CLINICAL STUDY PROTOCOL

A PHASE 2, MULTICENTER, OPEN-LABEL STUDY OF DS-8201A IN SUBJECTS WITH HER2-EXPRESSING ADVANCED GASTRIC OR GASTROESOPHAGEAL JUNCTION ADENOCARCINOMA

[DESTINY-Gastric0l]

DS8201-A-J202

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DAIICHI SANKYO

INVESTIGATOR AGREEMENT

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Sponsor Approval:

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

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

Investigator's Signature:

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

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

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

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms (CRFs). 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

Protocol Number:	DS8201-A-J202
Investigational Product:	DS-8201a
Active Ingredient(s)/INN:	Trastuzumab deruxtecan
Study Title:	A Phase 2, multicenter, open-label study of DS-820la in subjects with HER2-expressing advanced gastric or gastroesophageal junction adenocarcinoma [DESTINY-Gastric01]
Study Phase:	Phase 2
Indication Under Investigation:	Human epidermal growth factor receptor 2 (HER2)-overexpressing locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma
Study Objective:	**Primary Cohort** • To compare the efficacy and safety of DS-820 la and physician's choice treatment in HER2-overexpressing advanced gastric or gastroesophageal junctio n adenocarcinoma subjects who have progressed on 2 prior regimens including fluorop yrimidine agent, platinum agent, and trastuzumab (brand, approved biosimilar). **Exploratory Cohort 1** • To determine the efficacy and safety of DS-820la in subjects with HER2 irnmunohistochemistry (IHC) 2+/in situ hybridization (ISH) negative advanced gastric or gastroesophageal junction adenocarcinoma. **Exploratory Cohort 2** • To determine the efficacy and safety of DS-8201a in subjects with HER2 IHC 1+ advanced gastric or gastroesophageal junction adenocarcinoma.
Study Design:	Phase 2, multi-center, open-label, 3-coho rt study **Primary Cohort** Primary Cohort is a randomized study to compare the efficacy and safety of DS-820 la and the physician's choice treatment in subjects with HER2-overexpressing (IHC 3+ or IHC 2+/ISH +) advanced gastric or gastroesophageal

	junction adenocarcinoma who have progressed on 2 prior regimens including fluoropyrimidine agent, platinum agent, and trastuzumab (brand, approved biosimilar). Randomization will be done in a 2:1 ratio into the 2 groups (DS-820l a: physician's choice treatment). **Exploratory Cohort 1** Exploratory Cohort 1 is a non-randomized cohort to assess the efficacy and safety of DS-820 l a to subjects with HER2 IHC 2+/ISH negative advanced gastric or gastroesophageal junction adenocarcinoma who are treatment naive of anti-HER2 therapy. **Exploratory Cohort 2** Exploratory Cohort 2 is a non-randomized cohort to assess the efficacy and safety of DS-820l a to subjec ts with HER2 IHC 1+ advanced gastric or gastroesophageal junction adenocarcinoma who are treatment naive of anti-HER2 therapy.
Study Duration:	Enrollment is planned to occur over approximately 10 months with treatment, and follow-up is projected to be continued for at least l0 months after last subject enrolled. Thus, the anticipated duration of the study is at least 20 months. The study will be continued until either the completion of follow-up assessments for all the subjects who discontinue st udy treatment or at the time of DS-8201a approval for this target indication.
Study Sites and Location:	See Supplement 1
Subject Eligibility Criteria:	**Common Inclusion Criteria (Primary Cohort, Exploratory Cohorts 1 and 2)** 1. Age 20 years. 2. Has a pathologically documented locally advanced or metastatic adenocarcinoma of gastric or gastroesophageal junction. 3. Progression on and after at least 2 prior regimens which had to include a fluoropyrimidine and a platinum. • Progression within 6 months of prior adjuvant or neoadjuvant chemotherapy will count as "rapid progressor" in neo-adjuvant/adjuvant setting, and thus equivalent to advanced/metastatic disease failing l regimen of therapy. • If prior combination therapy discontinued due to an adverse event (AE), and then one of the

agents continued, this is considered to be " 1 prior regimen" and not "2 prior regimens"

- The change in dosage form of 5-Fluorouracil medication (intravenous administration, oral administration) without progression is considered to be "1 prior regimen" and not " 2 prior regimens"
- If patient has received prior therapy with one of the drugs in physician's choice (i.e. irinotecan or paclitaxel) and has progressed on it then patient can be eligible if treating physician considers it appropriate to treat the patient with the other drng option from the physician's choice options. For example, if patient has received prior paclitaxel as a monotherapy or in combination with other drugs (e.g. ramucirumab) and has progressed on it then the patient will be eligible to receive irinotecan as long as they have not received and progressed on prior irinotecan therapy in this setting. Any patient who has received prior paclitaxel and irinotecan either as monotherapy or as combination therapy and have progressed on each one of these therapies (i.e. paclitaxel and irinotecan), would be ineligible for study participation. (Primary cohort only)

4. Is willing and able to provide an adequate archived tumor sample available for tissue sc reening to confirm HER2 status by Central Laboratory (based on most recent archived tumor tissue sample). If archived sample is not available, fresh sample is required.
5. Agree to submit fresh tumor samples for an assessment of HER2 status before the registration if primary tumor is accessible by endoscopy.
6. Has measurable disease assessed by the investigator based on Response Evaluation Criteria in Solid Tumours (RECIST) version l.l.
7. Has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of O to 1.
8. Has left ventricular ejection fraction (LVEF) 250% by either echocardiogram (ECHO) or multigated acquisition (MUGA) scan within 28 days before registration.

9. Has adequate organ function within 14 days before registration, defined as:

Item	Laboratory value
Platelet count	100000/mm^3 (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin	8.0 g/dL (Red blood ce ll transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count	l 500/mm^3 (G-CSF administration is not allowed within 1 week prior to screening assessment)
Creatinine	Creatinine clearance 30 mL/min as calculated using the Cockcroft-Gault equation
ALT/AST	3 x ULN (if liver metastases are present, 5 x ULN)
Total bilirubin	1.5 x ULN or < 3 x ULN in the presence of documented Gilbe1t' s Syndrome or liver metastases at baseline
Albumin	2.5 g/dL
International normalized ratio (INR)/Prothromb in time (PT) and activated partial thromboplastin time (aPTT)	1.5 x ULN

l0. Has adequate treatment washout period before study drug treatment, defined as:

Treatment	Washout period
Major surgery	4 weeks
Radiation therapy	4 weeks (if palliative stereotactic radiation therapy without abdominal radiation, 2 weeks)

Chemotherapy (including antibody drug therapy and retinoid therapy)	23 weeks (22 weeks for 5-fluorouracil-based agents, folinate agents and/or weekly Paclitaxel. 26 weeks for nitrosoureas or mitomycin C)
Immunotherapy	24 weeks
Cytochrome P450 (CYP) 3A4 strong inhibitor and orgamc amon transporting polypeptide (OATP) inhibitor 1B	23 x the elimination half-life of the inhibitor
Other study drugs	23 weeks

11. Male and Female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception, avoid intercourse, or reliable contraceptive measures (double barrier met hods, which include a combination of any 2 of the following: diaphragm, condom, sponge, spermicide, bilateral tubal ligation, or vasectomy) during and upon completion of the study and for at least 7 months for females and 4 months for males after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception including:

    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable

- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy or Vasectomized partner
- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 months for females and 4 months for males after the last dose of study drug. Periodic abstinence(calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception

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

Men who are fertile and sexually active should be willing to use highly effective methods of contraception if their partners are of reproductive potential.

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

Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.

12. Is able to provide written informed consent. Subjects must be fully informed about their illness and the investigationalnature of the study protocol (including foreseeable risks and possible toxicities) and must sign and date an Institutional Review Board (IRB)-approvedinformed consent form (ICF) before performance of any study-specific procedures or examinations.

Additional Inclusion Criteria for Primary Cohort

13. Centrally confirmed HER2 overexpression (IHC 3+ or IHC 2+/ISH*+)

    * ISH: fluorescent in situ hybridization (FISH) or dual in situ hybridization (DISH)

14. Progression on a trastuzumab containing regimen (can include an approved trastuzumab biosimilar). Progression on trastuzumab not required to be the most recent regimen.

Additional Inclusion Criteria for Exploratory Cohort 1

15. Centrally confirmed HER2 IHC 2+/ISH*negat ive

    * ISH: FISH or DISH

16. Treatment nai"ve with anti-HER2 targeted therapy including approved trastuzumab biosimilar.

Additional Inclusion Criteria for Exploratory Cohort 2

17. Centrally confirmed HER2 IHC 1+**

    **: ISH does not matter.

18. Treatment nai"ve with anti-HER2 targeted therapy including approved trastuzumab biosimilar.

Exclusion Criteria

1. Medical history of myocardial infarction within 6 months before registration, symptomaticcongestive

heart failure (CHF) (New York Heart Association Class II to IV, Section 17.4), troponin levels consistent with myocardial infarction as defined by manufacture, unstable angina, or serious cardiac arrh ythmia requiring treatment within 28 days before randomization/registration.

2. Has corrected QT interval by Fridericia's formula (QTcF) prolongation to >470 msec (females) or >450 msec (males) based on average of the screening triplicatel 2-lead electrocardiogram (ECG).
3. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
4. Has a pleural effusion, ascites or pericardia! effusion that requires drainage, peritoneal shunt, or Ce ll-free and Concentrated Ascites Reinfusion Therapy (CART). (Drainage and CART are not allowed within 2 weeks prior to screening assessment)
5. Has uncontrolled infection requiring intravenous (IV) injection of antibiotics, antivirals, or antifungals.
6. Have been diagnosed with human immunodeficiency virus (HIV) infection
7. Known active hepatitis B or C infection.
8. 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 do not require treatment with steroids for at least three weeks may be included in the study if they have recovered from the acute toxic effect of radiotherapy.
9. Has clinically significant corneal disease in the opinion of the investigator.
10. Prior treatment with an antibody-drug conjugate (ADC) which consists of an exatecan derivative that is a topoisomerase I inhibitor.
11. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than chronic

	toxicities per the discretion of the investigator,eg, alopecia, peripheral neuropathy, proteinuria, controllable hypertension, and controllable diabetes) not yet resolved to National Cancer lnstitute' s Common Te1minology Criteria for Adverse Events (NCI-CTCAE) version 4.03, Grade :Sl o r ba seline. 12. Has a diarrhea (watery stool), ileus, jaundi ce, or intestinal paralysis. 13. Has a concomitant medical condition that would increase the risk of toxicity in the opinion of the investigator. 14. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product. 15. Has history of severe hypersensitivityreactions to other monoclonal antibodies. 16. Has had non-gastric or gastroesop hageal junction primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, other curatively treated solid tumors. 17. 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 14 days before registration.
Dosage Form, Dose and Route of Administration:	**Study Drug (DS-8201a)** DS-820la for Injection 100 mg,. DP: The DS-820l a drug product is prov ided as a-QOwder containing 100 mg of DS-8201a in a glass vial - DP). DS-820l a will be administered as an IV solution. S ubjects will receive the 6.4 mg/kg of DS-820la on Day **1** of each cycle, once every 3 weeks (Q3W). **Physician's choice Treatment (Irinotecan or Paclitaxel)** The physician's choice treatment is a limited choice of one of two standard regimens (irinotecan monotherapy or paclitaxel monotherapy). The investigator will pre-select the physician's choice treatment before the randomization of each subject. Irinotecan monotherapy

	Starting dosage and usage is 150 mg/m^2 biweekly. or Paclitaxel monotherapy Starting dosage and usage is 80 mg/m^2 weekly.
Study Endpoints:	**Primary Endpoint:** • The objective response rate (ORR) assessed by the independent central imaging facility review based on RECIST version l. **l** (for Primary Cohort) **Secondary Endpoints:** • Efficacy endpoints (based on central review unless otherwise stated): - Overall survival (OS) , not based on central review - PFS - Duration of response (DoR) - Diseasecontrol rate (DCR) - Time to treatment failure (TTF) - ORR assessed by the investigator based on RECIST version 1.1 - ORR (for each Exploratory Cohort l and 2) • Safety endpoints: - Serious adve rse events (SAEs) - Treatment-emergent adverse events (TEAEs) - AE of special interest (AESI) - Discontinuation due to AE - Discontinuation due to AESI - Physical examination findings (including ECOG PS) - Vital sign measurements - Standard clinical laboratory parameters - Elevated troponin levels - ECG parameters - ECHO/MUGA findings

	- Ophthalmologic findings - Anti-drug antibodies (ADA) • Pharmacokinetic endpoints (DS-820la, total anti-HER2 antibody and MAAA-l18la): - Pharmacokinetics (PK) parameters: Cmax, Tmax, AUClast, and area under the serum concentration-time curve up to 21 days (AUC0-21d) - Serum concentrations. • HEOR endpoints (in Primary Cohort only): - Functiona l Assessment of Cancer Therapy-Gastric (FACT-Ga) - EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) - Health care resourceutilization **Exploratory Endpoints** (based on central review unless otherwise stated): • Exploratory efficacy endpoints (based on central review unless otherwise stated): - Time to response - Best percent change in the sum of diameters of measurable tumors - PFS based on investigator assessment • Serum extracellular domain of HER2 (HER2ECD) • Biomarker analysis using cell free DNA (cfDNA) • Analysis of pre-treatment and post-progression biopsies for mechanisms of resistance to DS-820la
Planned Sample Size:	The total planned number of subjects is approx imately 220. Primary Cohort: approximately 180 (DS-820l a group: 120, physician ' s choice group: 60) Exploratory Cohort 1: approximately 20 Exploratory Cohort 2: approximately 20
Statistical Analyses:	The primary analysis for ORR and a formal interim analysis for OS will be performed when all subjec ts have completed tumor assessment approximately at 24 weeks (or discontinuedfrom the study) in Primary Cohort. The final

OS analysis will be performed when about 133 OS events are observed in Primary Cohort.

Efficacy analyses:

Primary efficacy analysis will be performed for all randomized subjects who received at least one dose of the study treatment and had measura ble tumors based on central review at baseline in Primary Cohort. The primary endpoint is ORR assessed by independent central imaging facility review based on RECIST version 1.1. A Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR between the treatment groups. The primary efficacy analysis for ORR will be assessed for statistical significance at 2-sided alpha = 0.05. The estimate of ORR and its 2-sided 95% exact CI will be provided for each cohort/treatment group. In addition, ORR by fixed time points (eg, 3, 6, 9, 12 months) along with their 2-sided 95% exact Cis will be provided for each cohort/treatment group.

The secondary efficacy endpoints include OS, PFS, DoR, DCR, TTF, and ORR assessed by the investigator based on RECIST version 1.1. OS and PFS will be compared between the treatment groups using stratified log-rank tests in Primary Cohort. To control the family-wise type I error rate (FWER) for primary and secondary efficacy endpoints, a serial hierarchically ordered gatekeeping strategy will be applied. The tests will be performed in the followi ng order: ORR, OS. The sequence oftests will continue until the test does not meet the significance level of 2-sided alpha= 0.05. The HRs and their 95% Cis will be estimated, using stratified Cox proportional hazards models. Kaplan-Meier estimates and survival curves will also be presented for each cohort/treatment group. OS, PFS, DoR, and TTF will be summarized with median event times and their 2-sided 95% CI for the median using Brookmeyer and Crowley methods for each cohort/treatment group. DCR and ORR assessed by the investigator based on RECIST version 1.1 will be analyzed in the same manner as ORR analysis.

Safety analyses:

The safety endpoints will include SAEs, TEAEs, AESis, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, elevated troponin levels, ECG parameters, ECHO/MUGA findings, ADA, and ophthalmologic fmdings. TEAEs will be graded according to NCI-CTCAE version 4.03. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Pharmacokinetic analyses:

PK parameter s for each subject will be estimated using non-compartmental methods. Descriptive statistics will be provided for all serum concentration data by cohort/treatment arm at each time and PK parameter by cohort/treatment arm. The population pharmacokinetics (pop-PK) analysis to evaluate the effect of intrinsic and extrinsic factors ofDS-820la, and if appropriate, total anti-HER2 antibody, and MAAA-118l a will be characterized including available PK data from the Phase 1 (DS8201-A-Jl Ol).

