who provide written informed consent will be assigned by interactive response technology (IRT), encompassing both interactive voice response systems (IVRS) utilizing the telephone or tone dialers and interactive web response systems (IWRS) utilizing the internet. The date of registration is defined as the date that subject is successfully enrolled as eligible in the IRT system. The date of screen failure is defined as the date that subject is successfully enrolled as ineligible in the IRT system.

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

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 1.5.2.

A subject is considered to be enrolled as eligible in the study upon the Investigator's or designee's obtaining written informed consent from the subject (Section 1.5.2) and upon determination of all inclusion and exclusion criteria having been satisfied. After assigning Site Subject Identifier to each subject at the time of screening in 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. After assessment by Investigators, subject enrollment is conducted at central IRT. In Part 1 (Dose Escalation), more than 16% of the eligible subjects (eg, 1 per 6 subjects) are expected to be HER2 expression (IHC 2+ or 3+). In Part 2 (Dose Expansion), the eligible subjects will be enrolled in the five arms (Part 2a to Part 2e), respectively, according to the following Additional Inclusion Criteria (See Sections 4.1.1.3, 4.1.1.4, 4.1.1.5 and 4.1.1.6).

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

4.1.1. Inclusion Criteria

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

4.1.1.1. Common Inclusion Criteria (Part 1 and Part 2)

1. Age ≥ 20 years in Japan, ≥ 18 years in the United States.
2. Has an ECOG PS 0-1.
3. Has LVEF ≥ 50% by either ECHO or MUGA within 28 days before registration.
4. Has adequate organ function within 7 days before registration, defined as:

Item	Laboratory value
Platelet count	≥ 100 000/mm^3
Hemoglobin (Hb)	≥ 8.5 g/dL
Absolute neutrophil count (ANC)	≥ 1500/mm^3
Creatinine	≤ 1.5 × ULN, or creatinine clearance ≥ 60 mL/min as calculated using the modification Cockcroft-Gault equation
AST/ALT	≤ 3 × ULN (if liver metastases are present, ≤ 5 × ULN)
Total bilirubin	≤ 1.5 × ULN or < 3 × ULN in the presence of documented Gilbert's Syndrome or liver metastases at baseline
Prothrombin time and activated partial thromboplastin time	≤ 1.5 × ULN

5. Has adequate treatment washout period before registration, defined as:

Treatment	Washout period
Major surgery	≥ 4 weeks
Radiation therapy	≥ 4 weeks (if palliative stereotactic radiation therapy without abdominal, ≥ 2 weeks)
Autologous transplantation	≥ 3 months
Hormonal therapy	≥ 3 weeks
Chemotherapy (including antibody drug therapy)	≥ 3 weeks (≥ 2 weeks for 5-fluorouracil-based agents, folinate agents and/or weekly Paclitaxel. ≥ 6 weeks for nitrosoureas or mitomycin C, > 1 week for TKIs approved for the treatment of NSCLC - baseline CT scan must be completed after discontinuation of TKI)
Immunotherapy	≥ 4 weeks
CYP3A4 strong inhibitor	≥ 3 elimination half-lives of the inhibitor
Organic anion transporting polypeptide (OATP) inhibitor	≥ 3 elimination half-lives of the inhibitor

6. Is able to provide written informed consent. Subject must be fully informed about their illness and the investigational nature of the study protocol (including foreseeable risks and possible toxicities) and must sign and date an IRB approved ICF (including HIPAA authorization, if applicable) before performance of any study-specific procedures or examinations.
7. Is willing to provide pre-existing diagnostic or resected tumor samples.

8. Has a life expectancy of ≥ 3 months.

4.1.1.2. Additional Inclusion Criteria for Part 1 (Dose Escalation)

9. Has a pathologically documented advanced/unresectable or metastatic breast cancer or gastric or gastroesophageal junction adenocarcinoma that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.

4.1.1.3. Additional Inclusion Criteria for Part 2a (Dose Expansion)

10. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER2 overexpression (IHC 3+ or ISH* +) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.
    * ISH: FISH or DISH
11. Treated with T-DM1.
12. Has measurable disease based on RECIST version 1.1.

4.1.1.4. Additional Inclusion Criteria for Part 2b (Dose Expansion)

13. Has a pathologically documented advanced/unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma with HER2 overexpression (IHC 3+ or IHC 2+/ISH* +) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. It is recommended to obtain HER2 status after completing the last HER2-targeting treatment.
    * ISH: FISH or DISH
14. Treated with trastuzumab.
15. Has measurable disease based on RECIST version 1.1.

4.1.1.5. Additional Inclusion Criteria for Part 2c (Dose Expansion)

16. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER2 low expression (IHC 2+/ISH* –, IHC 1+/ISH* –, or IHC 1+/ISH* untested) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available. Subjects with HER2 low expression metastatic breast cancer who have exhausted treatments that can confer any clinically meaningful benefit (eg, other therapies such as hormonal therapy for patients who are hormone receptor positive) are also eligible.
    * ISH: FISH or DISH
17. Has measurable disease based on RECIST version 1.1.

4.1.1.6. Additional Inclusion Criteria for Part 2d (Dose Expansion)

18. Satisfy at least one of the following criteria.

    - Has a pathologically documented advanced/unresectable or metastatic solid malignant tumor with HER2 expression (determined by IHC, FISH, Next Generation Sequencing, or other analysis techniques as appropriate) other than breast and gastric

or gastroesophageal junction adenocarcinoma that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.

- Has a pathologically documented advanced/unresectable or metastatic tumor with HER2 mutation (determined by Next Generation Sequencing or other analysis techniques as appropriate) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.

23. Is able to provide fresh tumor biopsy specimen.
19. Has measurable disease based on RECIST version 1.1.

4.1.1.7. Additional Inclusion Criteria for Part 2e (Dose Expansion)

20. Has a pathologically documented advanced/unresectable or metastatic breast cancer with HER2 expression (IHC 1+, IHC 2+, IHC 3+ and/or ISH*+) that is refractory to or intolerable with standard treatment, or for which no standard treatment is available.
    * ISH: FISH or DISH
21. Treated with T-DM1 (patients with HER2 overexpression only).
22. Has measurable disease based on RECIST version 1.1.

4.1.2. Exclusion Criteria

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

1. Has a medical history of symptomatic CHF (NYHA classes II-IV) or serious cardiac arrhythmia requiring treatment. [1)]
2. Has a medical history of myocardial infarction or unstable angina within 6 months before registration or troponin levels consistent with myocardial infarction as defined according to manufacturer. [1)]
3. Has a QTc prolongation to > 450 millisecond (ms) in males and > 470 ms in females based on 12-lead ECG in triplicate. [1)]
4. 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. [1)]
5. Has an uncontrolled infection requiring IV of antibiotics, antivirals, or antifungals. [1)]
6. Known HIV infection, or active hepatitis B or C infection. [1)]
7. Is a lactating mother (Women who are willing to temporarily interrupt breastfeeding will also be excluded), or pregnant as confirmed by pregnancy tests performed within 7 days before registration. [1)]
8. Male and female subjects who are unwilling to use adequate contraceptive methods (eg, concomitant use of a spermatocidal agent and barrier contraceptive, intrauterine contraceptive, which are approved or certificated in Japan [for Japanese subjects] and US [for US subjects]) during the study and for at least 7 months after the last dose of DS-8201a. [2)]

9. Has clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms. Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with steroids may be included in the study if they have recovered from the acute toxic effect of radiotherapy. [1)]
10. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to NCI-CTCAE version 4.0, grade ≤ 1 or baseline. Subjects with chronic grade 2 toxicities may be eligible per the discretion of the Investigator. [1)]
11. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the Investigator. [1)]
12. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product. [1)]
14. Has a history of severe hypersensitivity reactions to other monoclonal antibodies.