After establishment of the pop-PK model, a population pharmacokinetics/pharmacodynamics (pop-PK/PD) model will be developed to evaluate the relationship between exposure and efficacy and toxicity.

The pop-PK and pop-PK/PD will be reported in a separate report from the clinical study report.

HEOR analyses:

HEOR endpoints (eg, EQ-5D-5L, FACT-Ga, health care resource utilization) will be summarized using standard methods of analysis for the corresponding questionnaires in Primary Cohort.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ACC	American College of Cardiology
ADA	anti-drug antibodies
ADC	antibody-drug conjugate
[redacted]	[redacted]
AE	adverse event
ALP	alkaline phosphatase
ALT	L-alanine aminotransferase
AST	L-aspartate aminotransferase
AUC	area under the plasma/serum concentration-time curve
AUC21d	area under the plasma/serum concentration-timecurve up to 21 days
AUCinf	area under the plasma/serum concentration-time curve up to infinity
AUClast	area under the plasma/serum concentration-time curve up to the last quantifiable time
BCRP	breast cancer resistance protein
Bl	before infusion
BSEP	bile salt export pump
CART	Cell-free and Concentrated Ascites Reinfusion Therapy
CDlSC	Clinical Data InterchangeStandards Consortium
cfDNA	cell free DNA
CHF	congestive heart failure
CL	total body clearance
Cmax	maximum plasma/serum concentration
COVID-19	coronavirus disease 2019
CR	Complete Response
CrCI	creat inin e clearance
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450

ABBREVIATION	DEFINITION
DAR	drug-to-antibody ratio
DCR	disease control rate
DISH	dual in situ hybridizat ion
DLT	dose limiting toxicity
DNA	deoxyribonucle ic acid
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOGPS	Eastern Cooperative Oncology Group Performance Status
eCRF	electroniccase report form
EDC	electronic data capture
El U	Exposure 1n Utero
EOl	end of infusion
EOT	end of treatment
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-Ga	Functional Assessment of Cancer Therapy-Gastric
FAS	full analysis set
Fili	first-in-human
FISH	fluoresce nt in situ hybridization
FWER	family-wise type **I** error rate
GCP	Good Clinical Practice
GEJ	gastro-esophageal junction
HER2	human epidermal growth factor receptor 2
HER2ECD	extracellular domain of HER2
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
1B	Investigator 's Brochure
lCF	informed consent form
lCH	International Conference on Harmonization
lgGl	immunoglobulin G**1**

ABBREVIATION	DEFINITION
IHC	immunohistoc hemistry
ILD	inte rstitial lung disease
INN	international nonproprietary name
lRB	Institutional Review Board
ISH	in situ hybridization
IV	intravenous(ly)
IXRS	interactive web/voice response system
LVEF	left ventricular eject ion fraction
MAAA-118la	the drug component of DS-8201a - a derivative of exatecan, a topoisomerase I inhibitor
MAAL-9001	the antibody component of DS-8201a - a humanized IgGl monoclonal antibody produced in-house with reference to the same amino acid sequence of trastuzumab
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regu latory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
MUGA	multigated acquis ition (scan)
NAB	neutralizing anti-drug antibody
NCI	Nationa l Cancer Institute
NE	Not Evaluable
NRU	neu tral red uptake
OAT	organic anion transporter
OATP	organic anion transport ing polypep tide
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival
PD	Progressive Disease
PFS	progression-free survival
P-gp	P-glycoprote in
PK	pha rmacoki netics
pop-PK	population pharmacokinetics
pop-PK/PD	population pharmacok inetics/pharmacodyn amics

ABBREVIATION	DEFINITION
PR	Partial Response
PRO	patient reported outcomes
PT	Preferred Term
Q3W	once every 3 weeks
QoL	quality of life
QTc	corrected QT interval
QTcF	correcte d QT interval by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAYER	Serious Adverse Event Report
SD	Stable Disease
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	standard operating procedure
SpO2	per iph era l oxygen saturation
STD10	se verely toxic dose in 10% of the animals
SUS AR	Suspected Unexpected Serious Adverse Reaction
t1/2	te rminal elimination half-life
T-DM1	trastuzumab emtansine
TEAE	treatment-emergent adverse event
Tmax	time to reach maximum plasma/serum concentration
TTF	time to treatme nt failure
ULN	upper limit of normal
Vss	volume of dis tribution at the steady state

1. INTRODUCTION

1.1. Background

Gastric cancer is the fifth most common cancer worldwide; there are approximately 950,000 new cases diagnosed and 720,000 deaths worldwide annually. Among various geog raphical regions in the world, the highest incidence and mortality of gastric cancer were registered from North-Eastern Asian countries, including Japan and Korea, accounting for more than half of the world.[1] In Korea and Japan, gastric cancer is more likely to be diagnosed at an early stage, resulting in more favorable 5-year survival rates of 55.6% to 66.0%,[2] and 50.0%, respectively.[3] In patients with gastric cancer who are refractory to standard therapies, the median life expectancy is a maximum of approximately 6 months, and there remain high unmet medical needs.[4]

DS-820la is an antibody-drug conjugate (ADC) targeting human epidermal growth factor receptor 2 (HER2). In the ongoing Phase 1 clinical study, DS8201-A-Jl01, in subjects with advanced solid tumors, DS-820la was well tolerated at repeated doses of up to 8.0 mg/kg intravenously (IV) once every 3 weeks (Q3W).

1.2. Treatment of Gastric Cancer

Across Asian populations, HER2 overexpression (immunohistochernistry [IHC] 3+ and IHC 2+/in situ hybridization [ISH] +) in gastric cancer is reported in approximately 9.8% to 23.0% of cases,[5,6,7,8,9,10] HER2 IHC 2+/ISH negative is 2.5% to 20.1%, HER2 IHC 1+ is 14.0% to 42.9% of cases,[5,8,9,10] and it is considered to be an important target molecule for gastric cancer therapy due to initiation of a strong pro-tumorigenic signalingcascade.[11] Trastuzumab is the only approved anti-HER2 therapy worldwide for gastric cancer patients with HER2-overexpressing tumors that are defined as either IHC 3+ or IHC 2+/fluorescent in situ hybridization (FISH) positive. The addition of trastuzumab to chemotherapy with capecitabine (or 5-FU) and cisplatin is recommended as first-line chemotherapy for patients with HER2-overexpressingadvanced gastric cancer in Japan and Korea. However, after treatment failure of trastuzumab, there is no anti-HER2-specific treatment for the patients. As a second line, combination therapy of ramucirumab plus paclitaxel is recommended. In patients with good performance status, agents that had not been used in the previo us chemotherapy are selected as the third-line therapy (Irinotecan or Taxane), with response rates of about 3.0% to 23.2%, median progression-free survival (PFS) of 2.3 to 3.5 months, and median overall survival(OS) of 4.0 to 6.7 months.[12,13,14,15] Anti-PD-l antibody, nivolumab was compared with placebo for the treatment of subjects who had progressed after treatment with standard therapies. Nivolumab improved median OS from 4.14 to 5.26 mo.[16]

It is known that trastuzumab has an impact on changes in HER2 expression. It is reported that loss of HER2 positivity after progression of trastuzumab treatment was observed in 14/48 (29.2%).[17] The majority of patients with HER2-overexpressing advanced gastric cancer eventually acquire resistance or show intolerance to these drugs. In addition, after failure of tras tuzumab as first line treatment, there is no HER2 specific treatment option as second line or latter. Therefore, HER2-overexpressing advanced gastric cancer is considered a serious and life-threateningdisease and this patient population has a high unmet medical need.

1.3. Investigational Product

1.3.1. Description

DS-820l a consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component, MAAA-l 18 la. MAAL-9001 is an in-house humanized immunoglobulin G**1** (IgG**1)** monoclonal antibody with the same amino acid sequence as trastuzumab. MAAA-118la, an exatecan derivative,[18,19,20] is a topoisomerase I inhibitor that is cell-membrane permeable, and more potent than SN-38 (active metabolite of irinotecan). This ADC achieves a high drug-to-antibody ratio (DAR) (7 to 8) with homogeneous conjugation with MAAA-l 18la.[21] DS-820la is cleaved by lysosomal enzymes and releases MAAA-l 18la in the cytoplasm after it binds to the HER2 receptor, and gets internalized in tumor cells.

The DS-820la Phase I clinical study, DS8201-A-J101, was injtiated with the antibod y component. MAAL-9001, [redacted]. To support *1202* studv, [redacted], transition is being made to MAAL-900- [redacted] Analytic comparison of the two [redacted] products have shown comparability across a wide range of variables. [redacted] However, in a xenograft study, no difference was seen in antitumor activity between the two products. Following single IV administration ofDS-820la to cynomolgus monkeys, mean Cmax ofDS-820la was similar, whlle AUClast was approximately 22% lower, for [redacted] material as compared to [redacted] material. DS-820 Ia drug product manufactured from [redacted] material will be supplied to thls study.

1.3.2. Nonclinical Studies

1.3.2.1. Pharmacology

DS-820la inhlbits tumor growth mainly by topoisomerase I inhibition-derived DNA damage, and induces apoptosis by the payload that is released from DS-8201a after internalization in cancer cells via HER2. DS-8201a is expected to inhibit tumor growth [redacted] The results of in vitro cell growth inhlbition studies conducted using several cancer cell lines have shown that DS-820la has more potent growth inhlbition against HER2-positive cells than the monoclonal antibody alone, suggesting that the conjugation of the warhead enhances the growth-inhibitory action of DS-8201a. Moreover, no growth inhibition was observed in HER2-negative cells, thus confinning 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 (NCI-N87) was studied, it was confirmed that DS-820 l a exhibited potent, dose-dependentantitumor activity with tumor regression, and that thls activity was even stronger than that of the antibody portion alone. In addition, in vivo studies in tumor-bearing mouse models have confirmed that DS-820l a has antitumor activity even against HER2 low-expressing tumors that are insensitive to other anti-HER2 therapies. DS-8201a is therefore expected to be effective against HER2 low-expressing tumors, and is also expected to be effective against trastuzumab insensitive tumors.[21] Moreover, DS-8201a demonstrated potent efficacy in mice inoculated with a mixture of

HER2-positive and -negative cells while trastuzumab emtansine (T-DM1) did not, due to more potent bystander killing and higher cell membrane permeability of the conjugated toxin.[21,22] The effect therefore supports the efficacy ofDS-820la against tumors with HER2 heterogeneity.

1.3.2.2. Safety Pharmacology

In a safety pharmacology study in monkeys treated with single intravenous doses of DS-820l a, no effects on the cardiovasc ular syste m, 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-l 18la, MAAA-l 18ladid not inhibit the hERG channel current at concentrations of up to 10 µmol/L (approximately 5000 ng/mL).

1.3.2.3. Pharmacokinetics and Drug Metabolism

The plasma DS-820l a concentrations decreased exponentially following a single intravenous administration ofDS-820la at 0.1 mg/kg to 3.0 mg/kg to cynomolgus monkeys. The volume of distributionat the steady state (Vss) was close to the plasma volume. CL decreased as the dose increased, and the pharmacokinetics (PK) were found to be non-linear. Both DS-820 l a and the total antibody, bound and unbound antibody combined, exhibited similar plasma concentration-t ime profiles at all dose levels, as well as similar AUC. All individual plasma concentrations ofMAAA-l18la, the released drug from DS-820la, were below the lower limit of quanti fication(0.100 ng/mL) at 0.1and 0.3 mg/kg. A low-plasma level of MAAA-l 18la was detected at limited time points with 1.0 and 3.0 mg/kg. No anti-DS-820l a antibodies were detected in any of the animals.

The mean plasma protein binding ratios of MAAA-1181a at l O 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 ofMAAA-l l81a from DS-820la gradually increased throughout the incubation period in mouse, rat, and monkey plasma with 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 release rates from 2.2% to 2.4%. These results indicate that most DS-820l a is stable in plasma.

No major differences were found between the metabolite profiles of DS-8201a in rat, monkey, and human hepatocytes. MAAA- l 18la was metabolized by cytochrome P450 (CYP) enzymes; CYP3A4 was the primary CYP enzyme in the metabolism ofMAAA-118l a, while CYP3A5 and CYP2D6 were also involved in the metabolism.

In monkeys, excretion of radioactivityfrom administered ^{14}C-DS-820 l a into feces was predominant. In rats, excretion of radioactivity from administered ^{14}C-labeled MAAA- l 18la (^{14}C-MAAA-l 18la) into feces via bile was predominant.

MAAA-118 la did not show any inhibition potential to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2Cl9, CYP2D6, and CYP3A (50% inhibitory concentration [ICso] >50 µmol/L). MAAA-l 18la did not show any induction potential to CYP3A4, CYP1A2, and CYP2B6 up to 30 µmol/L. MAAA-1181a did not inhibit organic anion transporter (OAT) 3, organic cation transporter (OCT) 1, OCT2, organic anion transporting polypeptide (OATP) 1B3, multidrug and toxin extrusion (MATE) 1, MATE2-K, P-

glycoprotein (P-gp), breast cancer resistance protein (BCRP), and bile salt export pump (BSEP) (ICso >30 µmol/L). MAAA-l18la inhibited OATl and OATPlBl with the ICso values of 12.7 and 14.4 µmol/L, respectively, however the values were much higher than the Cmax ofMAAA-l18la in humans (9.25 ng/rnL [0.019 µmol/L] at 8.0 mg/kg ofDS-820la). In addition, MAAA-l18la was found to be a substrate of OATPlBl and 1B3.

1.3.2.4. Toxicology

In a study of intermittent intravenous dosing of DS-820 la 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, incisor tooth, and renal toxicity at dose levels of 60 mg/kg and greater. Except for the testicular and incisor tooth changes, these changes all recovered.

In an intermittent intravenous dosing study ofDS-820la 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 kidneys. The cause of the moribundity appeared to be 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 survivinganimals 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 toxic ity, and electrocardiogram (ECG) abnormalities (shortened PR interval and corrected QT interval [QTc] prolongation) were found at 78.8 mg/kg. Except for pulmonary and skin toxicity (pigmentation), these findings tended to recover.

Thus, as described above, the severely toxic dose in 10% of the animals (STD10) in a rat intermittent intravenous dosing study ofDS-820la was found to be greater than 197 mg/kg. In the monkey study, due to observed moribundity at 78.8 mg/kg and evidence of critical pulmonary toxicity (eg, interstitial inflammation and/or alveolar edema) in the surviving animals, it was concluded that the highest non-severely toxic dose (HNSTD) is 30 mg/kg.

In an intermittent intravenous dose toxicity study of MAAA-1181a (monohydrate) (once weekly dosing for 4 weeks), findings in the lymphatic/hematopoieticsystem, intestinal tract, and the cornea of the eye were observed at 3 mg/kg and greater in rats but there were no deaths or moribundity up to 30 mg/kg. Findings similar to those in rats were observed in cynomolgus monkeys at dose levels of l 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 death and moribundity. The common adverse findings in both DS-820la and MAAA-l 18la studies were intestinal and lymphatic/hematopoieticsystem toxicities. For DS-820la treatment, pulmonary, testicular, skin and renal toxicities were observed while heart, liver, and corneal toxicities were found only in the MAAA-118la study.

In a human cross-reactivity study ofDS-820la with a panel of human tissues, DS-820l a-related cell membrane staining was found only in the placenta. In a cross-reactivity study of DS-820l a with selected cynomolgus monkey tissues (eg, brain, liver, kidney, lung, heart, intestines, lymphoid organs, testes, and skin), neither membranous nor cytoplasmic staining was noted in any tissues.

In an in vitro 3T3 neutral red uptake (NRU) phototoxicity study, **MAAA-l** 18la was found to be phototoxic to Balb/c 3T3 mouse fibrobla sts . However, in an in vivo single dose phototoxicity study of MAAA-l 181a in pigmented rats, no phototoxic reaction was noted at 3 mg/kg, the highest dose tested.