4.1.2.1. Additional Exclusion Criteria for Part 2 (Dose Expansion)

13. Has multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other solid tumors curatively treated, or contralateral breast cancer. [3)]

Rationale for Exclusion Criteria and Additional Exclusion Criteria:

These criteria are included to

1) Minimize the risk for subject safety
2) Prevent pregnancy during treatment
3) Ensure enrollment of representative subjects for the planned indication

4.2. Removal of Subjects From Therapy

4.2.1. Reasons for Withdrawal/Early Discontinuation

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

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

- PD [per RECIST]
- Clinical Progression (provide date)
- AE
- Death
- Withdrawal by subject
- Lost to follow-up (F/U)

- Protocol violation (specify)
- Study terminated by 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 treatment should complete protocol specified withdrawal procedures (Section 4.2.2).

4.2.2. Withdrawal Procedures

Protocol-specified withdrawal procedures will involve an EOT visit and a F/U visit 28 days (- 7 days) after the last administration of 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).

4.2.3. Subject Replacement

Subject replacement is not allowed for this study.

4.2.4. Subject Re-screening Procedures

The study will allow re-screening for any subject who failed to meet eligibility criteria upon initial screening. For Part 1 and Part 2, the Site Subject Identifier 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. TREATMENTS ADMINISTERED

5.1. Investigational Products

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

Two types of DS-8201a drug product, FL-DP1 and FL-DP2, will be supplied in this study. FL-DP1 drug product will be used for Part 1, Part 2a, 2b, 2c and 2d. FL-DP2 drug product will be used for Part 2e.

The FL-DP1 clinical material is provided for infusion as a [redacted] of DS-8201a in a glass vial. FL-DP2 clinical material is provided for infusion as a [redacted] of DS-8201a in a glass vial.

It is supplied in single-use glass vials of sterile drug product solution.

5.1.1. Method of Assigning Subjects to Treatments and Blinding

5.1.1.1. Randomization

Not applicable.

5.1.1.2. Blinding

Both parts of the study are open-label and no blinding will be performed.

5.1.2. Method of Assessing Treatment Compliance

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

5.1.3. Labeling and Packaging

DS-8201a will be supplied by Sponsor. Study drug supplies will be packaged in cartons containing [redacted] FL-DP1 [redacted] and [redacted] FL-DP2 [redacted]. The packaging will be clearly labeled "For Clinical Study Use Only," and will show the display name of the investigational product, the investigational product manufacturing code, storage condition and other required information in accordance with local regulations.

5.1.4. Preparation

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

5.1.5. Storage

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

- Stored below -15°C (protected from light).

If storage conditions are not maintained per specified requirements, Sponsor or CRO should be contacted.

5.1.6. Drug Accountability

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

A Drug Accountability Record will be provided for the investigational product. The record must be kept current and should contain, the dates and quantities of drug received, subject's (identification number and/or initials or supply number as applicable), for whom the investigational product was dispensed, the date and quantity of investigational product 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 Sponsor. Investigational Product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of Investigational Product must be documented and the documentation included in the shipment. At the end of the study, a final Investigational Product reconciliation statement must be completed by the Investigator or designee and provided to the Sponsor. Unused drug supplies may be destroyed by the supervisor of investigational products in Japan and Investigator in the United States when approved in writing by Sponsor and Sponsor has received copies of the site's drug handling and disposition SOPs.

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

5.1.7. Retention Samples

Not applicable.

5.2. Concomitant Medications

Medications used from Day 1 of Cycle 1 to 28 days (– 7 days) after the last administration of DS-8201a will be recorded. All concomitant medications will be recorded on the eCRF.

5.2.1. Prohibited Concomitant Medications/Activities

The following medications and products will be prohibited:

- Other anticancer therapy, including cytotoxics, targeted agents, immunotherapy or endocrine therapy.
- Other investigational agents.
- CYP3A4 strong inhibitors listed in Supplement 6.
  If concomitant use of strong CYP3A4 inhibitors is unavoidable, consider delaying DS-8201a treatment until the strong CYP3A4 inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a strong CYP3A4 inhibitor is co-administered and DS-8201a treatment cannot be delayed, patients should be closely monitored for adverse reactions.
- Foods containing hypericum perforatum (Saint John's wort).
- Foods or beverages containing grapefruit.
- Avoid strong inducers of CYP3A4 listed in Supplement 6 in Part 1.
- OATP inhibitors listed in Supplement 6.
  If concomitant use of OATP inhibitors is unavoidable, consider delaying DS-8201a treatment until the OATP inhibitors have cleared from the circulation (approximately 3 elimination half-lives of the inhibitors) when possible. If a OATP inhibitor is co-administered and DS-8201a treatment cannot be delayed, patients should be closely monitored for adverse reactions.

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in 17.6 (Part 1 and Part 2).

6.1. Screening

Obtain of a signed and dated ICF before any study-related procedures or assessments are conducted. In this study, registration will be performed (See Section 4.1).

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

Before registration

- Assign a Site Subject Identifier.
- Record demographic (eg, birth date, sex, race, ethnicity [specifically for United States residents]), primary cancer history, significant medical history information and prior treatment history information for cancer.
- Record historical HER2 status.

  For Part 2b only: HER2 status should be evaluated based on a HER2 assessment that is taken after the last HER2-targeting treatment if tumor is available.
- Assess subjects for AEs.

Within 7 days before registration

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Assess functional status using the ECOG Performance Status Scale (Section 17.1).
- Obtain blood samples for safety laboratories (Section 9.8), prothrombin time and activated partial thromboplastin time, HER2ECD, troponin (preferably high-sensitivity troponin T) testing by study site, and cardiac troponin I (cTnI) testing by central lab (Section 6.8.5).
- 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.
- 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 90 days before registration

- Perform a HIV antibody test. HIV antibody test must be performed for Japanese subjects, and is optional for US subjects unless required by local regulations or IRB.

Before the first dose of study drug administration

- Perform a complete physical examination and record height.
- If there is no archived sample, Investigator performs a tumor biopsy before the first dose of study drug. Ten tumor slides for assessment of HER2 by IHC/FISH and HERmark are needed. The detailed procedures for preparing and submitting tumor samples will be provided in Section 6.8.2.
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5). Investigators may opt out of obtaining blood samples for immune monitoring analysis depending on a subject's condition.
- For Part 2d only:
  Perform a tumor biopsy before the first dose of study drug. Tumor tissue will be sent to the central laboratory for an exploratory biomarker analysis. Further details will be provided in the laboratory manual (Section 6.8.2.2).
  If tumor is not accessible for biopsy, the Investigators should discuss with the Sponsor whether a patient can be enrolled or not.
- [Optional] Obtain blood samples for cell free DNA (cfDNA) analysis (Section 6.8.5).

Within 28 days before registration

- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, and fundoscopy.
- Perform either ECHO or MUGA (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 17.2).

6.2. Randomization

Not applicable.

6.3. Treatment Period

In consideration of the subject's safety, the subjects will be hospitalized from Day 1 to Day 21 on Cycle 1 of Part 1 to allow for careful safety monitoring. However, temporary stay over outside the hospital is permitted at the Investigator's discretion. Investigator should examine the subject carefully before permission and the study site should train the subject about an emergency contact.

Instruct subject to refrain from prolonged exposure to ultraviolet rays. Additional safety assessments should be conducted as needed, at the Investigator's discretion.

For Part 2d, it is recommended to perform a tumor biopsy one time during Day 8 to 22 (prior to the subsequent study drug administration) of any cycle. Investigators may opt out of obtaining blood samples for immune monitoring analysis depending on a subject's condition.

6.3.1. Tumor assessment

The same imaging tumor assessment as at the time of screening by CT or MRI scans will be performed every 6 weeks (± 7 days) in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks (± 7 days) regardless of delay in dosing. The assessment will be conducted before Day 1 of each Cycle as possible. CT or MRI scans of the chest, abdomen and pelvis are mandatory. However, if there is no brain metastasis at the time of screening, CT or MRI should only be done when symptoms associated with brain metastasis occur. If no clinical symptoms are observed, brain CT or MRI is not mandatory. (Section 17.2).

In addition to the investigator's tumor assessment, review by independent central imaging facility will be performed. The detail 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 pre-dose on Day 1. If assessments at screening are performed within this period, they can be considered to be Day 1 data and there is no need to repeat them.

- Assess subjects for AEs.

Within 8 hours before administration

- Obtain PK blood sample (Section 6.8.3).
- Obtain blood sample for ADA (Section 6.8.6).

Latest data within 3 days before administration

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG Performance Status Scale (Section 17.1).
- Obtain blood samples for safety laboratories (Section 9.8).
- Perform a 12-lead ECG in triplicate.

6.3.2.2. Administration and after Infusion

- Administer DS-8201a per Section 3.1.2.

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

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

- Perform a 12-lead ECG in triplicate within 30 minutes after end of infusion (EOI), and 2 to 4 hours after the start of administration.
- Obtain PK blood samples at the following time points: within 15 minutes after EOI, 2, 4 and 7 hours (± 15 minutes) after the start of administration (Section 6.8.3).
- Obtain blood samples for cTnI testing by central lab (Section 6.8.5).
- Obtain blood samples for troponin (preferably high-sensitivity troponin T) testing by study site 2 to 3 hours after EOI (Section 6.8.5). If repeat testing is conducted, Investigator obtains blood samples for both troponin testing by study site and cTnI testing by central lab.
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn.
    If troponin levels are above the upper limit of normal at baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin level is not Grade 3.
    If the troponin level at 3 hours (6 hours post infusion):
    - Significantly increases, then repeat troponin testing 6 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
    - Otherwise, then repeat troponin testing 6 hours (± 1 hour) or 24 hours (± 2 hours) after initial troponin test was drawn.
- 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 and body temperature).
- Obtain blood samples for safety laboratories (Section 9.8).
- Obtain PK blood samples at the 24 hours (± 2 hours) after the start of Day 1 administration (Section 6.8.3).
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5).
- 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 (± 1 day for Part 2).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the 72 hours (± 2 hours for Part 1, ± 1 day for Part 2) after the start of Day 1 administration (Section 6.8.3).
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5).
- Record concomitant medications.
- Assess subjects for AEs.

6.3.5. Cycle 1, Day 8

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories (Section 9.8).
- Obtain PK blood samples on Day 8 (Section 6.8.3).
- Obtain a blood sample for ADA (Section 6.8.6).
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5).
- Perform a 12-lead ECG in triplicate.
- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

6.3.6. Cycle 1, Day 15

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories (Section 9.8).
- Obtain PK blood samples on Day 15 (Section 6.8.3).
- Perform a 12-lead ECG in triplicate.

- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

6.3.7. Cycle 1, Day 22

If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, the following procedures will be performed on Day 22 (± 2 days).

- Obtain PK blood samples on Day 22 (Section 6.8.3).
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5).
- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

6.3.8. Cycle 2, Day 1

6.3.8.1. Before Infusion

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

- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5). This is not necessary if blood samples are obtained on Cycle 1, Day 22.
- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

Within 8 hours before administration

- Obtain PK blood sample (Section 6.8.3).
  If blood sample is collected on Day 22 of Cycle 1, the blood sample will be collected at BI on Day 1 of Cycle 2 if possible.
- Obtain a blood sample for ADA (Section 6.8.6).

Latest data within 3 days before administration

- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, and fundoscopy. If the planned date of study drug administration is delayed after examination of ophthalmologic assessments, and there are no

abnormal findings on the examination, ophthalmologic assessments may not be repeated at the investigator's judgment.

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG Performance Status Scale (Section 17.1).
- Obtain blood samples for safety laboratories (Section 9.8).
- Perform either ECHO or MUGA (LVEF). If the planned date of study drug administration is delayed after examination of ECHO or MUGA, and there are no abnormal findings on the examination, ECHO or MUGA may not be repeated at the investigator's judgment.
- Perform a 12-lead ECG in triplicate.

6.3.8.2. Administration and after Infusion

The following procedures will be completed on Day 1 (+ 2 days).

- Administer DS-8201a per Section 3.1.2.

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the end of administration within 15 minutes after EOI (Section 6.8.3).
- Obtain blood samples for cTnI testing by central lab (Section 6.8.5).
- Perform a 12-lead ECG in triplicate.
- Obtain blood samples for troponin (preferably high-sensitivity troponin T) testing by study site 2 to 3 hours after EOI (Section 6.8.5). If repeat testing is conducted, Investigator obtains blood samples for both troponin testing by study site and cTnI testing by central lab.
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn.
    If troponin levels are above the upper limit of normal at baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin

level is not Grade 3.
If the troponin level at 3 hours (6 hours post infusion):

- Significantly increases, then repeat troponin testing 6 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
- Otherwise, then repeat troponin testing 6 hours (± 1 hour) or 24 hours (± 2 hours) after initial troponin test was drawn.

- 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 and Day 15 (± 2 days).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories (Section 9.8).
- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

6.3.10. Cycle 2, Day 22

If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, the following procedures will be performed on Day 22 (± 2 days).

- Obtain PK blood samples during the Cycle 2, Day 22 (Section 6.8.3).
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5).
- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

6.3.11. Cycle 3, Day 1

6.3.11.1. Before Infusion

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

- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5). This is not necessary if blood samples are obtained on Cycle 2, Day 22.

- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

Within 8 hours before administration

- Obtain PK blood sample (Section 6.8.3)
  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.
- Obtain blood sample for HER2ECD (Section 6.8.5).

Latest data within 3 days before administration

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG Performance Status Scale (Section 17.1).
- Obtain blood samples for safety laboratories (Section 9.8).
- Perform either ECHO or MUGA (LVEF). If the planned date of study drug administration is delayed after examination of ECHO or MUGA, and there are no abnormal findings on the examination, ECHO or MUGA may not be repeated at the investigator's judgment.
- Perform a 12-lead ECG in triplicate.

6.3.11.2. Administration and after Infusion

The following procedures will be completed on Day 1 (+ 2 days).

- Administer DS-8201a per Section 3.1.2.

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain PK blood samples at the following time points:

  In Part 1 Dose Escalation, within 15 minutes after EOI and 4 hours (± 15 minutes) after the start of administration (Section 6.8.3).

  In Part 2 Dose Expansion, within 15 minutes after EOI (Section 6.8.3).
- Obtain blood samples for cTnI testing by central lab (Section 6.8.5).
- Obtain blood samples for troponin (preferably high-sensitivity troponin T) testing by study site 2 to 3 hours after EOI (Section 6.8.5). If repeat testing is conducted, Investigator obtains blood samples for both troponin testing by study site and cTnI testing by central lab.

  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn.
    If troponin levels are above the upper limit of normal at baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin level is not Grade 3.
    If the troponin level at 3 hours (6 hours post infusion):
    - Significantly increases, then repeat troponin testing 6 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
    - Otherwise, then repeat troponin testing 6 hours (± 1 hour) or 24 hours (± 2 hours) after initial troponin test was drawn.

- Record concomitant medications.
- Assess subjects for AEs.

6.3.12. Cycle 3, Day 8 and Day 15

The following procedures will be performed on Day 8 and Day 15 (± 2 days).

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain blood samples for safety laboratories (Section 9.8).
- Obtain PK blood samples during the Cycle 3, Day 8 and Day 15 visit (Section 6.8.3).
- Record concomitant medications.
- Assess subjects for AEs.
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

6.3.13. Cycle 3, Day 22

If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, the following procedures will be performed on Day 22 (± 2 days).

- Obtain PK blood samples on Day 22 (Section 6.8.3).
- Record concomitant medications.
- Assess subjects for AEs.

- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

6.3.14. Cycle 4 and Subsequent Cycles, Day 1

6.3.14.1. Before Infusion

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

- Record concomitant medications.
- Assess subjects for AEs.
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis one time during treatment period (Section 6.8.5).
- [Optional] For Part 2d only: Perform a tumor biopsy one time during treatment period (Section 6.8.2.2).

Within 8 hours before administration

At Day 1 in Cycle 4, 6, and 8.

- Obtain PK blood sample (Section 6.8.3).
  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.

At Day 1 every 2 cycles from Cycle 3 to the EOT (eg, Day 1 in Cycle 3, 5, 7, 9, 11...)

- Obtain blood samples for HER2ECD (Section 6.8.5). This is applicable until protocol version 11.0. No further blood sampling for HER2ECD is necessary once protocol version 12.0 is applied for a subject.