1.3.3. Clinical Experience

The DS-820la first-in-human(FIH) study (Protocol DS8201-A-Jl01) is an open-label, dose-finding study to assess the safety and tolerability of DS-820la in subjects with advanced solid tumors. The study is being conducted in 2 parts; dose escalation (Part 1) and dose expansion (Part 2): Part l was a dose escalation phase in patients with either advanced breast cancer or gastric/gastro-esophageal junction (GEJ) adenocarcinoma. Part 2 is the expansion phase and focuses on HER2 -positive breast cancer, HER2-positive gastric/GEJ junction adenocarcinoma, and HER2 low breast cancer, as well as other HER2-expressing solid cancers.

Preliminary results from Part 1 indicate that DS-820 la has an acceptable safety and PK profile and antitumor activity in gastric cancer patient s, with tumors that were previously treated with trastuzumab.

As of the 8 June 2017, 148 subjects received DS-820la in this study.

In the Part 1, a total of 24 subjects, 3 in 0.8 mg/kg cohort, 3 in 1.6 mg/kg cohort, 3 in 3.2 mg/kg cohort, 6 in 5.4 mg/kg cohort, 6 in 6.4 mg/kg cohort and 3 in 8.0 mg/kg cohort, received DS-820 l a. 17 Breast cancer patients, 6 gastric cancer patients and 1 gastroesophageal junction cancer patient have been enrolled. No DLTs (defined as occurring during cycle 1) were reported in any subject. Two doses, 5.4 mg/kg and 6.4 mg/kg were chosen for expansion in Part 2.

In Part 2, a total of 124 subjects, 48 in Part 2a, 41 in Part 2b, 10 in Part 2c and 25 in Part 2d, received DS-820la. Of those, 47 subjects, 30 subjects in Part 2a and 17 subjects in Part 2b, received 5.4 mg/kg, and the other 77 subjects received 6.4 mg/kg of DS-820 l a. In Part 2d, 11 colorectal cancer patients, 6 non-small cell lung cancer patients, 4 parotid/submandibular gland cancer patients, 2 Paget' s disease patients, 1 cholangiocarcinoma patient and 1 esophageal cancer patient have been enrolled.

In Part 1 and 2, For 148 subjects who have received DS-820la in the study, the most common AEs{>20%) of any grades were nausea (65%), decreased appetite (53%), vomiting (34%), platelet count decreased (31%), anemia (28%), alopecia (26%), diarrhea (24%), constipation (24%), neutrophil count decreased (24%), white blood cell count decreased (24%), and malaise (22%). The majority of the AEs were of Grade 1 or 2 severity; 52 of 148 subjects (35 .1%) experience d Grade 3 AEs and 10 subjects (6.8%) experienced Grade 4 AEs as the worst grade experienced.

Adverse events of special interest (AESI) detailed in the Phase 1 protocol included infusion reactions, cardiac events, and interstitial lung disease. Periodic cardiac

assessments are performed including echocardiogram (ECHO) or multigated acquisition (MUGA) scan performed at every 2 cycles (42 days) and 12 lead triplicate ECGs performed at least every cycle (21 days). As of 8 June 2017, a total of 13 (8.7%) subjects exper ienced TEAEs relating to cardiotoxicity in the on-going study. Of these 13 subjects, 9 experienced QT prolongation(7 Grade 1 and 2 Grade 2, all non-serious), all considered related to the study therapy. Two subjects experienced ejection fraction decreased (Grade 2, non-serious, related), **1** subject experienced Grade 2 tachycardia and 1 subject experienced heart rate decreased (related). No action was taken regarding the study drug therapy and no subjects discontinued study therapy. Pulmonary assessments are performed at the time of imaging for tumor assessments as well as evaluation of peripheral oxygen saturation (SpO2) on Day **l** of every cycle and at end of treatment (EOT). In the event of suspicion of drug induced lung disease, recommendat ions include consultation with a pulmonologist and interruption of DS-820 l a treatment pending finaldiagnosis. Study treatment is permanently discontinued upon confirmation of drug induced interstitial lung disease (ILD) or pneumonitis of any grade. As of 8 June 2017, there were 3 subjects (where one received 8.0 mg/kg and the other 2 received 6.4 mg/kg) who had expe rienced one serious and 2 non-serious pneumonitis (one was Grade **l** and the other as Grade 2). There were also 2 subjects who experienced interstitial lung disease (l serious and Grade 3 in severity, and the other non-se rious; with Grade **1** severity).

Overall efficacy results from all cohorts in Part 1 demonstrated an objective response rate (ORR) of 34.8% and disease control rate (DCR) of 91.3%. Subjects in the higher dose levels (2::5. 4 m g/kg, 15 subjects) showed ORR of 53.3%.

Overall efficacy results from all cohorts in Part 2 demonstrated an ORR of 48.8% and DCR of 85.7%. Breast cancer cohorts with HER2 positive and low expression,Part 2a and 2c, showed ORR of 61.5% and 50.0%, and DCR of 96.2% and 90.0% respectively. The HER2 positive gastric cancer cohort showed ORR of 48.4% and DCR of 80.6%.

Please refer to the current 1Bof updated clinical study information for DS-8201a.

1.3.4. Summary of Clinical Pharmacokinetics

PK was evaluated in 24 Japanese subjects who received DS-8201a. Following a single intravenous administration, PK parameters at 5.4, 6.4, and 8.0 mg/kg are shown in Table l. l , Table 1.2, and Table 1.3. The maximum serum co ncentration (Cmax)of DS-820la at 6.4 mg/kg was achieved with median time to reach Cmax (Tmax) of 0.09 d (2.16 h). Cmax and AUClast at 6.4 mg/kg were 181 µg/mL and 90 l µg d/mL, respectively. The systemic exposure at 6.4 mg/kg in subjects in Cycle l exceeded the systemic efficacious expos ure observed during non-clinical pharmacology evaluation. Mean tl l2of DS -820 l a was 7.33 d at 6.4 mg/kg. The Vss for DS-820la is 58.6 mL/kg, which is similar to the serum volume.

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

Cmax and AUClast were 6.80 ng/mL and 31.0 ng d/mL at 6.4 mg/kg, respectively,which were quite low. The t112 ofMAAA-l181a was similarto that of DS-8201a.

Table 1.1: Phar macokinetic Parameters of DS-8201a

Dose (mg/kg)	C max (Jtg/mL)	T max (h)	AUClast (J•g•d/ mL)	AUCinf (J•g•d/ mL)	h 12 (d)	CL (mL/d/ kg)	Vss (mL/ kg)
5.4 (N = 6)	127 (17.2)	1.92 (1.92, 2.16)	544 (165)	590 (186)	6.03 (0.603)	10.1 (3.90)	75.2 (24.2)
6.4 (N = 6)	181 (33.1)	2.16 (1.44, 4.08)	901 (155)	1030 (209)	7.33 (1.64)	6.41 (1.12)	58.6 (11.0)
8.0 (N = 3)	216 (52.0)	1.92 (1.92, 2.16)	914 (235)	1020 (279)	6.97 (0.36)	8.17 (1.93)	69.7 (13.1)

AUC = area under the serum concentration-time curve; AUClast = area under the serum concentration-time curve up to the last quantifiable time; AUCinf = area under the serum concentration-time curve up to infinity; CL= total body clearance; Cmax = maximum serum concentration; **N** = number; tl/2 = terminal elimination half-life; Tmax = time to Cmax; Vss = volume of distribution at the steady state.

Table 1.2: Pharmacokinetic Parameters of Total Antibody

Dose (mg/kg)	**Cmax (Jtg/mL)**	**T max (h)**	**AUClast (11g•d / mL)**	**AUCinf (11g•d/mL)**	t112 **(d)**
5.4 (N = 6)	116 (13.9)	1.92 (1.92, 6.96)	609 (151)	682 (172)	6.78 (2.39)
6.4 (N = 6)	146 (18.9)	3.84 (2.16, 6.96)	878 (97.1)	1050 (149)	8.25 (2.16)
8.0 **(N** = 3)	178 (18.5)	2.16(1.92, 6.72)	1090 (213)	1270 (296)	7.35 (0.417)

AUC = area under the serum concentration-time curve; AUClast = area under the serum concentration-time curve up to the last quantifiable time; AUCinf = area under the serum concentration-time curve up to infinity; Cmax = maximumserum concentration; N = number; 1112 = terminal elimination half-life; Tmax = time to Cmax.

Table 1.3: Pharmacokinetic Parameters of MAAA-1181a

Dose (mg/kg)	**C max (ng/mL)**	**Tmax (h)**	**AUClast (ng•d/mL)**	**AUCinf (ng•d/mL)**	***tin* (d)**
5.4 (N = 6)	10.8 (7.56)	5.28 (3.84, 23.76)	40.6 (19.8)	43.6 (21.2)	6.11 (0.811)
6.4 (N=6)	6.80 (1.72)	6.72 (4.08, 7.20)	31.0 (5.11)	34.2 (5.63)	6.28 (1.17)
8.0 (N= 3)	9.25 (3.18)	6.72 (6.72, 6.96)	39.4 (6.43)	43.4 (9.16)	6.36 (1.53)

AUC = area under the serum concentration-time curve; AUClast = area under the serum concentration-time curve up to the last quantifiable time; AUCinf = area under the serum concentration-time curve up to infinity; Cmax = maximumserum concentration; N = number; 1112 = terminal elimination half-life; Tmax = time to Cmax.

1.4. Study Rationale

HER2 is a member of the HER superfamily that initiates signal transduction via the PI3K/AKT and RAS/MAPK pathways.[23 24] In human advanced solid tumors, expression of HER2 protein has been reported in various tumor tissues and in a variety of cultured tumor cell lines including breast cancer,[25] gastric cancer,[26 27] pancreatic cancer,[28] lung cancer,[29] colorectal cancer,[30] and ovarian cancer.[31]

DS-820l a is an ADC that targets HER2. A humanized IgGl 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-820la is expected to inhibit tumor growth based on the follow ing reasons [redacted] the MAAA-l 18la that is released from DS-820 la after the internalization induces apoptos is by inhibiting topoisomerase I.

In nonclinical studies, the fact that DS-8201a binds specifically to the extrace llular domain ofHER2 (HER2ECD) and does not bind to other HER family proteins has been confinned. In vitro studies indicate that DS-820l a 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-820Ia . h1 vivo studies using a tumor-bearing mouse model suggest that administration ofDS-8201a results in the regression of not only HER2-overexpressing tumors but also HER2 low expressing tumors. DS-820 l a exhibit s an anti-tumor effect with tumor regression in tumors that express low levels of HER2 and is therefore also expected to be effective against tumors that express low levels of HER2, for which HER2 therapy including trastuzumab has not been approved. One reason for this may be that the DAR for DS-8201a is approxin1ately 8, compared to an average DAR of 3.5 for cunently approved ADC's for other indications.

In the Phase 1 study, DS8201-A-Jl O1, the preliminary results as of 8 June 2017, indicate that DS-8201a has tolerable safety and PK profiles, and antitumor activity. There have been no reported DLTs, and MTD was not reached in the 0.8 mg/kg to 8.0 mg/kg Q3W cohorts. HER2-positive gastric cancer subjects from Phase! Part 2b cohort, ORR was 48.4% (N = 15/31) and DCR was 80.6% (N = 25/31). DoR was 4.7 months.

Based on preclinical and clinical observations in the Phase 1 study (DS8201-A-Jl 01), DS-820la was well tolerated and antitumor activity in HER2-overexpressing gastric cancer subjects was observed. For the past few decades, the main approach to treatment of patients who failed trastuzumab treatment as first line depended on the use of conventional cytotoxic chemotherapies and non-HER2 specific antibody. Therefore the Phase 2 study is conducted to detennine the efficacy and safety profile of DS-8201a for HER2-overexpressing gastric cancer as a Primary Cohort. In addition, the efficacy and safety of HER2 low-expressing patients (IHC 2+/ISH negative or IHC 1+) will be exploratively assessed in Exploraty Cohort 1 and 2, respectively.

1.5. Risks and Benefits for Study Subjects

Based on the clinical observations in the Phase 1 study (DS8201-A-Jl O1), DS -82 01 a d e monstrated antitumor activity in HER2-overexpressing gastric cancer subjects (see Section 1.3.3).

Overall, the reported AEs (see Section 1.3.3) were consistent with the safety profile of DS-820l a, expected based on the nonclinical toxicology data. The following TEAEs were considered as identified risk: nausea, decreased appetite, vomiting, platelet count decreased, anaemia, alopecia, diarrhoea, neutrophil count decreased, and white blood cell count decreased. The majority of the TEAEs were of Grade 1 and Grade 2 severity. Subjects receiving DS-8201a should be monitored for signs and symptoms of any of the

toxicities observed in nonclinical studies and to other products of the same class, which are discussed below.

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

In addition to these toxicities, as with other products of the same class, the possibility of cardiotoxicity, related to the potential for QT prolongation were found in association with the administration of DS-8201a and cannot be excluded. Left ventricular ejection fraction (LVEF) will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs, will be evaluated by the investigator or delegated physician to monitor cardiac function and troponin will be evaluated to assess cardiac function.

Pulmonary toxicity was observed in association with the administration of DS-8201a in both pre-clinical and clinical studies. Interstitial lung disease/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the DS8201-A-J101 clinical study as well as the results of potential interstitial lung disease (ILD)/pneumonitis cases reviewed by the independent ILD Adjudication Committee (AC), available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.

Additional safety assessments should be conducted as needed, at the investigator's discretion. It can also not be denied that hepatotoxicity, embryo-fetal toxicity, or visual disturbances/corneal toxicity may occur in subjects receiving DS-8201a. As with any therapeutic antibodies, there is a possibility of infusion related reactions, and immune responses causing allergic or anaphylactic reactions of DS-8201a.

Based on the efficacy and safety data observed in the nonclinical studies, the current clinical experience of the Phase 1 study, and the information from other products of the same class, the benefit-risk balance supports clinical development of DS-8201a in this patient population. For up to date assessments of risks and benefits to subjects, please refer to the current IB for DS-8201a.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

Primary Cohort

- To compare the efficacy and safety of DS-8201a and physician's choice treatment in HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma subjects who have progressed on 2 prior regimens including fluoropyrimidine agent, platinum agent and trastuzumab (brand, approved biosimilar).

Exploratory Cohort 1

- To determine the efficacy and safety of DS-8201a in subjects with HER2 IHC 2+/ISH negative advanced gastric or gastroesophageal junction adenocarcinoma.

Exploratory Cohort 2

- To determine the efficacy and safety of DS-8201a in subjects with HER2 IHC 1+ advanced gastric or gastroesophageal junction adenocarcinoma.