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

- Obtain an blood sample for ADA (Section 6.8.6)

Latest data within 3 days before administration

- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG Performance Status Scale (Section 17.1).
- Obtain blood samples for safety laboratories (Section 9.8).
- Perform a 12-lead ECG in triplicate.

At Day 1 every 2 cycles from Cycle 3 to the EOT (eg, Day 1 in Cycle 3, 5, 7, 9, 11...)

- Perform either ECHO or MUGA (LVEF).
  If the planned date of study drug administration is delayed after examination of

ECHO or MUGA, and there are no abnormal findings on the examination, ECHO or MUGA may not be repeated at the investigator's judgment.

At Day 1 every 4 cycles from Cycle 5 to the EOT (eg, Day 1 in Cycle 5, 9, 13...)

- 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.

6.3.14.2. Administration and after Infusion

The following procedures will be completed on Day 1 (+ 2 days).

- Administer DS-8201a per Section 3.1.2.

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

- Obtain blood samples for cTnI testing by central lab (Section 6.8.5).
- Obtain blood samples for troponin (preferably high-sensitivity troponin T) testing by study site 2 to 3 hours after EOI (Section 6.8.5). If repeat testing is conducted, Investigator obtains blood samples for both troponin testing by study site and cTnI testing by central lab.
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform a 12-lead ECG in triplicate, repeat troponin testing 6 hours (± 1 hour) and 12 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), repeat troponin testing 3 hours (± 1 hour) after initial troponin test was drawn.
    If troponin levels are above the upper limit of normal at baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin level is not Grade 3.
    If the troponin level at 3 hours (6 hours post infusion):
    - Significantly increases, then repeat troponin testing 6 hours (± 1 hour) after initial troponin test was drawn, and follow institutional guidelines.
    - Otherwise, then repeat troponin testing 6 hours (± 1 hour) or 24 hours (± 2 hours) after initial troponin test was drawn.
- Record concomitant medications.
- Assess subjects for AEs.

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

- Obtain PK blood sample at the end of administration within 15 minutes after EOI (Section 6.8.3).

6.4. End of Treatment

The date of discontinuation of treatment is defined as the date of decision by Investigator. The following assessments will be performed at EOT visit (within 7 days after the date of discontinuation). If assessment at EOT are performed in the treatment period, they can be considered to be the EOT data and there is no need to repeat them based on consultation between the Investigators and the Sponsor.

For Part 2d, it is recommended to perform a tumor biopsy if the subject discontinues from the study treatment due to PD. It is also recommended to obtain blood samples for cfDNA analysis.

- Ophthalmologic assessments. The assessments will include visual acuity testing, slit lamp examination, and fundoscopy.
- Perform a complete physical examination and record weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO_2).
- Assess functional status using the ECOG Performance Status Scale (Section 17.1).
- Obtain blood samples for safety laboratories (Section 9.8) and ADA (Section 6.8.6).
- Obtain blood samples for HER2ECD (Section 6.8.5). This is applicable until protocol version 11.0. No further blood sampling for HER2ECD is necessary once protocol version 12.0 is applied for a subject.
- Obtain blood samples for cTnI testing by central lab and troponin (preferably high-sensitivity troponin T) testing by study site (Section 6.8.5).
- 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 (LVEF).
- Perform same imaging tumor assessment as at the time of screening by CT or MRI scans. CT or MRI scans of the chest, abdomen and pelvis are mandatory. However, if there is no brain metastasis at the time of screening, CT or MRI should only be done when symptoms associated with brain metastasis occur. If no clinical symptoms are observed, brain CT or MRI is not mandatory (Section 17.2). 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.
- For Japanese subjects in Part 2d only:
  Obtain blood samples for immune monitoring analysis (Section 6.8.5).
- [Optional] Obtain blood samples for cfDNA analysis (Section 6.8.5).
- [Optional] For Part 2d only: Perform a tumor biopsy (Section 6.8.2.2).

6.5. Follow-up

The F/U visit should occur 28 days (– 7 days) after the last administration of DS-8201a. If the subject begins another anticancer therapy before the end of the 28 days (– 7 days), every effort will be made to complete all the F/U assessments prior to commencing the new therapy. In case of unresolved AEs, the Investigator will follow the AEs until the event has resolved or the condition has stabilized as possible. If assessments at EOT or 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 28 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 and body temperature).
- Perform a complete physical examination and record weight.
- Assess functional status using the ECOG Performance Status Scale (Section 17.1).
- Obtain blood samples for safety laboratories (Section 9.8) and ADA (Section 6.8.6). For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months (± 1 month) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if ADA titer becomes less than baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
- Obtain blood samples for cTnI testing by central lab and troponin (preferably high-sensitivity troponin T) testing by study site (Section 6.8.5).
- Record concomitant medications.
- Assess subjects for AEs.

6.6. New Cancer Treatment and Survival Follow-up

After completing the F/U visit, a subject will be followed via a phone call or site visit to confirm new cancer treatments and survival status every 3 months (± 1 month) until death or the data cut-

off date, whichever comes first. Even if the subject moves to another hospital, the Investigator will confirm new anticancer therapy and survival status, if possible.

6.7. Protocol Deviations

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

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

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

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

The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

6.8. Pharmacokinetic (PK), Pharmacodynamic (PDy), Exploratory Biomarker and Human Anti-human Antibodies

6.8.1. Serum Sampling

Blood samples for PK, Exploratory Biomarker (eg, HER2ECD, cTnI testing by central lab, immune monitoring and cfDNA) and ADA will be collected into blood sampling tubes supplied by the Sponsor. The collected blood will be centrifuged to separate the serum. The serum samples will be shipped to a central laboratory.

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

6.8.2. Tumor Sampling

6.8.2.1. Tumor Samples (For all subjects)

Ten slides of tumor tissue sections (4 µm to 5 µm thick) which are obtained before the first study drug administration for Biomarker (eg, HER2 assessment by IHC, FISH, and HERmark) will be submitted to a central laboratory for exploratory assessment of the biomarker.

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

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

Paraffin-embedded tissue blocks of formalin-fixed tissue specimens will be prepared by the standard procedure at the study center and the unstained slides with tissue sections (4 µm to 5 µm thick) will be submitted to the courier assigned by the Sponsor.

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

6.8.2.2. Tumor Samples for Exploratory Biomarker (Additional for Part 2d only)

Fresh biopsy samples which are obtained during the study will be examined for exploratory biomarkers (eg, HER2 mutations and expression, immunoprofiling). Remaining samples will be retained for up to 15 years or until it is exhausted.

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

6.8.3. Pharmacokinetic (PK)

Blood samples of approximately 7 mL for PKs analyses will be collected at the time points specified in Table 6.1.

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

Table 6.1: Pharmacokinetic Sampling Time Points (Part 1 and Part 2)

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

Table 6.1: Pharmacokinetic Sampling Time Points (Part 1 and Part 2) (Continued)

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

6.8.4. Pharmacodynamic (PDy)

Not applicable.

6.8.5. Exploratory Biomarker

Based on the evaluation of pre-treatment tumor sample, the levels of HER2 will be assessed by IHC and FISH. The exploratory biomarkers (eg, HER2ECD, HER2 by HERmark, cTnI testing by central lab) will be measured.

Blood samples of approximately 6 mL for HER2ECDs analyses will be collected at the time points specified in Table 6.2. This is applicable until protocol version 11.0. No further blood sampling for HER2ECD is necessary once protocol version 12.0 is applied for a subject.

Table 6.2: HER2ECD Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Screening	-	Within 7 days before registration
After Cycle 3 at every 2 cycles (eg, Cycle 3, 5, 7, 9, 11...)	Day 1	BI (– 8 hours)
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days).

In addition to troponin testing by study site, blood samples of approximately 6 mL for cTnIs analyses by central lab will be collected at the time points specified in Table 6.3.

Table 6.3: cTnI Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Screening	-	Within 7 days before registration
Every Cycle	Day 1	EOI
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days).
F/U	-	28 days (– 7 days) after the last administration of DS-8201a.