2.2. Study Hypotheses

DS-8201a confers a significant ORR benefit comparing physician's choice treatment in HER2-overexpressing advanced gastric cancer patients who have been treated and progressed with at least 2 prior regimens

2.3. Study Endpoints

2.3.1. Primary Endpoint

- ORR assessed by the independent central imaging facility review based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (for Primary Cohort)

2.3.2. Secondary Endpoints

- Efficacy endpoints (based on central review unless otherwise stated):
  - OS (not central review)
  - PFS
  - DoR
  - DCR
  - Time to treatment failure (TTF)
  - ORR assessed by the investigator based on RECIST version 1.1
  - ORR (for each Exploratory Cohort 1 and 2)

- Safety endpoints:
  - Serious adverse events (SAEs)
  - TEAEs
  - AESI
  - Discontinuation due to AE
  - Discontinuation due to AESI (AE of special interest)
  - Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS])
  - Vital sign measurements
  - Standard clinical laboratory parameters
  - Elevated troponin levels
  - ECG parameters
  - ECHO/MUGA findings
  - Ophthalmologic findings
  - Anti-drug antibodies **(ADA)**
- Pharmacokinetic endpoints (DS-8201a, total anti-HER2 antibody and MAAA-1181a):
  - **PK** parameters: Cmax, Tmax, and AUClast, AUC0-21d
  - Serum concentrations
- HEOR endpoints (in Primary Cohort)
  - EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L)
  - Functional Assessment of Cancer Therapy-Gastric (FACT-Ga)
  - Health care resource utilization

2.3.3. Exploratory Endpoints

- Exploratory efficacy endpoints (based on central review unless otherwise stated):
  - Time to response
  - Best percent change in the sum of diameters of measurable tumors
  - PFS based on investigator assessment
- Serum extracellular domain of HER2 (HER2ECD)
- Biomarker analysis using cell free DNA (cfDNA)

- Analysis of pre-treatment and post-progression biopsies for mechanisms of resistance to DS-8201a

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

This is a Phase 2, multi-center, open-label, 3-cohort study to investigatethe efficacy and safety of DS-820la in subjects with HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma who have progressed on 2 prior regimens including fluoropyrimidine agent, platinum agent and trastuzumab (brand, approved biosimilar) when compared to treatment of physician' s choice. Additional exploratory cohorts in treatment naive subjects with HER2 expressing advanced gastric or gastroesophageal junction adenocarcinoma. The study design schema is shown in Figure 3.1

Primary Cohort

Primary Cohort is a randomized cohort to compare the efficacy and safety of DS-820la and the physician's choice treatment in subjects with HER2-overexpressing (IHC 3+ or IHC 2+ / ISH +) advanced gastric or gastroesophagea l junction adenocarcinoma who have progressed on 2 prior regimens including fluoropyrimidine agent, platinum agent and trastuzumab (brand, approved biosimilar). Randomization will be done in a 2:1 ratio into the 2 groups (DS-820l a: physician's choice treatment). Randomization will be stratified by region (Japan or Korea), ECOG PS (0 or 1), and HER2 status (IHC 3+ or IHC 2+/ISH +).

Exploratory Cohort 1

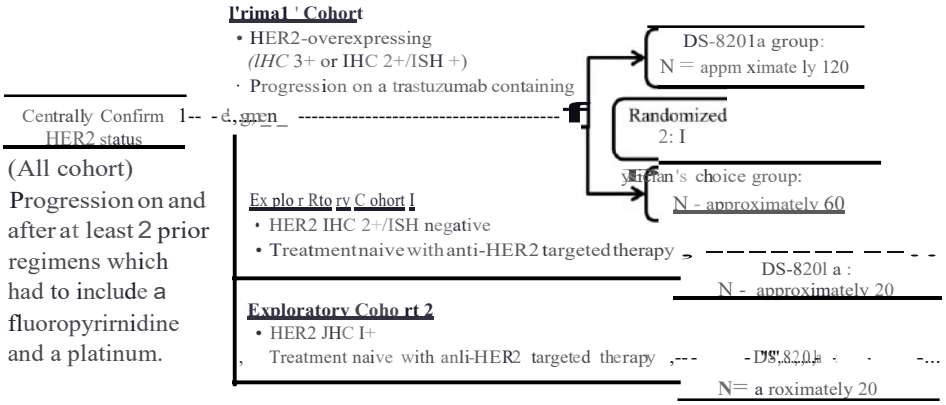
Exploratory Cohort l is a non-randomized cohort to assess the efficacy and safety ofDS-820la to subjectswithHER2 IHC 2+/ISH negative advanced gastric or gastroesophageal junction adenocarcinoma who are in treatment nai"ve of anti-HER2 therapy.

Exploratory Cohort 2

Exploratory Cohort 2 is a non-randomized cohort to assess the efficacy and safety ofDS-820la to subjects with HER2 IHC 1+ advanced gastric or gastroesophageal junction adenocarcinoma who are in treatment na:ive of anti-HER2 therapy.

The total number of subjects planned is approximately 220 (Primary Cohort: approximately 180, Exploratory Cohort 1: approximately 20, and Exploratory Cohort 2: approximate ly 20).

Figure 3.1: Study Design Schema of DS8201-A-J202



3.1.2. Duration of the Study

Enrollment is planned to occur over approximately l O months with treatment, and follow-up is projected to be contin ued for at least l O months after last subject enro lled. Th us, the anticipated duration of the study is at least 20 months. The study will be contin ued until either the completion of follow-up assessments for all the subjects who discontinue study treatment or at the time of DS-820l a approval for this target indication.

3.1.3. Duration of Subject Participation

Subjects will receive study medication until a discontinuation criterion is met.

After discontinuation from study treatment, all subjects, regardless of whether they discontinuedprio r to or subsequent to disease progression, may be contacted every 3 months until death or until follow-up data collection is no longer needed (at the Daiichi Sankyo's discretion), to obtain info1mation about subseq uent treatment(s) and survival status.

3.2. Discussion of Study Design

3.2.1. Selection of Dose and Usage

DS-820la

DS-820la was administered at 0.8 mg/kg to 8.0 mg/kg Q3W in the prior Phase 1 study (DS8201-A-Jl01), and DLT did not occurred and the MTD was not reached up to 8.0 mg/kg. Although 8.0 mg/kg was shown to be tolerable, dose reductions were observed two out of three patients, and subsequent exposure-response analysissupported 5.4 mg/kg and 6.4 mg/kg are appropriate assessment dose in expansion cohort of Phase! study. On the basis of efficacy, tolerability and PK profile established in the Phase 1 study and pre-clinical studies, the dose of 6.4 mg/kg will be used inthis trial.

Irinotecan monotherapy

Starting dosage and usage is 150 mg/m^2 biweekly.

Paclitaxel monotherapy

Starting dosage and usage is 80 mg/m^2 weekly.

3.2.2. Treatment Cycle Period

Each treatment cycle of DS-8201a will be 21 days. Dosing for the every 3 weeks treatment will occur on Day1 of each cycle. Cycle allowance is ± 3 days. Treatment after 25 days (Day 26) from previous treatment is regarded as treatment delay.

4. STUDY POPULATION

Subjects, who must satisfy all of the following inclusion criteria, not meet any of the following exclusion criteria, and have given their written informed consent freely, are included in the study.

4.1. Inclusion Criteria

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

Common Inclusion Criteria (Primary Cohort, Exploratory Cohorts 1 and 2)

1. Age 20 years.
2. Has a pathologically documented locally advanced or metastatic adenocarcinoma of gastric or gastroesophageal junction.
3. Progression on and after at least 2 prior regimens which had to include a fluoropyrimidine and a platinum.
    - Progression within 6 months of prior adjuvant or neoadjuvant chemotherapy will count as "rapid progressor" in neo-adjuvant/adjuvant setting, and thus equivalent to advanced/metastatic disease failing 1 regimen of therapy.
    - If prior combination therapy discontinueddue to an AE, and then one of the agents continued, this is considered to be " 1 prior regimen" and not "2 prior regimens"
    - The change in dosage form of 5-Fluorouracil medication (intravenous administration, oral administration) without progression is considered to be "1 prior regimen" and not "2 prior regimens"
    - If patient has received prior therapy with one of the dmg in physician' s choice (i.e. irinotecanor paclitxel) and has progressed on it than patient can be eligible if treating physician considers it appropriate to treat the patient with the other dmg option from the physician's choice options. For example, if patient has received prior paclitaxel as a monotherapy or in combination with other drugs (e.g. ramuciruma b) and has progressed on it then the patient will be eligible to receive irinotecan as long as they have not received and progressed on prior irinotecan therapy in this setting. Any patient who has received prior paclitaxel and irinotecan either as monotherapy or as combination therapy and have progressed on each one of these therapies (i.e. paclitaxel and irinotecan), would be ineligible for study participation. (Primary cohort only)
4. Is willing and able to provide an adequate archived tumor sample available for tissue screening to confirm HER2 status by Central Laboratory (based on most recent archived tumor tissue samp le). If archived sample is not available, fresh sample is required.
5. Agree to submit fresh tumor samples for an assessment of HER2 status before the registration if primary tumor is accessible by endoscopy
6. Has measurable disease assessed by the investigator based on RECIST version 1.1.
7. Has an ECOG PS of0 to 1.

8. Has LVEF 50% by either ECHO or MUGA scan within 28 days before registration.

9. Has adequate organ function within 14 days before registration, defined as:

Item	Laboratory value
Platelet count	2 I00000/mm^3 (Platelet transfusion is not allowed within I week prior to screening assessment)
Hemoglobin	28.0 g/dL(Red blood cell transfusion is not allowed within I week prior to screening assessment)
Absolute neutrophil count	21500/mm^3 (G-CSF administration is not allowed within I week prior to screening assessment)
Creatinine	Creatinine clearance 230 mL/min as calculated using the Cockcroft-Gault equation
ALT/AST	:S3 x ULN (ifl iver metastases are present, :S5 x ULN)
Total bilirubin	:Sl. 5 x ULN or < 3 x ULN in the presence of documented Gilbe11' s Syndrome or liver metastases at baseline
Albumin	.5 g/dL
International normalized ratio (INR)/Prothrombin time (PT) and activated partial thromboplastin time (aPTT)	:::; 1.5 x ULN

l 0. Has adequate treatment washout period before study drug treatment, defined as:

Treatment	Washout period
Major surgery	24 weeks
Radiation therapy	24 weeks (if palliative stereotactic radiation therapy without abdominal radiation, 22 weeks)
Chemotherapy (including antibody drug therapy and retinoid therapy)	23 weeks (22 weeks for 5-fluorouracil-based agents, folinate agents and/or weekly Paclitaxel. 26 weeks for nitrosoureas or mitomycin C)
Immunotherapy	4 weeks
CYP3A4 strong inhibitor and organic anion transporting polypeptide (OATP) inhibitor 1B	23 x the elimination half-life of the inhibitor
Other study drugs	23 weeks

11. Male and Female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception, avoid intercourse, or reliable contraceptive measures (double barrier methods, which include a combination of any 2 of the following: diaphragm, condom, sponge, spermicide, bilateral tubal ligation, or vasectomy) during and upon completion of the study and for at least 7 months for females and 4 months for males after the last dose of study drug. For the purpose of this protocol, methods considered as highly effective methods of contraception including:

    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

      -Oral

      - Intravaginal

      - Transdermal

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

      -Oral

      - Injectable

      - Implantable

    - Intrauterine device (IUD)

    - Intrauterine hormone-releasingsystem (IUS)

    - Bilateral tubal occlusion

    - Vasectomy or Vasectornized partner

- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 months for females and 4 months for males after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception

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

Men who are fertile and sexually active should be willing to use highly effective methods of contraception if their partners are ofr eproductive potential.

Male subj ects must not freeze or donate sperm starting at Screening and througho ut the study period, and at least 4 months after the final study drug administration. Preservation of sperm should be considered prior to enrolment in this study.

Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.

12. Is able to provide written informed consent. Subjects must be fully informed about their illness and the investigational nature of the study protocol (including foreseea ble risks and possible toxicities) and must sign and date an Institutional Review Board (IRB)-approved informed consent form (ICF) before performance of any study-specific procedures or examinations.

Additional Inclusion Criteria for Primary Cohort

13. Centrally confirmed HER2 overexpression (IHC 3+ or IHC 2+/ISH*+).

    * IS H: FISH or dual in situ hybridization (DISH)

14. Progression on a trastuzumab containing regimen (can include an approved trastuzumab biosimilar). Progression on trastuzumab not required to be the most recent regimen.

Additional Inclusion Criteria for Exploratory Cohort 1

15. Centrally confirmed HER2 IHC 2+/ISH*negative.

    * ISH: FISH or DISH

16. Treatment nai've with anti-HER2 targeted therapy including approved trastuzumab biosirnilar.

Additional Inclusion Criteria for Exploratory Cohort 2

17. Centrally confirmed HER2 IHC 1+**.

    * *: ISH does not matter.

18. Treatment nai've with anti-HER2 targeted therapy including approved trastuzumab biosimilar.

4.2. Exclusion Criteria

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

1. Medical history of myocardial infarction within 6 months before registration, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV, Section 17.4), troponin levels consistent with myocardial infarction as defined by manufacture , unstable angina, or se rious cardiac arrhythmia requiring treatment within 28 days before randomization/registration.
2. Has a corrected QT interval by Fridericia's formula (QTcF) prolongation to >470 msec (females) or >450 msec (males) based on average of the screening triplicatel 2-lead ECG.
3. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
4. Has a pleural effusion, ascites or pericardia! effusion that requires drainage, peritoneal shunt, or Cell-free and Concentrated Ascites Reinfusion Therapy (CART). (Drainage and CART are not allowed within 2 weeks prior to screening assessment)
5. Has uncontrolled infection requiring IV injection of antibiotics, antivirals, or antifungals.
6. Have been diagno sed with human immunodeficiency virus (HIV) infection
7. Known active hepatitis B or C infection.
8. 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 do not require treatment with steroids for at least three weeks may be included in the study if they have recovered from the acute toxic effect ofr adiotherapy.
9. Has clinically significant corneal disease in the opinion of the investigator.
10. Prior treatment with an ADC which consists of a n exatecan derivative that is a topoisomerase I inhibitor.
11. Has unreso lved toxicitie s from previous anticancer therapy, defined as toxicities (other than chronic toxicities per the discretion of the investigator, eg, alopecia, peripheral neuropathy, proteinuria, controllable hypertension, and controllable diabetes) not yet resolved to National Cancer Institute's Common Tenninology Criteria for Adverse Events (NCI-CTCAE) version 4.03, Grade :Sl or baseline.
12. Has a diarrhea (watery stool), ileus, jaundice , or intestina l para lysis.
13. Has a concomitant medical condition that would increase the risk of toxicity in the opinion of the investigato r.
14. Has known hypersensitivity to either the drug substances or inactive ingredients in the drug product.
15. Has history of severe hypersensitivity reactions to other monoclonal antibodies.
16. Has had non-gastric or gastroesophageal junction primary malignancies within 3 years, except adequate ly resected non-melanoma skin cancer, curatively treated in-situ disease, other curatively treated solid tumors.

17. 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 14 days before registration.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Method of Cohort Allocation

Subjects are allocated to each cohort acco rding to the centrally confirmed HER2 status.

Primary Cohort

HER2-overexpressing (IHC 3+ or IHC 2+/ISH +)

Exploratory Cohort 1

HER2 IHC 2+/ISH negative

Exploratory Cohort 2

HER2 IHC 1+•

* : IS H d oes not matter.

5.1.2. Treatment Group(s)

Primary Cohort

Subjects will be randomized to either the DS-820 la group or the physician's choice group.

For subjects randomized to DS-820 la the starting dose will be 6.4 mg/kg.

The physician's choice treatment is a limited choice of one of two standard regimens (irinotecan monotherapy or paclitaxel monotherapy). The investigator will pre-select the physician' s choice treatment before the randomization of each subject. Physician's choice treatment will be administered in accordance with Section 5.3.

Exploratory Cohort 1 and 2

All subjects in Exploratory Cohort 1 and 2 will be assigned to the DS-8201 a treatment of the 6.4 mg/kg.

5.1.3. Blin ding

This study is an open-label study and no blinding will be performed. It is not feasible to blind treatment allocations for individual subjects because of different treatment schedules and different AE profiles between DS-8201 a and physician's choice treatment. To reduce any potential bias, the primary endpoint of ORR is assessed with blinded condition by the independent central imaging facility review based on RECIST version 1.1. The treatment arm will not be provided to the reviewer. Additionally, Daiichi Sankyo will not have access to aggregate efficacy data except when data from both the DS-820 la and the physician's choice groups are combined in the Primary Cohort. No interim analysis will be performed except the interim analysis specified in Section 11.5.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug(DS-8201a)

5.2.1. Description

DS-8201a for Injection100 mg,. DP:

The DS -820 1a drug product [redacted] Each vial is designed for single use only and is not to be used to treat more than one subjec t.

5.2.2. Labeling and Packaging

DS-820I a drug product will be supplied by Daiichi Sankyo. This will be clinical labeled in compliance with the regulatory requirements and packaged. The packaging will clearly display the name of the investigational product, the investiga tional product manufacturing code, the drug number, storage conditions, and other required information in accordance with local regulations.

5.2.3. Preparation

The drug so lution for IV infusion is prepared by dilution of the required volume of the drug product calculated based on the subject' s body weight. Pi-epared medicinal solutions should be used immediately. The preparation will be conducted in accordance with the pharmacy instructions provided by Daiichi Sankyo. Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study si te. Refer to the pharmacy instruction for detailed info rmation about preparation and administration of DS-820 1a.

5.2.4. Administration

The study drug will be administered every 3 weeks at 6.4 mg/kg. The initial dose of DS-8201a will be infused in trave nously into each subject for approximately 90 minutes on Day I of Cycle I . If there is no infusion-related reaction after the initial dose , the secon d and thereafter dose ofDS-8201a will be infused intraveno us ly 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.

5.2.5. Storage

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

- Stored [redacted]

If storage con d itio ns are not maintained per spec ified requirements, Daiichi Sankyo or contract research organization (CRO) should be contacted.

5.2.6. Drug Accountability

When a study drug shipment is received, the investigato r or designee will check the amount and condition of the drug, check the appropriateness of the label, drug expiration

date and sign the Receipt of Shipment Form provided by Daiichi Sankyo. 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 Daiichi Sankyo as soon as possible if there is a problem with the shipment.

A Drug Accounta bility Record will be provided for the study drug. The record must be kept current and should contain the dates and quantities of study drng received, subject's information (the site subject ident ifier and the subject ID) for whom the study drug was dispensed, the drug number, the date and quantity of study drug dispensed and remaining, as well as the initials or seal of the dispenser.

At the endof the study, or as directed, all unused DS-820la will be returned to a designee as instructed by Daiichi Sankyo. The study drug will be returned only after the study monitor has completed a final inventoryto verify the quantity that should be returned. Return of the study drug must be documented and the docume ntation must be included in the shipment. At the end of the study, a final study drug reconciliation statement must be completed by the investigator or designeeand provided by Daiichi Sankyo. Other procedures related to study drug management and collection will be performed in accordance with the pharmacy instructions provided by Daiichi Sankyo.

All investigational product invento ry forms must be made available for inspection by a sponsor-authorized represe ntativeor designee and regulatory agency inspectors. The supervisor of investigational products is responsible for the accountability of all used and unused study supplies at the site.

5.2.7. Dose Interruptions and Reductions

The investigatorwill evaluate which toxicities are attributa ble to DS-8201a and adjust the dose of DS-820la as recommended below. All dose modifications should be based on the worst preceding toxicity (NCI-CTCAE version 4.03). Specific criteria for interruption, reinitiation, dose reduction, and/or discontinuation of DS-820la are listed in Table 5.2. All interruptions or modifications must be recorded on the case report form (CRF). Appropriate clinical experts should be consulted as deemed necessary.

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

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

Dose Reduction Guidelines:

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

Two dose reductions will be permitted. The adjustment for a reduced dosing of DS-820la is as shown in Table5.1.

Table 5.1: Dose Reduction Levels of DS-8201a

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

Once the dose of DS-820 la has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. **More than 2 dose reductions are not allowed and the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.** However, further dose reduction may be conducted based on consultation between the Investigator and Daiichi Sankyo. DS-820l a dose increases are not allowed in the study.

Dose Interru ption and Modification Guidelines:

A dose can be delayed for up to 28 days (Day 50) from the planned date of administration. If a subject is assessed as requiring a dose delay of longer than 28 days, the subject will be withdrawn from the study.

Treatment cycles for a subjec t for whom DS-820l a dosing is temporarily withheld for any reason may have future cycles scheduled based on the date of the last DS-8201a dose.

All confirmed or suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection events must be recorded in the eCRF. Please refer to Appendix 17.6 for additional information on dose modification.

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

Worst toxicity NCI-CTCAE v4.03 Grade(unless otherwise specified)	Dose or schedule modification for DS-8201a
No toxicity	Maintain dose and schedule
Infusion Related Reaction	
Grade I (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	• If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate sho uld be reduced by 50% and subjects should be closely monitored. • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.

Table 5.2: **Dose or schedule modificationfor DS-8201a (Continued)**

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
Grade 2 (Therapy or infusion interruptionindicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for :::;24 hr s)	• Administrationof DS-8201a should be interrupted and symptomatic treatment started (e.g. antihistamines, NSAIDs, narcotics, IV fluids). • If the event resolves or improves to grade I, infusion can be re-started at a 50% reducedinfusionrate. • Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	• A dministration 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.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	Delay dose until resolved to :::;Grade 2, then mai n tain dose
Grade 4	• Delay dose until resolved to :::;Grade2 • Red uce dose I level
Febrile Neutropenia (absolute neutrophil count <I x $I0^9$/L, fever >38.3°C or a sustained temperature of 2:'.38°C for more than one hour)	• Delay dose until resolved • Reduce dose I level
Lymphocyte Count Decreased [1]	
Grade I to Grade 3 lymphopenia	No dose modification
Grade 4 (<0.2 x J09JL)	Delay dose until resolved to :::;G ra de 2: If resolved in :::;14 days from day of onset, maintain dose If resolved in >14 days from day of onset, reduce dose I level

Table 5.2: **Dose or schedule modificationfor DS-8201a (Continued)**

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
Anaemia	
Grade 3 (Hemoglobin (Hb) <8.0 g/dL); transfusion indicated	Delay dose until resolved to :;;Grade 2, then main tain dose
Grade 4 Life threatening consequences; urgent intervention indicated	Delay dose until resolved to :;;Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (plate lets <50 - 25 x 10^9/L)	Delay dose until resolved to :;;Grade 1: • If resolved in9 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (platelets <25 x 10^9/L)	Delay dose until resolved to :;;Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic CHF	Discontinue subject from study treatment
Decrease in LVEF I0% to 20% (absolute value), but LVEF >45%	Contin ue treatme nt wit h DS-82 0 l a
LVEF 40% to :;;45% and decrease is <10% (absolute value) from baseline	Contin ue treatment with DS-8201a Repeat LVEF assessment within 3 weeks
LVEF 40% to 45% and decrease is 10-20% (absolute value) from baseline	Interrupt DS-820l a dosing Repeat LVEF assessment within 3 weeks If LVEF has not recovere d to within 10% (absol ute value) from baseline, discontinuesubject from study treatment If LVEF recovers to within 10% from baseline, resume study drug treatment
LVEF <40% or >20% (absolute value) drop from baseline	Interrupt DS-8201a dosing Repeat LVEF assessment within 3 weeks If LVEF <40% or >20% drop from baseline is confirmed, discontinue subject from study treatment
Electrocardiogram QT prolonged	
Grade 3 (QTc>500 ms on 2 separate ECGs)	Delay dose until resolved to :;;Grade 1 (corrected QT :;; 480 ms) , determine if another medication the subject was taking may be responsible and can be adjusted or if there are any changes in serum electrolytes that can be corrected, then if attributed to DS-8201a, reduce dose I level

Table 5.2: **Dose or schedule modificationfor DS-8201a (Continued)**

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
Grade 4 (QTc >500 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment
Troponin	
Grade 1 (Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer)	If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3. For new diagnosed Grade 1, repeat troponin testing at 3 ± 1 hours after initial troponin test. • If repeat troponin level at 3 ± 1 hours rises significantly per institutional guidelines, - perform ECG in triplicate; - repeat troponin testing at 6 ± 1 hours after initial troponin test; - follow institutional guidelines for management of detectable troponin testing. • Ifr epeat troponin level at 3 ± 1 hours does not rise significantly per institutional guidelines, - repeat troponin testing at 6 ± 1 hours or at 24 ± 2 hours after initial troponin test. Continue treatment with DS-8201a.
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	Perform ECG in triplicate Repeat troponin testing at 6 hours (±1 hr) and 12 hours (±**1** hr) after initial troponin test. Follow institutional guidelines for management of detectable troponin testing.If AMI confirmed, discontinue subject from study therapy. Otherwise: Delay dose until resolved to S Grade 1: • If resolved in :S 7 days from day of onset, maintain dose • If resolved in > 7 days from day of onset, reduce dose 1 level

Table 5.2: **Dose or schedule modificationfor DS-8201a (Continued)**

Worst toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
Pulmonary Toxicity	If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: · high resolution CT · pulmonologist consultation(Infectious Disease consultation as clinically indicated) · blood culture and CBC. Other blood tests could be considered as needed · consider bronchoscopy and bronchoalveolar lavage if clinica lly indicated and feasible · pulmonary function tests and pulse oximetry (Sp0 2) · arte rial blood gases if clinically indicated · one blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, iffeasible. Other tests could be considered, as needed. If the AE is confirmed to be ILD/pneumonitis, follow the ILD management guidance as outlined below. All events ofI LD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drugdiscontinuation.

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

Worst toxicity NCI-CTCAE v4.03Grade (unless otherwisespecified)	**Dose or schedule modification for DS-8201a**
Grade I	The administration of DS-820 Ia must be interrupted for any ILD/pneumonitis events regardless of grade. · Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry · Consider follow-up imaging in 1-2 weeks (or as clinically indicated). · Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. · If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* For Grade I events, DS-820 la can be restarted only if the event is fully resolved to Grade 0: • If resolved in 98 days from day of onset, maintain dose • If resolved in >28 days from day of onset, reduce dose I level However, if the event grade I ILD/pneumonitis occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued. * If subject is asymptomatic, then subject should still be considered as Grade l even if steroid treatment is given
Grade 2	Permanently discontinue subject from study treatment. · Promptly start and treat with systemic steroids (e.g., at least I mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. · Monitor symptoms closely. · Re-image as clinically indicated. · If worsening or no improvement in clinical or diagnostic observations in 5 days, · Consider increasing dose of steroids (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to IV (e.g. methylpredniso lone). · Re-consider additional work-up for alternative etiologies as described above. · Escalate care as clinically indicated.

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

Worst toxicity NCI-CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8 201a**
Grade 3 and 4	Permanently discontinue subject from study treatment. · Hospitalization required. · Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. · Re-image as clinically indicated. · If still no improvement within 3 to 5 days, Re-consider additional work-up for alternati ve etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.
Ocular	
Grade 3	Delay dose until resolved to :S::Grade 1 : If resolved in9 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose **1** level
Grade 4	Discontinue subject from study treatment
Blood creatinine increased	
Grade 3 (>3.0 to 6.0 x upper limit of normal [ULN])	Delay dose until resolved to :S::Grade 2 or base l ine , then reduce dose 1 level
Grade 4 (>6.0 x ULN)	Discontinue subject from study treatment
Hepatic Toxicity	
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) with simultaneous Total bilirubin (TBL)	
AST/ALT 2:3.0 x ULN with simultaneous TBL >2.0 x ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of stu dy drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic workup, permanently discontinue study treatment. Monitor AST/ALT and TBL twice weekly until resolution or return to baseline.

Table 5.2: **Dose or schedule modificationfor DS-8201a (Continued)**

Worst toxicity NCI-CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	
Grade 2 (>3.0 to 5.0 x ULN)	No action for Grade 2 ALT/AST
Grade 3: >5.0 to 20.0 x ULN In subjects witho ut liver metastases and subjects with liver metastases and baseline level :::;3 x ULN:	Repeat testing within 3 days. Delay dose until resolved to :::;Grade 1 if baseline :::; 3 x ULN, othe1w ise delay dose until resolved to :::; baseline, then: • If resolved in9 days from day of onset, maintain dose If resolved in >7 days from day ofonset, reduce dose l level
Grade 3: >8.0 to 20.0 x ULN) In subjects with liver metastases, if the baseline level was >3 x ULN	Repeat testing within 3 days. Delay dose until resolved to :::;baseline level, then: • If resolved in :::;7 days from day of onset, maintain dose If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4 (>20 x ULN)	Discontinue subject from study treatment
Total Bilirubin increased	
Grade 2 (>1.5 to 3.0 x ULN)	If no documented Gilbe1i's syndrome or liver metastases at baseline, delay dose until resolved to :::;Grade 1: • If resolved in :::;7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level If documented Gilbe1i's syndrome or liver metastases at baseline, continue study treatment
Grade 3 (>3.0 to 10.0 x ULN)	If no documented Gilbe1i's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to :::;Grade 1: • If resolved in :::;7 days from day of onset, reduce dose 1 level • If resolved in >7 days from day ofonset, discontinue DS-82 01a If docum ented Gilbe1i's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to< Grade 2: • If resolved in :::; 7 days from day of onset, reduce dose 1 level • If resolved in> 7 days from day of onset, discontinue DS-8201a
Grade 4 (>10.0 x ULN)	Discontinue subject from study treatment
Blood Alkaline Phosphatase Increased	
Grade 3 or 4 (>5.0 x ULN)	No modification unless determined by the investigator to be clinically significant or life-threatening.

Table 5.2: **Dose or schedule modificationfor DS-8201a (Continued)**

Worst toxicity NCI-CTCAE v4.03 Grade (unless otherwise specified)	**Dose or schedule modification for DS-8201a**
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to :SGrade 1 • If resolved in :S7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose I level
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to :SGrade 1 • If resolved in :S3 days from day of onset, maintain dose • If resolved in >3 days from day of onset, reduce dose I level
Grade 4	Discontinue subject from study treatment
Other Laboratory AEs	
Grade 3	Delay dose until resolved to :SGrade 1 or baseline level: • If resolved in :S7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose I level
Grade 4	Discontinue subject from study treatment
Other Non-laboratory AEs	
Grade 3	Delay dose1mtil resolved to :SGrade 1 or baseline: • If resolved in :S7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment

[1] There will be no dose modifications for Grade I to Grade 3 lymphopenia
All dose modifications should be based on the worst preceding toxicity.
NCI: National Cancer Institute, CTCAE: Common Terminology Criteria for Adverse Events.

In addition, investigators may consider dose reductions or discontinuatio ns of the study drug according to the subject' s conditionand after discussion with the Daiichi Sankyo's Clinical Study Lead or designee.

5.3. Physician's Choice (Irinotecan or Paclitaxel)

The physician's choice treatment is a limited choice of one of two standard regimens (irinotecanmonotherapy or paclitaxel monotherapy). The investigator will pre-select the physician's choice treatment before the randomization of each subject and record the decision in medical record.

Dose reductions of the physician's choice treatment are allowed for toxicity and must be documented in the source record. Once a dose reduction is made, there is no dose re-escalation allowed. Switching between irinotecan and paclitaxel during this study is not allowed. Tumor assessments are done every 6 weeks from the day of first dosing, irrespective of dose delays or interruptions, until investigator-assessedPD, death, or post treatment after discontinuation.

5.3.1. Dosage and Usage

Treatment is continued with the following regimen until the criteria defined in Section 5.6.l.

5.3.1.1. Irinotecan monotherapy

Starting dosage and usage is 150 mg/m^2 biweekly,and two dose reductions will be permitted.

The adjustment for a reduced dosing of irinotecan is referred as shown in Table 5.3.

Table 5.3: Dose Reduction Levels ofIrinotecan

Starting Dose	Dose Level -1	Dose Level - 2
150 mg/m^2	120 mg/m^2	100 mg/m^2

Once the dose of irinotecan has been reduced because of toxicity, all subsequent treatments should be administered at that lower dose level unless further dose reduction is required. **More than 2 dose reductions are not allowed and the subject will be withdrawn from the study treatment** if **further toxicity meeting the requirement for dose reduction occurs.** However, further dose reduction may be conducted based on consu ltation between the Investigator and Daiichi Sankyo. Irinotecan dose increases are not allowed in the study.

5.3.1.2. Paclitaxel monotherapy

Starting dosage and usage is 80 mg/m^2 weekly, and one dose reduction will be permitted. The adjustment for a reduced dosing of paclitaxel is referred as shown in Table 5.4.

Table 5.4: Dose Reduction Levels of Paclitaxel

Starting Dose	Dose Level -1
80 mg/m^2	60 mg/m^2

Once the dose of pac litaxel has been reduced because of toxicity, all subseq uent treatment should be administered at that lower dose level unless further dose reduction is required. **More than one dose reductions are not allowed and the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.** However, further dose reduction may be conducted based on consulta tio n be tween the Investigator and Daiichi Sankyo. Paclitaxel dose increases are not allowed in the study.