Blood samples of approximately 20 mL for immune monitoring analysis will be collected from Japanese subjects in Part 2d at the time points specified in Table 6.4.

Table 6.4: Immune Monitoring Sampling Time Points (Japanese subjects in Part 2d only)

Cycle	Day	Sampling Time Point (Acceptable Range)
Screening – BI at Cycle 1 Day 1	-	-
Cycle 1	Day 2	-
	Day 4	-
	Day 8	-
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of administration (± 2 days)
Cycle 2	Day 1	BI. This is not necessary if blood samples are obtained on Cycle 1, Day 22.
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample 21 days after the start of administration (± 2 days)
Cycle 3	Day 1	BI. This is not necessary if blood samples are obtained on Cycle 2, Day 22.
Cycle 4 and subsequent cycles	Day 1	BI. One time during treatment period.
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days).

Blood samples of approximately 20 mL for cfDNA analysis will be collected at the time points specified in Table 6.5.

Table 6.5: Cell Free DNA Sampling Time Points (Optional)

Cycle	Day	Sampling Time Point (Acceptable Range)
Screening – BI at Cycle 1 Day 1	-	-
EOT	-	The date Investigator decides the discontinuation of the study treatment (+ 7 days).

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

6.8.6. Anti-drug Antibody

Blood samples for ADA of approximately 4 mL analyses will be collected at the time points specified in Table 6.6. Serum concentrations of DS-8201a and/or total anti-HER2 antibody may be measured using the same ADA samples for purpose of anti-drug antibody assessment.

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

Table 6.6: ADA Sampling Time Points

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

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

7. EFFICACY ASSESSMENTS

Efficacy assessments will be based on tumor assessments to be performed at screening and every 6 weeks in the first 24 weeks after Day 1 of Cycle 1 and thereafter every 12 weeks while the subject remains on study drug. The clinical activity of DS-8201a will be assessed by evaluating tumor response. Tumor response will be evaluated using RECIST version 1.1 (Section 17.2).

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

The following efficacy variables will be assessed. The Efficacy Variable(s) will be also evaluated at 18 weeks after Day 1 of Cycle 1.

- ORR (the sum of CR rate and PR rate)
- DCR (the sum of CR rate, PR rate, and SD rate)
- Response duration
- Duration of SD
- TTR
- PFS
- OS
- Percent change in target lesion
- Time on therapy of the most recent prior regimen the subject received and that of DS-8201a.

7.1. Primary Efficacy Variable(s)

Not applicable.

7.2. Secondary Efficacy Variable(s)

Not applicable.

7.3. Exploratory Efficacy Variable(s)

Not applicable.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Variable(s)

The serum PK parameters listed in Table 8.1 of DS-8201a, total anti-HER2 antibody and MAAA-1181 for each subject will be estimated using standard noncompartmental methods. The other PK parameter (AUCinf, Kel, $T_{1/2}$, CL, Vz and, Vss) will be calculated if data permits. The details of PK analysis are to be specified in the Pharmacokinetic Analysis Plan.

Table 8.1: Pharmacokinetic Parameters

	PK parameters
DS-8201a, total anti-HER2 antibody and MAAA-1181	AUClast, AUCtau, Cmax, Tmax, Ctrough

8.2. Pharmacodynamic (PDy) Variable(s)

Not applicable.

8.3. Biomarker and Exploratory Variable(s)

Tumor samples will be examined for HER2 status (eg mutations and expression). Exploratory biomarker research may be conducted on any samples. These studies would extend the search for other potential biomarkers relevant to the effects of DS-8201a, cancer and/or the resistance to the treatment. This may include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

9. SAFETY ASSESSMENTS

9.1. Adverse Events

All clinical AEs occurring after the subject signs the ICF and up to F/U visit after the last dose of study medication, whether observed by the Investigator or reported by the subject, will be recorded on the AE case report form (CRF) page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 9.5 SAE Reporting-Procedure for Investigators. Always report 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) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs (see Section 9.4 for Definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. Progressive disease is a study endpoint and consequently, should not be reported as an AE/SAE. However, when a subject dies from progressive disease with no other immediate causes, "Progressive disease" should be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, 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 study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature. All laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be recorded as an AE on the CRF, and if serious, report as an SAE following the procedures in Section 9.5.

Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized as possible. In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

9.2. Safety Endpoints

Safety endpoints will include DLTs, SAEs, TEAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and ophthalmologic assessments. TEAEs will be graded according to the NCI-CTCAE version 4.0. Dose escalation will be determined by the incidence of DLTs.

9.3. Events of Special Interest

Relevant Information regarding the Adverse Events of Special Interest (AESIs) specified below for the DS-8201a clinical program regardless of seriousness will be collected through the targeted questionnaires, built within the applicable eCRFs in the clinical study database.

Please refer to the IB for additional information.

9.3.1. Cardiotoxicity (Cardiac-related events including QT Prolongation and LVEF Decrease)

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.

Management Guidance:

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

9.3.2. Interstitial Lung Disease/Pneumonitis

Clinical Summary:

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

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

Management Guidance:

ILD/pneumonitis should be ruled out if a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the designated "All other non-hematological toxicities, except alopecia" dose modification section of the study protocol.

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high resolution CT, pulmonologist consultation, pulmonary function tests and pulse oximetry (SpO_2), arterial blood gases if clinically indicated, and one blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible. As soon as ILD/pneumonitis is suspected, corticosteroid treatment should be started promptly as per clinical treatment guidelines (Kubo K, et al 2013 for guidance). [18]

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in Section 3.1.9.3 of the study protocol.

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

9.3.2.1. 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 MedDRA preferred terms (PT) from the current ILD Standard MedDRA Query (SMQ).

9.3.3. Infusion-related reactions

Clinical Summary:

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

Management Guidance:

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

9.4. Definitions

9.4.1. Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A

Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

9.4.2. Serious Adverse Event (SAE)

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:

- 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 treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

9.4.3. AE Severity

All AEs will be graded (1 to 5; see below) according to the NCI-CTCAE version 4.0:

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

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

9.4.4. Causality Assessment

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

- 1 = 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).
  - 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.
- 2 = Not Related:
  - The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding the Study Product

- 1 = Dose Not Changed: No change in study drug dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Dose Reduced: The dosage of study product was reduced.
- 4 = Drug Interrupted: The study product was temporarily stopped.
- 5 = Dose Increased: The dosage of study product was increased.

9.4.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed.
- 2 = Recovering/Resolving
  - The AE improved but has not fully resolved.

- 3 = Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- 4 = Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- 5 = Fatal
  - Fatal should be used when death is a direct outcome of the adverse event.
- 6 = Unknown

9.4.7. Other Action Taken for Event

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

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

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

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

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

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source

documents (including medical reports) will be retained at the study center and should not be submitted to the Sponsor for SAE reporting purposes.

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

In the event that eCRF is unavailable, report SAEs on a Serious Adverse Event Report (SAVER) form (Supplement 1). All completed SAVER forms must be signed by the Investigator, and e-mailed or faxed to the Sponsor or the CRO using the provided fax transmittal form and the appropriate fax number provided for your country. Once eCRF becomes available, please enter SAEs into eCRF.

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

9.6. Notifying Regulatory Authorities, Investigators, IRB/EC, and Competent Authorities

Daiichi Sankyo and/or CRO will inform Investigators, IRBs (Institutional Review Board)/ECs (Ethics Committees), and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in other study centers or other Daiichi Sankyo studies of the investigational product, as appropriate per local reporting requirements.

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

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

9.7. Exposure In Utero During Clinical Studies

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

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 female partner of a male subject using the Exposure In Utero (EIU) Reporting form (Supplement 2). Reporting after follow-up visit or early termination is done voluntarily by the investigator. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

Laboratory tests	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	Total protein, albumin, ALP, ALT, AST, total bilirubin, BUN, Ca, Cl, serum creatinine, LDH, K, Na, Mg)

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.
- HIV antibody test must be performed during the Screening Period for Japanese subjects. HIV antibody test is optional for US subjects unless required by local regulations or IRB.