5.3.2. Administration Criteria

Administration of the physician's choice treatment can be delayed for up to 49 days (Day 50) from the date of last administration. If toxicities are not resolve within the authorised dose delay period, subjects discontinue study treatment.

If a subject develops an acute onset of new or worsening pulm onary or other related signs/symptoms such as dyspnea, cough or feve r, follow the indication of Pulmonary Toxicity described in Table 5.2.

Prior to commencing treatment, the following criteria are referred as shown in Table 5.5.

Table 5.5: Administration Criteria for Irinotecan and Paclitaxel

Administration Criteria	l rinotecan Monotherapy	Paclitaxel Monotherapy
White blood cell count	2':2 ,8 0 0 / mm^3 and <15,000/mm^3	2':2 , 0 0 0/mm^3 and <15,000/mm^3
Platelet count	2':7 5 ,0 0 0/mm^3	2':7 5 ,0 00/mm^3
ALT/AST	:S3 x ULN or baseline	:S3 x ULN or baseline
Total bilirubin	:Sl. 5 mg/dL	:Sl. 5 mg/dL
Creatinine	:Sl .5 mg/dL	:Sl. 5 mg/dL
Nausea/Vomiting/Stomatitis	≤Grade 1	≤G rade l
Di a rrhea	≤Grade 1	≤G rade 2
Neuropathy/Arthralgia/Myalgia	≤Grade 2	≤G rade 2
Non-inflammatory Pulmonary Tox icity	≤Grade 1	≤G rade l

5.3.3. Dose Reductions

Dose levels in both treatments must be reduced to Level- 1 when any of the following AEs are observed after the previous drug administration.

If a subject develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, follow the indication of Pulmonary Toxicity described in Table 5.2.

Table 5.6: Dose Reduction Criteria

Dose Reduction Criteria	Both Treatments (lrinotecan and Paclitaxel)
White blood cell count decreased	:=::Grade 3
Pl atelet co unt decreased	:=::Grade 3
Neutrophil count decreased	:=::Grade 3
Infection	Documented clinically, infection of unknown origin
Diarrhea, stomatitis, neuropathy, arthralgia, m yalgia	:=::Grade 3
Increase in ALT/AST	:=::Grade 3
Others	When administration criteria are not fulfilled and treatment delay for 2 consecut ive weeks was required because of AEs
	When the treating physician judged that dose reduction was required because of AEs

lf Grade 4 nonhematological toxicity occurred in subjects with anorexia or abnormal serum sodium and potassium levels are observed, treatment is discontinued at the treating physician's discretion. When paclitaxel monotherapy subjects experienced Grade 3 allergic reactions, treatment is discontinued.

Subjects experienced Grade 3 non-inflammatory pulmonary toxicity, treatment is discontinued.

lf subjects receiving irinotecan monotherapy are found to be homozygo us fo r the *UGTJA1*6* or *UGTJA1*28* allele *(UGT JA1*6 /*6, UGTJ A1*28/*28)* or heterozygousfor both alleles *(UGTJAJ *6!*28),* and if they meet the abovementioned criteria, dose reduction to Level - 2 (100 mg/m^2) is allowed.

5.4. 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 administration of the study treatment. Start and stop date/time of injection, amount of drug administered, and reason for change or interruption (if applicable) must be recorded in medical record by clinical study personnel.

5.5. Prophylactic Treatment and Concomitant Medications

5.5.1. ProphylacticTreatment

Base d on the currently avai lable clinical safety data, it is recommended that subjects receive prophylactic anti-emeticagents prior to infusion of DS-820la and on subseq uent days. Antiemetics such as 5- hydroxytryptamine receptor (5-HT3) antagonists or Neurokinin-1 (NKl) receptorantagonists and/or steroids (e.g. dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

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

5.5.2. Concomitant Medications

Medications used from the time the subject signs the informed consent for study participation to the follow-up 40 days visit (+7 days) after the last administration ofDS-820la/physician's choice treatment will be recorded. All concomitant medications will be recorded in the electronic case report form (eCRF).

5.5.3. Prohibited Concomitant Medications/Activities

For all subjects (DS-820l a and physician' s choice treatment): The following medications and products will be prohibited:

- Other anticancer therapy, including cytotoxics, targeted agents, immunotherapy, antibodies, or surgery
- Other investigatio nal therapeuticagents
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response and it does not interrupt treatment for longer than the maximum time specified in the dose modification section)
- Radiotherapy to the thorax

For subjects receiving DS-820la: The following medications and products will also be prohibited:

- Concomitant use of chronic systemic corticosteroids or other immunosuppressive medications except if it is standardpractice for managing specific adverse events. Inhaled steroids or intra articular steroid injections are permitted in this study.
  - Subjects with bronchopulmonarydisorders who require intermittent use of bronchodilators (such as al butero l) will not be excluded from this study.
- Concomitant treatment with chloroquine or hydroxychloroquine is notallowed during the study treatment. Refer to Appendix 17.6 for further details.

Restricted Therapies/Products

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

Concomitant use of dietary supplements, medication s not prescribed by the investigator, and alternative/complementarytreatments is discouraged, but not prohibited.

5.6. Subject Withdrawal/Discontinuation

Any subject may withdraw their consent to participate in the study at any time without specifying a reason. It must also be documented (in the eCRF) whether the subject agrees to participate in post-treatment follow-up st udy assessments.

5.6.1. Reasons for Discontinuation of Study Treatment

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

1. Progressive disease per RECIST version 1. 1 assessed by the investigator;
2. Clinical progression (definitive clinical signs of disease progression, but a recent radiographicassessment did not meet the criteria for PD according to RECIST version 1. 1);
3. AE;
4. Death;
5. Withdrawal of consent bysubject;
6. Lost to follow-up;
7. Physician Decision;
8. Pregnancy;
9. Study terminated by Daiichi Sankyo;
10. Others, specify.

If there is evidence that the subject is receiving benefit from treatment even though the subject has met a criterion for discontinuationas listed above, the subject may remain on study treatment after discussion with the Daiichi Sankyo's Clinical Study Lead or designee.

All subjects who are withdrawn from the study treatment should complete protocol-specified withdrawal procedures (Section 5.6.3) and follow-up procedures (Section 6.3).

Record the reason for any subject who discontinues study treatment. Discontinued subjects will be followed for survival.

5.6.2. Reasons for Discontinuation of Study Follow-up

Subjects may be withdrawn from study follow-up after signing an informed consent for the following reasons:

1. Withdra wal of consent to participate in study procedures;
2. Death;
3. Lost to follow-up;
4. Study terminated by Daiichi Sankyo;
5. Others, specify

5.6.3. Withdrawal Procedures

If a subject is withdrawn from the stud y, the investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of the 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, post cancer treatment, or lost to follow-up.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be obtained during the EOT visit (+7 days) and the follow-up 40 days visit (+7 days) conducted after the last administration of DS-820la or the physician's choice treatment.

When the investigator receive request of withdrawn from the study, the investigator also confirm the continuity of biomarker research.

5.6.4. Subject Replacement

Subjects that have been randomized will not be replaced in Primary Cohort. It is allowable to replace a subject that was enrolled but was not administered any study medication in Exploratory Cohort 1 or 2.

5.6.5. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet the eligibility criteria in the initial screening. The limit of re-screening is each 1 time in tissue screening (See Section 6.1.1) and screening (See Section 6.1.2). Tissue sample for re-screening is the sample obtained after trastuzurnab (brand, approved biosimilar) treatment if ava ilable. Subjects that have been randomized will not be re-screened. The site subject identifier and the subject ID 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 in the Screen ing Log.

6. STUDY PROCEDURES

Obtain a signed and dated ICF before any study-related procedures or assessments are conducted . A separate tissue screening ICF may be used to obtain consent to send the sample to the central laboratory, if desired.

After obtaining informed consent, the investigator or designee assign a site subject ident ifier and enter subject' s background data in the interactive web/voice response system (IXRS).

Informed consent for pharmacogenomics study will be obtained separately.

A study visit sc hedule in tabular format is provided below in Section 18. The following activities will be performed at each visit and recorded in the eCRF.

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

6.1. Screening

6.1.1. Tissue Screening

To determine eligibility, subjects must meet the tumor biomarker criteria. The procedure for preparing tumor tissue is shown in the study laboratory manual for required tumor sample specifications and shippinginstructions.

Note: A separate tissue screening ICF may be used to obtain consent to send the sample to the central laboratory, if desired. Subjects may continue on prior therapy while tissue testing takes place.

The following activities will be performed:

- Obtain adequate archived tumor sample for tissue screening to confirm HER2 status. Archive tissue samples from surgery, endoscopy, or needle biopsy already collected and formalin-fixed paraffin-embedded will be used. If both of the arch ived and fresh samples are available for one pat ient, it is recommended to submit both samples to the central laboratory. If an archived tissue sample is not available or adequate, fresh sample is required. Registration is based on the HER2 status of archived sample, but in case archived sample could not detect HER2 status, fresh sample is utilized for enrollment.
- Paraffin-embedded tissue blocks of forma lin-fixed tiss ue spec imens will be prepared by the standard procedure at the study site and submitted to the central laboratoryas soon as possible to determine HER2 status.
- The central laboratory will assess the measured HER2 status and report it to the investigatorand Daiichi Sankyo.
- If a tumor biopsy is needed, record any SAEs directly related to this tissue screening procedure.
- For subjects who sign only the Informed Consent Form for tissue screening, report only serious adverse events (SAEs) directly related to tissue screening

procedure (ie, tumor biopsy). Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

6.1.2. Screening

In this study, registration will be performed (See Section 5.1.1). If the subject is a screening failure, the subject is recorded as ineligible in the IXRS.

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

Before registration

- Record demographic information (eg, birth date, sex), primary cancer history, significant medical history information and prior treatment for cancer history information.
- Review inclusion and exclusion criteria and confirm the subject' s eligibility when the results of all sc reening procedures have bee n obtained
- Record the historical HER2 status.
- Record the prior and concomitant medications.
- Assess the subject for AEs.
- **Obtain fresh tumor biopsy.**

  The subject who has a tumor is amenable to biopsy undergoes a fresh tumor biopsy. The investigator sends paraffin embedded and fixed tumor tissue to the central laboratory to assess the HER2 status exploratively. If not amenable, the investigatormust document why not amenable.
  If fresh tumor has been already submitted for this study and no chemotherapy or immunotherapy was conducted, re-submission is not necessary.
  Other biomarkers related to the activity of DS-820l a may be analyzed (eg, messenger RNA [mRNA] expression profile). These analyses are depending on tissue ava ilability.
  Further details will be provided in the laboratory manual.

Within 14 days before registration

- Perform a complete physical examination and record the weight and height.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature and SpO2).
- Assess ECOG PS Scale (Section 17.1).
- Obtain blood samples for laboratory tests (Section 9.8) and troponin.
- Perform urinalysis test
- Perform a 12-lead ECG in triplicate•.
  *: ECGs will be taken in close success ion, approximate ly 3 minutes apart, after the subject has been in a supine/semi-recumbent position.

- Obtain a serum or urine sample for pregnancy testing in women of childbearing potential. For postmenopausal subjects (no childbearing potential, as indicated by the elapse of at least 12 months after the last menstruation) or female subjects who have no possibilityof pregnancy due to ste rilization surgery, etc., no pregnancy test will be required. Female subjects who have been amenorrheic for 12 months or longer for medical reasons other than sterilizationsurgery (eg, effect of medication) will be regarded as women of child-bearingpotential and are required to undergo the pregnancy test.

Within 28 days before registration

- Perform either ECHO or MUGA scan(LVEF).
- Ophthalmologic assessments.
  The assessments will include visual acuity testing, slit lamp examination, and fundoscopy .
- Perform tumor assessme nt by CT or magnetic resonanceimaging (MRI) scans of the brain, chest, abdomen, pelvis, and any other sites of disease. The registration is based on local assessment of measurable disease.

6.1.3. Registration

The investigator or designeedetermines that all inclusion and exclusion criteria are satisfied, enter the subject registration data in the IXRS. A subject is consideredto be enrolled in the study when registration is completed in the IXRS.

The date of registration is defined as the date when the subject is registered as eligible in the IXRS. The date of screeningfailure is defined as the date when the subject is confirmed ineligible by the investigator.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned Subject ID. The unique Subject ID will be assigned by IXRS.

Investigators will maintain a confidential site subject identifier list. This confidential list of names of all subjects to whom Subject IDs have been allocated when they enrolled in the study, allows the investigator to reveal the identity of any subject when necessary.

The drug number will be sequence number in DS-820la to identify the vial status. All vials of DS-820 l a will be numbered and traced.

For screening failure subj ects, the inve stigator s will explain the reason of failure to the subject.

6.1.4. Randomization

Subjects in Primary Cohort will be randomized by IXRS into the two treatment groups in a 2:1 ratio (120 DS-820la group and 60 physician's choice group) and the randomization will be stratified by region, ECOG PS, and HER2 status.

- Region (Japan or Korea)
- ECOG PS (0 or **1)**

- HER2 status (IHC 3+ or IHC 2+/ISH +)

6.1.5. Discontinuation during the Screening Period

If study entry is discontinued after the subject is assigned a unique subject ID, the reason for disco ntin uation is recorded in the eCRF from the categories listed below.

- HER2 expression status is IHC O or not detected by the centra l laboratory.
- Eligibility is not matched, except for HER2 expression
- Withdrawa l by the subject
- Others

6.2. Treatment Period

In considerat ion of the subject's safety, additional safety assessments should be conducted as needed at the investigator' s discretion. If there are any non-scheduled data that are assessed, these are recorded in the eCRF when they are considered as an AE.

6.2.1. 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) from the first dosing (Cycle 1 Day l) until PD, starting new anticancer treatment, or withdrawal of consent by subject to participate in study procedures regard less of a delay in dosing from the day of first administration, DS-820la or the control treatment. The assessment will be conducted before treatment of each cycle. CT or MR I scans of the chest, abdomen and pelvis are mandatory. Brain CT or MRI assessment is mandatory at baseline, in cases of pre-existing brain metastases or symptoms. The assessment should be co nducted in the same way during the study treatment. Instructions for the assessment are included in a separate manual.

Handling of Images

Copies of CT or MRI images should be provided to central review vendor. This is all images use d for tumor assessment in this study including unscheduled visits. However, images that were not scanned at baseline should be provided only in case the new lesion is detected.

Copies of CT or MRI images should be immediately submitted to central vendor after the images taken, and they should be cond ucted within 2 weeks.

Before the transfer of data, personal informatio n such as name should be masked.

6.2.2. Patient Reported Outcomes (EQ-5D-5L and FACT-Ga)

Qua lity of Life questionnaire s (EQ SD SL, FACT-Ga) will be completed in both groups of Primary Cohort on Day 1 before any study related procedures, including blood collection, Day 15 (±1), and every 6 weeks from the beginning of the study (eg, Day 43 (±7), 85 (±7), 127 (±7), etc.), and EOT. EQ-5D-5L questio nnaire to be completed first and then FACT-Ga questionnaire.

6.2.3. Safety Monitoring for suspected ILD/pneumonitis

For suspected ILD/pneumonitis, study drug should be interrupted pending evaluation, which should include:

high resolution CT

pulmonologi st cons ultation (Infectious Disease consultation as clinically indicated)

blood culture and CBC. Other blood tests could be considered as needed

consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible

pulmonary function tests and pulse oximetry (SpO2)

arterial blood gases if clinically indicated

one blood sample collection for **PK** ana lysis as so on as ILD/pneumon itis is suspected, if feasible (for DS8201 group and exploratory cohort).

Other tests could be considered, as needed.

All events of ILD/pneumonitis regardle ss of sever ity or seriousness will be followed until resolution including after drug discontinuation.

6.2.4. Schedule of Activity and Assessments for Subjects Receiving DS-8201a

6.2.4.1. Cycle 1, Day 1

6.2.4.1.1. Before administration

The following procedures will be completed 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.
- Record concomitant medications.
- Obtain a blood sample for pharmacogenetic assessment. (This sample is not required for study participation and will be collected from subjects who have provided consent by signing the pharmacogenomic consent form.)

Within 8 hours before administration

- Obtain a PK blood sample (Section 8.1).
- Obtain blood sample for ADA (Section 8.7).

Latest data within 3 days before administration

- Perform a complete physical examination and record the weight.
- Obtain vital sign measurements(systolic and diastolic blood pressure and pulse rate, body temperature and SpO2).

- Assess the ECOG PS Scale (Section 17.1).
- Obtain blood samples for laboratory tests (Section 9.8), HER2ECD (Section 8.2.1), and cfDNA analysis.
- Perform a 12-lead ECG in triplicate.

6.2.4.1.2. Administration and after Infusion

- Administer DS-820la as per Section 5.2.4.

The following procedures will be completed 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: within 15 minutes after end of infusion (EOI), at 4 and 7 hours (±15 minutes) after the start of administration (Section 8.1).
- Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2-3 hours after end of infusion (EOI). An additional sample should be submitted for central lab troponin-T testing.
  - If troponin level is consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 ± 1 hours and 12 ± 1 hours after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin level is 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 ± 1 hours after initial troponin test was drawn. If troponin level is above upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not CTCAE Grade 3.
  - If repeat troponin level at 3 ± 1 hours rises significantly per institutional guidelines,

    perform ECG in triplicate;

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

    follow institutional guidelines for management of detectable troponin testing.
  - If repeat troponin level at 3 ± 1 hours does not rise significantly per institutional guidelines,

    repeat troponin testing at 6 ± 1 hours or at 24 ± 2 hours after initial troponin test.
- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.2. 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 laboratory tests (Section 9.8).
- Obtain a PK blood sample on Day 8 (Section 8.1).
- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.3. 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 laboratory tests (Section 9.8).
- Obtain a PK blood sample on Day 15 (Section 8.1).
- Record concomitant medications.
- Assess subjects for AEs.
- Quality of Life questionnaires (EQ SD SL, FACT-Ga)

6.2.4.4. Cycle 1, Day22

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 a PK blood sample on Day 22 (Section 8.1).
- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.5. Cycle 2, Day 1

6.2.4.5.1. Before Infusion

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

- Record concomitant medications.
- Assess subjects for AEs.

Within 8 hours before administration

- Obtain a PK blood sample (Section 8.1).
- Obtain a blood sample for ADA (Section 8.7).

Latest data within 3 days before administration

- Perform a complete physical examination and record the weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO2).
- Assess the ECOG PS Scale (Section 17.**1**).
- Obtain blood samples for laboratory tests (Section 9.8).
- 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 12-lead ECG in triplicate.

6.2.4.5.2. Administrationand after Infusion

- Administer DS-820la as per Section 5.2.4.

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

- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate and body temperature).
- Obtain a PK blood sample at the end of administration within 15 minutes after EOI (Section 8.1).
- Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2-3 hours after end of infusion (EOI). An additional sample should be submitted for central lab troponin-T testing.
  - If troponin level is consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 ± **1** hours and 12 ± 1 hours after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin level is above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade **l),** repeat troponin testing 3 ± **1**hours after initial troponin test was drawn.
  - If troponin level is above upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade l) at baseline, no repeat testing is required if the troponin level is not CTCAE Grade 3.
  - If repeat troponin level at 3 ± **1** hours rises significantlyper institutional guidelines,

    perform ECG in triplicate;

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

    follow institutional guidelines for management of detectable troponin testing.

- If repeat troponin level at 3 ± 1 hours does not rise significant!y per institutional guidelines,

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

- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.6. Cycle 2, Day22

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 a PK blood sample on Day 22 (Section 8.1).
- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.7. Cycle 3, Day 1

6.2.4.7.1. Before Infusion

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

- Record concomitant medications.
- Assess subjects for AEs.

Within 8 hours before administration

- Obtain a PK blood sample (Section 8.1)

Latest data within 3 days before administration

- Perform a complete physical examinationand record the weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, bodytemperature and SpO2).
- Assess the ECOG PS Scale (Section 17.1).
- Obtain blood samples for laboratory tests and HER2ECD (Section 8.2.1).
- Perform a 12-lead ECG in triplicate.

6.2.4.7.2. Administration and after Infusion

- Administer DS-8201a as per Section 5.2.4.

The following p rocedures will be completed 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 followi ng time points: within 15 minutes after EOI, 4 and 7 hours (± 15 minutes) after the start of administration (Section 8.1).

- Collect blood samples for troponin (preferably high-sensitivity troponin-T) 2-3 hours afte r end of infusion (EOI). An additional sample should be submitted for central lab troponin-T testing.
  - If troponin level is consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 ± l hours and 12 ± l hours after initial troponin test was drawn, and follow institutional guidelines.
  - lftroponin level is 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 ± l hours after initial troponin test was drawn.
  - If troponin level is above upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not CTCAE Grade 3.
  - If repeat troponin level at 3 ± 1 hours rises significantlyper institutional guidelines,

    perform ECG in triplicate;

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

    follow institutional guidelines for management of detectable troponin testing.
  - If repeat troponin level at 3 ± 1 hours does not rise significant!y per institutional guidelines,

    repeat troponin testing at 6 ± 1 hours or at 24 ± 2 hours after initial troponin test.
- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.8. Cycle 3, Day 8

The following procedures will be performed on Day 8 (±3 days).

- Obtain a PK blood sample on Day 8 (Section 8.1).
- Record concomitant medications.
- Assess subjects for AEs.

6,2.4.9, Cycle 3, Day 15

The following procedures will be performed on Day 15 (±3 days).

- Obtain a PK blood sample on Day 15 (Section 8.1).
- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.10. Cycle 3, Day22

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 a PK blood sample on Day 22 (Section 8.1).
- Record concomitant medications.
- Assess subjects for AEs.

6.2.4.11. Cycle 4 and Subsequent Cycles, Day 1

6.2.4.11.1. Before Infusion

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

- Record concomitant medications.
- Assess subjects for AEs.

Within 8 hours before administration

On Day 1 of Cycle 4, 6, and 8

- Obtain a PK blood sample (Section 8.1).

On Day 1 every 4 cycles from Cycle 4 to the EOT *(eg,* Day 1 of Cycle 4, 8,12,...)

- Obtain a blood sample for ADA (Section 8.7)

Latest data within 3 days before administration

- Perform a complete physical examination and record the weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO2).
- Assess the ECOG PS Scale (Section 17.1).
- Obtain blood samples for laboratory tests (Section 9.8).

On Day 1 every 2 cycles from Cycle 3 to the EOT *(eg,* Day 1 of Cycle 3, 5, 7, 9, lLJ

- Obtain blood samples for HER2ECD (Section 8.2.1). A portion of this HER2ECD blood sample from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 5 (Cycles 5, 9, 13, etc).

On Day 1 of Cycle 4 and the EOT

Obtain blood samples for exploratory biomarkers, such as cfDNA analysis in plasma.

Others

On Day 1 every 4 cycles (±7 days) from Cycle 5 to the EOT *(eg,* Day 1 of Cycle 5, 9,13,...)

- Perform either ECHO or MUGA scan (LVEF). If the planned date of study drug administration is delayed after examination of ECHO or MUGA scan, and there are no abnormal findings on the examination, ECHO or MUGA scan may not be repeated at the investigator' s judgment.
- Perform a 12-lead ECG in triplicate.

6.2.4.11.2. Administration and after Infusion

- Administer DS-820la as per Section 5.2.4.

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

- Record concomitant medications.
- Assess subjects for AEs.

On Day 1 of Cycle 4, 6, and 8

- Obtain a PK blood sample at the end of administration within 15 minutes after EOI (Section 8.1).

6.2.4.12. End of Treatment

The date of discontinuation of treatment is defined as the date of the decision by the investigator. The following assessments will be performed at the EOT visit (within 7 days after the date of discontinu ation).

- Perform a complete physical examination and record the weight.
- Obtain vital sign measurements (systolic and diastolic blood pressure and pulse rate, body temperature and SpO2).
- Assess the ECOGPS Scale (Section 17.1).
- Obtain blood samples for laboratory tests and troponin test (Section 9.8), HER2ECD (Section 8.2.1) and cfDNA analysis. A portion of this HER2ECD blood sample from each subject who provides consent will be use d for future central lab analysis for SARS-CoV-2 testing.
- Obtain a serum or urine sam ple 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. Fe male 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 are required to undergo the pregnancy test.
- Perform a 12-lead ECG in triplicate.
- Perform either ECHO or MUGA scan (LVEF).
- Ophthalmologic assessments.

The assessments will include visual acuity testing, slit lamp examination, and fundoscopy.

Perform the same imaging tumor assessment as at the time of screening by CT or MRI scans. CT or **MRI** sca ns of the chest, abdomen and pelvis are mandatory.If the previous scan was within the last 3 weeks, this assessment does not need to be performedat the EOT Visit.

- Record concomitant medications.
- Assess subjects for AEs.
- Record the reason for treatment discontinuation.
- Quality of Life questionnaires (EQ 5D 5L, FACT-Ga)
- **Obtain fresh tumor biopsy**

  Perform the post-treatment biopsy: perform a biopsy from EOT visit to the follow up visit and the investigator sends paraffin embedded and fixed tumor tissue to the central laboratory to assess post-treatment HER2 status exploratively. If the subject can not be performed a post-treatment biopsy, the investigatormust document why not performed.

  Other biomarkers related to the activity of DS-8201a may be analyzed (eg, mRNA expression profile). These analyses are depending on tissue ava ilability.

  Furtherdetails will be provided in the laboratory manual.

6.2.5. Schedule of Activity and Assessments for Subjects Receiving Physician's Choice Treatment

Treatment and procedures performedon treatment period and EOT are specified in Section 18.2. Procedures including physical examination, weight, ECOG PS assessment, 12-lead ECG, hematology, blood chemistry, and vital sign (including SpO2) are to be performed within 3 days before each treatment. Troponin is performed at after administration.

6.3. Follow-up

The Follow-up (F/U) visit should occur 40 days (+7 days) after the last administration. If the subject begins another anticancer therapy before the end of the 40 days (+7 days), every effort will be made to complete all the F/U assessments prior to commencing the new therapy. In case of unresolved AEs, the investigator will follow the AEs until the event has resolved or the condition has stabilized as far as possible. If assessments at EOT or the treatment period are performed within this period, they can be considered to be the F/U data and there is no need to repeat them. If discontinuation of treatment is decided later than 40 days after the last administration of DS-820la, there is no need to perform the F/U assessments except for obtaining a blood sample for ADA.

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 and SpO2).

- Perform a complete physical examination and record the weight.
- Assess the ECOG PS Scale (Section 17.1).
- Obtain blood samples for laboratory tests (Section 9.8) and ADA (only for subjects with DS-820la treatment, Section 8.7).
- Record concomitant medications.
- Assess subjects for AEs.

6.4. Survival Status and New Treatment Follow-up

After completing the post treatment follow-up period, subjects will be followed by visit or telephone contact approximately every 3 months (±14 days) to assess survival and new cancer treatment until death or the data cut-off date , wh ichever comes first. Even if a subject moves to another hospital, the investigator must confirm surv ival and anticance r therapy as far as possible. If survival status is lost to follow-up, the last contact date will be recorded. The following data are recorded in the eCRF.

- New treatment for cancer and the start date
- Subject outcome: Alive/dead/lost to follow-up
- Date of death/ date of last contact to be known alive

6.5. Follow-up of Anti-Drug Antibodies

For subjects with positive ADA at F/U visit, additional serum ADA samples may be collected every 3 months (±14 days) up to I year from the last dose of the study drug, or if the ADA becomes negative, or if the ADA titer becomes less than the baseline value (app lica ble when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first. This test is only for subjects in the DS-820l a treatment group.

7. EFFICACY ASSESSMENTS

7.1. Assessments of Efficacy Endpoint(s)

Efficacy assessments will be based on tumor assessments to be performed at screening and every 6 weeks from the day of first dosing (Cyclel Dayl) while the subject remains in this study. The primary efficacy endpoint is ORR assessed by independent central imaging facility review based on RECIST version 1.1. Refer to Section 17.3 for details regarding RECIST version 1.1 for radiological tumor assessments. All CT or MRI scans should be sent to the central imaging CRO selected by Daiichi Sankyo to confirm the existence of a measura ble lesion by RECIST version **1.1.**

CT or MRI scans of the chest, abdomen and pelvis are mandatory. Brain CT or MRI is requiredonly in cases of pre-existing brain metastases or symptoms. The assessment should be conducted in the same way during the study treatment.

The following efficacy variables will be assessed.

- Primary Endpoint
  - ORR (the sum of Complete Response [CR] rate and Partial Response [PR] rate) assessed by independent central imaging facility review based on RECIST version 1.1 (For Primary Cohort)
- Secondary Endpoints (based on central review unless otherwise stated)
  - OS *(not* central review)
  - PFS
  - DoR
  - DCR
  - TTF
  - ORR assessed by the investigator based on RECIST version 1.1
  - ORR (for each Exploratory Cohort 1 and 2)
- Exploratory Endpoints (based on central review unless otherwise stated)
  - Time to response
  - Best percent changein the sum of diameters of measurable tumors
  - PFS based on investigator assessment

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Assessment(s)

The serum PK parameters listed in Table 8. 1 of DS-820l a, total anti-HER2 antibody and MAAA-118 la for each subject will be estimated us ing standard noncompartmental methods. The details of PK analysis will be specified in the Statistical Analysis Plan.

Table 8.1: Pharmacokinetic Parameters

	PK parameters
DS-8201a, total anti-HER2 antibody and MAAA-118l a	Cmax, Tmax, AUClast, A UC2 1d

Blood samples for DS-820 la **PK** analyses will be obtained at the time points specified in Table 8.2. Instructions for the handling of blood samples and shipping of serum samples for DS-820 1a PK analyses are included in a separate document (eg, the laboratory manual). The actual time of study drug administration and the exact time of blood sampling for DS-820la PK analysis must be recorded in the CRF.

Table 8.2: Pharmacokinetic Sampling Time Points

Cycle	**Day**	**Sampling Time Point (Acceptable Range)**
Cycle 1	Day 1	Before infusion (Bl) (-8 hours) EOI: Within 15 minutes after EOI 4 hours after the start of administration (±15 minutes) 7 hours after the start of administration (±15 minutes)
	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 schedu le on Day I of the next cycle is delayed for 3 days or longer, or the subject is discontinued, collect a blood sample 21 days after the start of drug administration (±2 days)
Cycle 2	Day 1	Bl (-8 hours) If a blood samp le is collected on Day 22 of Cycle 1, the blood sample will be collected at Bl on Day 1 of Cycle 2. EOI: Within 15 minutes after EOI

Table 8.2: Pharmacokinetic Sampling Time Points (Continued)

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 2	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or longer, or the subject is discontinued, collect a blood sample 21 days after the start of drug administration (±2 days)
Cycle 3	Day 1	Bl (-8 hours) If a blood sample is collected on Day 22 of Cycle 2, the blood sample will be collected at Bl on Day 1 of Cycle 3. EOI: Within 15 minutes after EOI **4** hours after the start of administration (±15 minutes) 7 hours after the start of administration (±15 minutes)
	Day 8	7 days after the start of administration (±3 days)
	Day 15	**14** days after the start of administration (±3 days)
	Day 22	If the schedule on Day 1 of the next cycle is delayed for 3 days or longer, or the subject is discontinued, collect a blood samp le 21 days after the start of drug administration (±2 days)
Cycle 4, 6, 8	Day 1	Bl (- 8 hours) If a blood sample is collected on Day 22 of Cycle 3, the blood sample will be collected at Bl on Day 1 of Cycle 4. EOI: Within 15 minutes after EOI

In case of chloroquine or hydroxychloroquine administration for SARS-CoV-2 infection, additional PK serum samples should be collected at the time points specified in Table 8.3. The chloroquine or hydroxychloroquine administration time and the exact time of blood sampling for DS-820la PK analysis must be recorded in the CRF.