All laboratory values must be appraised by the Investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered clinically significant by the Investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, a SAVER form should be submitted and other relevant procedures must be followed (see Section 9.5). Abnormal laboratory values (NCI-CTCAE grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

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

9.10. Electrocardiograms

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

9.11. Physical Findings

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

9.12. Other Safety Assessments

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

Pulmonary Assessments

Pulmonary assessment will include CT or MRI of the chest, and SpO_2 will be performed as described in schedule of events. For more details please refer to Section 6 of the protocol. Additional safety assessments should be conducted as needed, at the Investigator's discretion.

10. OTHER ASSESSMENTS

Not applicable.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Enrolled Analysis Set

The enrolled analysis set will include all subjects who signed an ICF and were enrolled in either the Dose Escalation part or Dose Expansion part of the study.

11.1.2. Efficacy Analysis Set

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

11.1.3. Dose-Limiting Toxicity Evaluable Set

The DLT-evaluable set will include all subjects who received at least one dose of DS-8201a , with the exception of those subjects for whom DLT evaluation could not be adequately conducted.

11.1.4. Safety Analysis Set

The safety analysis set will include all subjects who received at least one dose of DS-8201a. Subjects will be summarized according to treatment actually received.

Three groups of subjects will be identified within the safety analysis set: (1) subjects in the Dose Escalation part, (2) subjects in the Dose Expansion part, and (3) all subjects in the study.

11.1.5. Pharmacokinetic Analysis Set

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

11.1.6. Biomarker Analysis Set

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

11.2. General Statistical Considerations

The primary analysis is to assess the safety and tolerability of DS-8201a in subjects with advanced solid malignant tumors and to determine the MTD/RP2D or establish the safety and tolerability of the maximum administered dose of DS-8201a.

The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or the last subject enrolled in Part 2 of the study has completed at least 6 months of study drug treatment. After the primary analysis, the main study will be closed and the data will be followed until completion.

The data analyses will also be conducted during Part 1.

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

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

Safety analyses will be performed based on the safety analysis set. Analysis of PK parameters will be based on the PK analysis sets and biomarker analyses will be based on the biomarker analysis sets. Efficacy endpoints will be analyzed based on the efficacy analysis set. Data will be summarized by dose level/cohort within each Part and overall.

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

11.3. Study Population Data

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

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

11.4. Efficacy Analyses

Efficacy variables will include ORR (the sum of CR and PR rates); DCR (the sum of CR rate, PR rate, and SD rate for a minimum of 5 weeks from the first dosing date), response duration, duration of SD, TTR, and PFS, using RECIST 1.1. Tumor assessment will be performed by both the investigator and independent central imaging facility.

The efficacy variables will be listed and summarized. For ORR and DCR, point estimates and 95% exact binomial confidence intervals will be provided. Time to event variables including PFS, TTR, response duration, and duration of SD will be summarized descriptively using the Kaplan-Meier method. PFS is defined as the time from the date of the first dose to the earlier of the dates of the first objective documentation of radiographic PD or death due to any cause. Censoring rules for the PFS analysis will be specified in the SAP. The growth modulation indices (the intrasubject ratio of PFS post-study treatment versus PFS post the most recent prior therapeutic regimen) will be summarized.

Descriptive statistics for the best percent change in the SLD of measurable tumors will be provided. A waterfall plot of the best percent change from screening in the SLD for each subject will be presented for subjects with advanced solid malignancies.

11.4.1. Primary Efficacy Analyses

Not applicable.

11.4.2. Secondary Efficacy Analyses

Not applicable.

11.4.3. Exploratory Efficacy Analyses

Not applicable.

11.5. Pharmacokinetic/Pharmacodynamic Analyses

11.5.1. Pharmacokinetic Analyses

PK analyses will be performed on the PK analysis set. Serum concentration-time data for DS-8201a, total anti-HER2 antibody and MAAA-1181 will be listed, plotted, and summarized using descriptive statistics by dose level/cohort within each Part at each point and in study period (Part 1 and Part 2).

PK parameters of DS-8201a, total anti-HER2 antibody and MAAA-1181 will be listed and summarized using descriptive statistics by dose level/cohort within each Part.

The comparison of the PK profile between each drug product (FL-DP1 and FL-DP2) will be assessed. The comparison of the PK profile between each region (Japan and the United States) will also be assessed.

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

11.5.2. Pharmacodynamic Analyses

Not applicable.

11.5.3. Biomarker and Exploratory Analyses

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

11.6. Safety Analyses

The safety profile will be based on AEs, physical examination findings, vital sign measurements, clinical laboratory measurements, ECG recordings, ECHO/MUGA findings, and ophthalmologic findings. AEs will be graded according to the NCI-CTCAE version 4.0. In the Dose Escalation part, the incidence of DLTs will also be evaluated.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics. In the Dose Escalation part, the number of DLTs identified

among the DLT-evaluable subjects in the DLT-evaluable set will be listed and summarized for each cohort of DS-8201a.

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

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

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

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

11.6.2. Clinical Laboratory Evaluation Analyses

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

Abnormal laboratory results will be graded according to NCI-CTCAE version 4.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed of clinical significance or of Grade 3 or 4 will be listed.

11.6.3. Vital Sign Analyses

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

11.6.4. Electrocardiogram Analyses

A shift table, presenting the 2-way frequency tabulation for baseline and each schedules time, including the EOT Visit according to the categories for ECG (normal and abnormal) will be provided.

11.6.5. Physical Finding Analyses

Physical examination findings including ECOG PS will be listed.

11.6.6. Other Safety Analyses

The ECHO/MUGA findings and ophthalmologic findings will be listed.

11.7. Other Analyses

Not applicable.

11.8. Interim Analyses

No formal interim analysis is planned, except for the assessment of the MTD after each escalation cohort in the Dose Escalation part.

11.9. Data and Safety Monitoring Board

Not applicable.

11.10. Sample Size Determination

The Dose Escalation part of this study (Part 1) consists of mCRM with EWOC design with at least 3 DLT-evaluable subjects per dose level. At least 18 DLT-evaluable subjects are needed to reach an accurate estimate of the MTD.

Sample size has been determined by practical considerations for the Dose Escalation part of the study. No formal statistical assessment has been performed.

For the Dose Expansion part (Part 2), approximately 260 subjects (100 subjects for Part 2a, 40 subjects for Part 2b, 20 to 40 subjects for Part 2c, 60 subjects for Part 2d and 20 subjects for Part 2e) will be enrolled.

Part 2a

If target ORR is more than 15% (null hypothesis: ORR $\leq$ 0.15, alternative hypothesis: ORR > 0.15), then the probability of less than 9 responders out of 100 subjects will be less than 5%. The probability that more than 21 responders out of 100 subjects (ORR > 21%) are observed will be less than 5% under the null hypothesis with ORR $\leq$ 0.15 but more than 90% under alternative hypothesis with ORR = 0.35.

Part 2b

If target ORR is more than 10% (null hypothesis: ORR $\leq$ 0.10, alternative hypothesis: ORR > 0.10), then the probability of no response out of 40 subjects will be less than 5%. The probability that more than 7 responders out of 40 subjects (ORR > 17.5%) are observed will be less than 5% under the null hypothesis with ORR $\leq$ 0.10 but more than 80% under alternative hypothesis with ORR = 0.25.

Part 2c and Part 2e

If target ORR is more than 15% (null hypothesis: ORR $\leq$ 0.15, alternative hypothesis: ORR > 0.15), then the probability of no response out of 20 subjects will be less than 5%. The probability that more than 4 responders out of 20 subjects (ORR > 20%) are observed will be less than 20% under the null hypothesis with ORR $\leq$ 0.15 but more than 75% under alternative hypothesis with ORR = 0.30.

Part 2d

If target ORR is more than 15% (null hypothesis: ORR ≤ 0.15, alternative hypothesis: ORR > 0.15), then the probability of less than 5 responders out of 60 subjects will be less than 5%. The probability that more than 14 responders out of 60 subjects (ORR > 23.3%) are observed will be less than 5% under the null hypothesis with ORR ≤ 0.15 but more than 80% under alternative hypothesis with ORR = 0.30.

The probability values for the sample size are derived based on binomial distribution using SAS® version 9.2.

11.11. Specification of Modified Continuous Reassessment Method With Escalation With Overdose Control

11.11.1. Bayesian Logistic Regression Model for Modified Continuous Reassessment Method

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

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

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

11.11.2. Prior Specification for Bayesian Logistic Regression Model Parameters

The Bayesian approach requires the specification of a prior distribution for the BLRM parameters. A minimally-informative bivariate normal prior for the model parameters (log(α),log(β)) is obtained as follows[17]:

- Based on extrapolation of nonclinical toxicology studies in monkeys, the MTD is projected to be greater than 9.7 mg/kg in humans (the HNSTD of monkeys is 30 mg/kg and assuming humans and monkeys are equally sensitive, the MTD is projected to be greater than 9.7 mg/kg in humans). The median prior probabilities of DLT are set to be approximately 8.0% and 24.5% at 0.8 mg/kg (projected starting dose for dose escalation using mCRM) and at 9.7 mg/kg, respectively.
- For the remaining doses, the medians of probability of DLT are assumed linear in log-dose on the logit-scale.
- Based on the above medians for the probability of DLT at each dose and wide prior credible intervals (obtained from minimally informative Beta distributions), the optimal parameters of the bivariate normal distribution can be obtained as follows:

Parameters	Means	Standard deviations	Correlation
log(α), log(β)	(-1.1502, -0.8951)	(2.0924, 1.1183)	-0.3448

11.11.3. Escalation With Overdose Control Principle

Dose recommendation for the next cohort will be based on summaries of the posterior probability of the DLT rate for provisional doses: 0.8, 1.6, 3.2, 5.0, 6.4, and 8.5 mg/kg. After subjects of each cohort complete DLT evaluation during Cycle 1, the posterior distributions of the DLT rate are derived for all provisional dose levels based on the BLRM using the DLT outcome data from all assessed doses and a pre-specified prior distribution for the model parameters. The posterior probability of the DLT rate in the following 4 intervals at each dose level will then be calculated: [0%, 16%] as the DLT rate interval for under-dosing, (16%, 33%] as the target DLT rate interval, (33%, 60%] as the DLT rate interval for excessive toxicity, and (60%, 100%] as the DLT rate interval for unacceptable toxicity, and used for dose recommendation for the next cohort according to the EWOC principle. The above provisional doses are based on an initial estimate of the human MTD of 9.7 mg/kg using the HNSTD of monkeys in nonclinical toxicology studies (30 mg/kg). It is therefore conceivable that the posterior probability of DLT rate for dose recommendation may be generated using alternative provisional doses as long as the predicted exposure increments are between 30% and 100% (Section 3.2.1.2.1).

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

12. DATA INTEGRITY AND QUALITY ASSURANCE

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

12.1. Monitoring and Inspections

The 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 monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research. 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.

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

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

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

12.2. Data Collection

The Investigator or study staff will enter the data in the eCRF (See Section 17.4) 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 e-signs according to the study data flow.

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

12.3. Data Management

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

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

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

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

All AEs will be coded using MedDRA.

All prior cancer therapy and prior/concomitant medications entered into the database will be coded by using the latest version of World Health Organization Drug Dictionary.

12.4. Study Documentation and Storage

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

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.

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

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

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

All essential documentation will be retained by the Investigator until at least 3 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have lapsed since the formal discontinuation of clinical development of the investigational product. 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.

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

12.5. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICF, 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 site. 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 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.

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 Sponsor or a CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury. Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

14. PUBLICATION POLICY

[redacted]

15. STUDY ADMINISTRATIVE INFORMATION

15.1. Protocol Amendments

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

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

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

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

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

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

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

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

15.3. Address List

15.3.1. Sponsor

Japan:

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

United States:

Daiichi Sankyo Pharma Development

211 Mount Airy Road, Basking Ridge, NJ 07920, United States

15.3.1.1. Sponsor's Responsible Medical Expert / Medical Monitor

[redacted]

15.3.1.2. Sponsor Clinical Study Leader

[redacted]

15.3.2. CRO

Part 1: Monitoring is conducted by the Sponsor and the following CRO.

Part 2: Monitoring is conducted by the following CRO.

Japan
IQVIA Services Japan K.K.
4-10-18 Takanawa, Minato-ku, Tokyo 108-0074 Japan

United States
IQVIA Inc.
4820 Emperor Boulevard, Durham, NC 27703, United States

15.3.2.1. CRO Medical Monitor for US

[redacted]

15.3.2.2. CRO Project Manager

[redacted]

15.3.3. Drug Safety

15.3.3.1. Sponsor

[redacted]

[redacted]

[redacted]

15.3.3.2. CRO

Japan
IQVIA Services Japan K.K.
[redacted]

US
IQVIA Inc.
[redacted]

15.3.4. Data Management

15.3.4.1. Sponsor

[redacted]

15.3.4.2. CRO for Biostatistics and Data Management

EPS Corporation
Acropolis TOKYO Bldg., 6-29 Shinogawamachi, Shinjuku-ku, Tokyo, 162-0814, Japan
[redacted]

15.3.4.3. EDC Vendor

Medidata Solutions Inc.
350 Hudson Street, 9th Floor, New York, New York 10014, USA
[redacted]

15.3.4.4. EDC System Support

Fujitsu Systems East Limited
Shinagawa season terrace 1-2-70 Konan, Minato-ku, Tokyo 108-0075 Japan
[redacted]

15.3.5. Biological Specimens

15.3.5.1. IHC and FISH Assessment

Mosaic Laboratories, LLC
12 Spectrum Pointe Drive, Lake Forest, CA 92630, USA
[redacted]

15.3.5.2. HER2ECD Test

BioAgilytix Labs, LLC
2300 Englert Dr., Durham, NC 27713, USA
[redacted]

15.3.5.3. HER2 by HERmark Test

Monogram Biosciences, Inc
345 Oyster Point Blvd, San Francisco, CA 94080, USA
[redacted]

15.3.5.4. Biological Specimens Management for Part 1 in Japan and cTnI Test

LSI Medience Corporation
3-30-1, Shimura, Itabashi-ku, Tokyo 174-8555, Japan
[redacted]

15.3.5.5. Biological Specimens Management for Part 1 in US and Part 2

Q Squared Solutions KK
4-10-18 Takanawa, Minato-ku, Tokyo 108-0074 Japan
[redacted]

15.3.5.6. HER2 Assessment Using Fresh Tumor Samples for Part 2d Subjects and HER2ECD Test

Covance Inc.
210 Carnegie Center, Princeton, NJ 08540-6233, USA
[redacted]

15.3.5.7. cfDNA Analysis

Guardant Health, Inc.
505 Penobscot Drive, Redwood City, CA 94063, USA
[redacted]

15.3.5.8. Immune Profiling and Monitoring

National Cancer Center Japan
5-1-1 Tsukiji Chuo-ku, Tokyo 104-0045, Japan
[redacted]

15.3.6. Interactive Response Technology (IRT)

PAREXEL Informatics
2-5-8 Imabashi, Chuo-ku, Osaka-shi, Osaka 541-0042, Japan
[redacted]

15.3.7. Genomics Laboratory

Not Applicable.

15.3.8. Bioanalytical Laboratory (PK and ADA assessment)

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

15.3.9. Central Imaging

Bioclinica Inc.
211 Carnegie Center Drive Princeton, New Jersey 08540 USA
[redacted]

15.3.10. Other

15.3.10.1. Safety Advisor

Suggest opinions or comments from the view of a medical oncologist as needed if sponsor asks opinion when serious safety issues are identified or suspected.

[redacted]

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17. APPENDICES

17.1. Eastern Cooperative Oncology Group Performance Status Scale

GRADE	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

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

17.2. Response Evaluation Criteria in Solid Tumors, Version 1.1

17.2.1. Measurability of Tumor at Baseline

17.2.1.1. Definitions

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

17.2.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in F/U, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

17.2.1.1.2. Non-measurable

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

17.2.1.1.3. Special Considerations Regarding Lesion Measurability

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

17.2.1.1.3.1. Bone Lesions

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

- Blastic bone lesions are non-measurable.

17.2.1.1.3.2. Cystic Lesions

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

17.2.1.1.3.3. Lesions with Prior Local Treatment

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

17.2.1.2. Specifications by Methods of Measurements

17.2.1.2.1. Measurement of Lesions

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

17.2.1.2.2. Method of Assessment

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

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

17.2.2. Tumor Response Evaluation

17.2.2.1. Assessment of Overall Tumor Burden and Measurable Disease

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

In Part 2 Dose Expansion of this study, only subjects with measurable disease at baseline should be included in the study.

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

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

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

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

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

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

17.2.2.3. Response Criteria

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

17.2.2.3.1. Evaluation of Target Lesions

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

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

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

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

17.2.2.3.2. Special Notes on the Assessment of Target Lesions

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

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

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

17.2.2.3.3. Evaluation of Non-target Lesions

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

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

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

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

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

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

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

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

17.2.2.3.5. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly

important when the subject's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

17.2.2.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the EOT. No confirmatory measurement for CR, PR, or SD is required in the study.

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

17.2.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 17.1 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

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

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

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

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

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

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

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

17.2.2.4.2. Missing Assessments and Inevaluable Designation

When no imaging/measurement is performed at all at a particular timepoint, the subject is not evaluable (NE) at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at F/U only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

17.2.2.4.3. Best Overall Response: All Time Points

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

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

17.2.2.4.4. Special Notes on Response Assessment

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

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

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

17.2.2.5. Frequency of Tumor Re-evaluation

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

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

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

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

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

17.3. New York Heart Association Functional Classification

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

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

17.4. 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 4, 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

17.5. Supplement List

Supplements are printed separately from protocol, and their versions are independent from study protocol. Some supplement will be applied to specific study sites or specific country. Supplement 3, 4 and 5 is only submitted for Japanese site's IRB.

Supplements are listed as follow:

- Supplement 1: Serious Adverse Event Report (SAVER) form
- Supplement 2: EIU Reporting Form
- Supplement 3: Labeling and Packaging of the study drug (for Japanese Study Center Only)
- Supplement 4: The list of Study Centers and Investigators (for Japanese Study Center Only)
- Supplement 5: Additional Information (for Japanese Study Center Only)
- Supplement 6: The list of CYP3A4 strong inhibitors, CYP3A4 strong inducers and OATP inhibitors

17.6. Schedule of Events (Part 1 and Part 2)

	SCR	Cycle 1							Cycle 2					Cycle 3					Cycle 4 and subsequent cycles		EOT [a]	F/U [b]
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)	Day 1		Day 8	Day 15	(Day 22)	Day 1		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		
Informed consent	X																					
Administration DS-8201a		X							X[u]					X[u]					X[u]			
Demographic information	X																					
Vital sign	X[c]	X[d]	X	X	X	X	X		X[d]	X	X	X		X[d]	X	X	X		X[d]		X	X
Physical examination	X[c]	X[d]							X[d]					X[d]					X[d]		X	X
SpO_2		X[d]							X[d]					X[d]					X[d]		X	
I/E Criteria	X																					
Height	X																					
Weight, ECOG PS	X[c]	X[d]							X[d]					X[d]					X[d]		X	X
Laboratory tests	X[c]	X[d]		X		X	X		X[d]		X	X		X[d]		X	X		X[d]		X	X
PK		X[e]	X[f,g]	X[h]	X[h]	X	X	(X)[i]	X[e]	X[f]			(X)[i]	X[e]	X[f,j]	X	X	(X)[i]	X[e]	X[f]		
ADA		X[k]				X			X[k]										X[k]		X	X[q]
HIV antibody test	X[l]																					
HER2ECD (blood)	X[c]													X[m]							X	
Troponin (blood)	X[c]		X[n]							X[n]					X[n]					X[n]	X	X
ECHO or MUGA (LVFF)	X[o]								X[d]					X[d,m]							X	
12-lead ECG in triplicate	X[c]	X[d]	X[p]	X		X	X		X[d]	X				X[d]					X[d]		X	
Pregnancy test	X[c]																				X	

	SCR	Cycle 1							Cycle 2					Cycle 3					Cycle 4 and subsequent cycles		EOT [a]	F/U [b]
		Day 1		Day 2	Day 4	Day 8	Day 15	(Day 22)	Day 1		Day 8	Day 15	(Day 22)	Day 1		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		
Tumor assessment	X[c]	Every 6 weeks (±7 days) in the first 24 weeks after Day 1 of Cycle 1, and thereafter every 12 weeks (±7 days)																			X	
Ophthalmologic assessments	X[c]								X[d] At Day 1 in Cycle 2 and every 4 cycles from Cycle 5 to the EOT (eg, Day 1 in Cycle 2, 5, 9, 13...)													X	
IHC/FISH, HERmark (tumor sample)	X																					
cfDNA (blood)	(X)																				(X)	
For Part 2d only: Immune monitoring (blood)	X			X	X	X		(X)[s]	X				(X)[s]	X					X[v]		X	
For Part 2d only: Exploratory biomarker (tumor sample)	X	(X)[t] One time during Day 8 to 22 (prior to the subsequent study drug administration) of any cycle																			(X)[t]	
Concomitant medications		X																				
AEs	X[r]																					

SCR: screening, F/U: follow-up, BI: before infusion, EOI: end of infusion, EOT: end of treatment

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

[b] 28 days (− 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first.

[c] Latest data within 7 days before registration. Troponin (preferably high-sensitivity troponin T) testing by study site and cTnI testing by central lab.

[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 (eg, 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 (eg, Cycle 1, 2, 3, 4, 6, 8).

[g] 2, 4, 7 hours after the start of administration (± 15 minutes)

[h] 24 (± 2 hours) and 72 hours (± 2 hours for Part 1, ± 1 day for Part 2) after the start of administration

[i] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample for PK analysis

[j] Part 1 (Dose escalation): Within 15 minutes at EOI, 4 hours after the start of administration (± 15 minutes), Part 2 (Dose expansion): Within 15 minutes at EOI

[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...)

[l] Latest data within 90 days before registration. HIV antibody test must be performed for Japanese subjects, and is optional for US subjects unless required by local regulations or IRB.

[m] Before administration for ECHO/MUGA and within 8 hours BI for HER2ECD. At every 2 cycles from Cycle 3 (eg, Cycle 3, 5, 7, 9...). For HER2ECD, this is applicable until protocol version 11.0. No further blood sampling for HER2ECD is necessary once protocol version 12.0 is applied for a subject.

[n] EOI for cTnI testing by central lab and 2 to 3 hours after EOI for troponin (preferably troponin T) testing at study site. Depending on the result of troponin testing at study sites 2 to 3 hours after EOI, additional testing(s) is needed.
If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 hours (±1 hr) and 12 hours (±1 hr) after initial troponin test was drawn, and follow institutional guidelines. If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), repeat troponin testing at 3 hours (±1 hr) 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 (±1 hr) and follow institutional guidelines. Otherwise, repeat troponin testing at 6 hours (±1 hr) or at 24 hours (±2 hours) after initial troponin test. If troponin levels are above the upper limit of normal at baseline and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1), no repeat testing is required after the first EOI 3-hour troponin test if the troponin level is not Grade 3.

[o] Latest data within 28 days before registration

[p] Within 30 minutes after end of infusion (EOI), and 2 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 (± 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] For suspected ILD/pneumonitis, treatment with study drug should be interrupted pending evaluation.
Evaluations should include:
- high resolution CT
- pulmonologist consultation
- pulmonary function tests and pulse oximetry (SpO_2)
- arterial blood gases if clinically indicated
- one blood sample collection for PK and exploratory biomarker analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

[s] If the schedule on Day 1 of the next cycle is delayed for 3 days or more, including if the subject cannot continue onto the next cycle, collect blood sample for immune monitoring analysis.

[t] It is recommended to perform a tumor biopsy one time during Day 8 to 22 (prior to the subsequent study drug administration), and EOT if the subject discontinues from the study treatment due to PD.

[u] 21 days (+ 2 days) from latest administration date.

[v] One time one time during treatment period.

For suspected ILD/pneumonitis, study drug should be interrupted pending evaluation.