Table 8.3: Schedule of PK Sample Collection for Subjects Administered Chloroquine or Hydroxychloroquine

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

CQ = chloroquine; HCQ = hydroxychloroquine.
a Washout period ofno less than 14 days is required before resumption of DS-8201a.

8.2. Biomarkers

In this study, biomarker analyses will be used to investigate the effect of the DS-820la at the molecular and cellular level as well as to determine how changes in the markers may relate to exposure and clinical outcomes. The sample collection information as required should be recorded on the eCRF page(s) and central laboratory requisition form(s). Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the laboratory manual.

8.2.1. Pharmacodynamic Assessments

8.2.1.1. Pharmacodynamic Assessments in BloodSamples

Pharmacodynamic biomarkers will be analyzed with the intent of monitoring the anti-tumor impact of treatment with DS-820la. The pharmacodynamic biomarkers are HER2ECD and cfDNA. Blood samples will be collected for HER2ECD analysis at the time points specified in Table 8.4 and cfDNA analysis at the time points specified in Table 8.5.

Biomarker samples will be shipped to a central laboratory. Sample collection, preparation, handling,storage, and shipping instructions are provided in the laboratory manual.

Table 8.4: Extracellular Domain of HER2 Sampling Time Points

Cycle	Sampling Time Point (Acceptable Range)
Cycle **1** Day I	Within 3 days before administration
Every 2 cycles from Cycle 3 (eg, Cycle 3, 5, 7, 9, 11...)	Within 3 days before administration
EOT	The date when the investigator decides on discontinuation of the study treatment (+7 days).

Table 8.5: Cell Free DNA Sampling Time Points

Cycle	Sampling Time Point (Acceptable Range)
Cycle **1** Day I	Within 3 days before administration
Cycle 4 Day I	Within 3 days before administration
EOT	The date when the investigator decides on discontinuation of the study treatment (+7 days).

8.2.1.2. Pharmacodynamic Assessments in Newly Obtained Tumor Specimens

Collection of paired tumor specimens is critical to assess the pharmacodynamic effect of DS-820la. Tumor specime ns will be used to assess the HER2 status using IHC and/or ISH, and mRNA expression profile using NGS technology and or other methods. The

detailed instructions for the handling of tumor samples and shipping of tumor samples are included in the laboratory manual. Timing of sample collection is baseline (before registration) and EOT.

8.2.1.3. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, 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-820la 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 cl inica l outcome, reagent and sample availability. If the patient agrees, the remaining samples (tumor tissues, blood and plasma) may be stored for up to 15 years.

8.2.1.4. Disclosure of the Results of Additional Biomarker Assessments

Becau se the nature and value of future additional biomarker assessments is unknown at this time, any results obtained from research involving samples will not be disclosed to the subject or investigators now or in the future.

8.3. SARS-CoV-2 Serum samples collection

Portion of HER2ECD blood sample from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing. Samples will be sent to the central laboratory and stored until the tests will become available.

8.4. Pharmacogenomic Analysis

8.4.1. Genomic or Genetic Banking Analysis

A single blood sample for pharmacogenornics analysis will be collected from each subject who has consented to this test on Day 1. Participation in this part of the study is optional for all subjects.

The following procedures will be used for the long-term preservation (banking) of DNA specimens extracted from subjects' blood samples. Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, meta bolism, elimination, safety, and efficacy of DS-820l a. Additionally, samples may be analyzed for genes involved in DS-820l a related signaling pathways, or to examine diseases or physiologic processes related to DS-8201a.

DNA samples will not be immortalized or sold to anyone. This information may be useful to increase knowledge about differences between indiv id uals in the way they respond to the study drug.

Specimen shipping and handling details will be included in the laboratory manual.

8.4.1.1. Disclosure of the Results of Genomic or Genetic Analysis

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

8.5. Anonymization of Samples

The samples should be submitted to the courier without any personal information such as name that can be used to identify individuals. The samples should be identified by the 'S ubject ID'.

The correspondence list which can link the Subject ID and the personal information should be kept strictly at the study center and the linkage between the Subject ID and personal information should not be informed the courier or the central laboratory.

8.6. Sample Storage and Disposal

The samples and any other components from the cells collected for the additional biomarker assessment and pharmacogenomicanalysis will be stored in the central laboratory up to 15 years.

[Only for the Korean Study Sites]

The investigatorshould ask subject how long samples can be stored when given informed consent. The storage period should be written by subject in the ICF.

If the subject withdra ws consent, samples should be disposed of by the following procedure depending on the location of the tumor samples. Obtained data will not be discarded if the assessments have already been performed before consent was withdrawn.

If samples are temporarily stored at the study site

The investigator will identify the samples of the relevant subject and dispose of them.

If samples are stored at the central laboratory

The investigator will notify Daiichi Sankyo about the identification number of the subject who withdrew consent. Daiichi Sankyo will instruct the central laboratory to dispose of the relevant samples. Eventually, after the end of the sample storage period, the central laboratory will dispose of allsamples as instructed by Daiichi Sankyo.

8.7. Immunogenicity

Blood samples will be collected for ADA analysis at the time points specified in Table 8.6. Serum concentrations of DS-820la and/or total anti-HER2 antibody may be measured using the same ADA samples for the purpose of anti-drug antibody assessment.

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

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

Table 8.6: Anti-Drug Antibodies (ADA) Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	Bl (- 8 hours)
Cycle 2	Day 1	Bl (- 8 hours)
Every4 cycles from Cycle 4 (eg, Cycle 4, 8, 12...)	Day 1	Bl (- 8 hours)
F/ U	-	40 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first
Q3F/U*	-	Every 3 months (±14 days).

* For subjects with positive ADA at the F/U visit, additional serum ADA samples may be collected every 3 months (±14 days) up to 1 year from the last dose of study drug, or if the ADA becomes negative, or if the ADA titer becomes less than at baseline (applicable when pre-existing ADA is observed), or if the subject starts another therapy for cancer, or withdraws consent for the study, whichever occurs first.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

Safety endpoints will include SAEs, TEAEs, AESI, discontinuation due to AE, discontinuationdue to AESI, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, elevated troponin levels, ECG parameters, ECHO/MUGA findings, and ophthalmologic findings. TEAEs will be graded according to NCI-CTCAE version 4.03. Safety analyses in general will be descriptive and will be presented in tab ular format with the appropriate summary statistics.

9.2. Adverse Event Collection and Reporting

All clinical AEs occurring after the subject signs the main ICF for study participatio n and up to 40 (+ 7) days after last treatment (ie, the follow-up period), whether observed by the investigator or reported by the subject, will be recorded on the AE CRF page. All SAEs occurring after the subject signs the main ICF for study participation and up to 40 (+ 7) days after last treatment will be recorded on CRF. For subjects who sign only the Informed Consent Form for tissue sc reening, report only serious adverse events (SAEs) directly related to tissue screening procedure (ie, tumor biopsy). Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening . 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 the medical history.

All AEs, SAEs are to be reported according to the procedures in Section 9.5 SAE Reporting Procedure for Investigators.

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

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

Always report the diagnosis as the AE or SAE term. When a diagnosis is not available; 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 AEs or SAEs.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not

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

In case of death, the unde rlying or immediate cause of death should a lways be reported as a SAE.

Progressive disease is a study endpoint and should therefore not be reported as an AE/SAE. However, when a subject dies from PD without other immediate causes, "Progressive disease" should be repo1ted as a SAE.

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

If any AEs occur, the investigator will take appropriate actions and report the event to Daiichi Sankyo if necessary. The AEs should be followed until they resolve if possible, even beyond the post treatment follow-up period. Howeve r, if the AEs are not expected to recover, then follow-up during the clinical study is terminated. Even if follow-up during the clinical study is terminated, treatment of the event will be continued. Once post anticancer treatment is started, follow-up of the AE is terminated.

9.3. Adverse Events of Special Interest

Additional relevant info rmation regarding the AESis ILD/pne umonitis,QT prolongation, and LVEF decrease, for the DS-8201a clinical program regardless of seriousness is to be collected through the targeted questio nnaires within eCRF. Additional relevant information regarding the AESI Infusion related reaction is to be collected through the narrative form within eCRF. In the event that eCRF is unavailable, report AESis on a paper form. Once eCRF becomes available, please enter AESis reported on the paper form into eCRF as soon as possible.

For broad surveillance of ILD/pneumonitis, relevant AEs under the MedDRA Standard MedDRA Query (SMQ) ofl nterstitial Lung Disease as well as preferred terms {PTs) of respiratory failure and acute respirato ry failure are included for enhanced data collections.

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

9.3.1. QT prolongation and LVEF decrease

QT prolongation and LVEF decrease in association with DS-8201a are considered to be important potential risks based on the available pre-clinical data, literature and available safety info rmation for drugs of similar class. Refer to the current IB for a summary of preliminary clinical trial data.

LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function. Troponin will be measured at screening and EOT and as needed based on subject reported

cardiac symptoms. Triplicate ECGs will be performed and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnormalities. Whether or not meas urement is performed, date performed, res ults, and findings for each parameter will be recorded in the eCRF.

9.3.2. Interstitial Lung Disease/Pneumonitis

Clinical Summary

ILD/pneumonitis is considered an important identified risk based on a comprehens ive cumulative review of the available safety data from the clinical development program 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 plausibilit y, and safety information from drugs of similar class. Refer to the current 1B for a summary of preliminary clinical study data.

Management Guidance:

ILD/pneumonitis should be ruled out if a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the designated "Other Non-Laboratory Adverse Events" dose modification section of the study protocol.

If the AE is suspected to be ILD/pneurnonitis, treatment with study drug should be interrupted pending further evaluations. Evaluation s should incl ude high resolution CT, pulmonologi st consultat ion (infectious disease consultation as clinically indicated), blood culture and CBC (other blood tests could be considered as needed), bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered, pulmonary function tests and pulse ox imetry (SpO2), arte rial blood gases if clinically indicated, and one blood sample collection for **PK** ana lysis as soon as ILD/pneurnonitis is suspected, if feasible. Other tests could be considered, as needed..

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated " Pulmonaiy Toxicity" dose modification section of the study protocol.

All events of ILD/pneumonit is regard less of sever ity 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-820la program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independentevaluation, 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 SMQ. Please refer the guideline for the additional data collection and submission to ILD Adjudication Committee.

9.3.3. Infusion-related Reactions

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-820l a clinical program. Subjects receiving DS-8201a should be monitored vital signs, physical examination, and signs and symptoms of infusion related reaction: chills, fever, hypotension, skin rash, etc. Refer to the current **1B** for a summary of preliminary clinical trial data.

9.3.4. Independent Data Monitoring Committee (IDMC)

IDMC will be established for this study. Details on the membership, responsibilities, and working procedures of the committee will be described in its own charter.

9.4. Adverse Events

9.4.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a subject signing the main ICF for study participation, and that does not necessarily have to have a causal relationship with the 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 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 clinical laboratory findings that should be considered AEs.

Definition of worsening of the underl ying tumor is described below.

- Tumor progression including new lesion is not AE. However, if outcome of tumor progression is death during observation period of AE, it must be SAE. (Name of SAE is tumor progression, and outcome is death.)
- If sign and worsening of symptoms along with tumor progression are detected, it is AE.
- Rising of tumor maker is not AE.

9.4.2. Serious Adverse Events

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

- Results in death,
- Is life threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,

- Results in persistent or significant disability/incapacity,
- ls a congenital anomaly/birth defect, or
- ls an important medical event.

Note: The te1m " life threatenin g" 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 exe rcised when deciding whether expedite d reporting is appropriate in other situations, such as impo rtant medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

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

9.4.3. Severity Assessment

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

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-threatening co nsequences; 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). Serio usness of an event is based upon a universal and global Regulatory definition for reporting SAEs to regulatory agencies. For example, the NCI-CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the Investigator as Grade 1 or 2, but if the sub ject presents to the emergency facility for evaluatio n and is hospitalized overnight for observation that immediately makes the event serious based upon hospitalization without regard to the investigator assessment of severity.

9.4.4. Causality Assessment

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

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

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

9.4.5. Actions Taken Regarding Study Drug(s)

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

9.4.6. Other Actions Taken for Events

- None
  - No treatment was required.
- Medication required
  - Prescription and/or OTC medication was required to treat the AE.
- Hospitalization or prolongation of hospitalizationrequired
  - Hospitalization was required or prolonged due to the AE, independent of whether medication was required or not.
- Others

9.4.7. Adverse Event Outcomes

- Recovered/Resolved
  - The subjectfully recovered from the AE and no residual effect is observed.

- Recovering/Resolving
  - The AE improved but has not fully resolved.
- Not Recovered/Not Resolved
  - The AE itself is still present and observable.
- Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/resid ual effects.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE.
- Unknown

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

All AEs, AESI, SAEs and medication errors including overdose, will be reported **in** the CRF.

Serious events that are also efficacy endpoints (eg, **PD)** will be exempted from SAE processing and expedited reporting. Disease progression should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, "disease progression" should be repo1ted as a SAE and captured on designated eCRF. These events are clinically anticipated events in the target treatment population, and will be periodically reviewed by the Daiichi Sankyo safety teams to ensure prompt identification of any clinically concerning safety issues.

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

- SAEs (see Section 9.4.2 for definition)
- All potential ILD/pneumonitiscases should be reported within 24 hours; including both serious and non-serious potent ial ILD/pne umonitis cases.
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) 2: 3 x ULN and an elevated TBL > 2 x ULN that may occur either at different time points or simultaneous ly during the study conduct. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.
- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medica lly important. An "excessiveand medically important" overdose includes any overdose in which either a serious adverse event, a non-serious adverse event, or no adverse event occurs and is considered by the Investigator as clinically relevant, i.e. poses an actual or potential risk to the subject.

- Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose includin g DS-820la dosage, clinical course, assoc iated AEs, and outcome must be captured in the Narrative form of the CRF withineCRF.

If any SAEs occur, the investigator should also immediately report the event to the heads of the study sites. An SAE report will be submitted to the heads of the study sites in accordance with the procedures and format of the study site.

All events (serious and non-serious) must be reported with the investigator's assessment of the event's seriousness, severity, and ca usality 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 the event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant to the event shouldalso be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to Daiichi Sankyo 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 unava ilable, report SAEs on a Serious Adverse Event Report (SAVER) form (Supplement 5). All completed SAVER forms must be signed by the investigator,and e-mailed or faxed to the CRO using the provided SAVER form and the appropriate fax number provided. Once eCRF becomes available, please enter SAEs reported on the SAVER Form into eCRF as soon as possible. Once eCRF becomes available, please enter SAEs reported on the SAVER Form into eCRF as soon as possible.

See Section 15.12.5 for contact information for SAE reporting. Please call the local SAE Hotline (see Study Manual) or your study monitor for any questions on SAE reporting.

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

Daiichi Sankyo and/or the CRO will inform investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any Suspected UnexpectedSerious Adverse Reactions (SUSARs) that have occurred at other study sites or in other studies of the study drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or the CRO will comply with any additional local safety reporting requirements.

9.7. Exposure In Utero During Clinical Studies

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

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important both for drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy of a female subject using the Exposure In Utero (EIU) Reporting form (Supplement 6). Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery or induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with the study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

Laboratory test	Parameters
Hematology	Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Blood Chemistry	Total protein, albumin, ALP, ALT, AST, total bilirubin, BUN, Ca, Cl, serum creatinine, LDH, K, Na, Mg, ln temational nonnalized ratio (INR)/Prothrombin time (PT) and activated partial thromboplastin time (aPTT)
Urinalysis test	Protein, glucose, blood, microscopy assessments (if indicated), and specific gravity

The following parameters will also be analyzed at the visits indicated in Section 18.

- 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 immediately be confirmed using a serum test.
- Troponin (preferably troponin-T) test must be performed at the visits indicated in Section 18. Additional troponin testing should be performed if subject reports cardiac symptoms. Same assay should be used for the subject thro ugh o ut their stud y participat ion.

All clinical laboratory values must be assesse d by the investigator for clinical sign ifi cance a nd used to take appropriate clinical manage ment measures. All abnormal clinical laboratory values considered clinically significant by the investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes a SAE, the event should be reported on the AE page of the eCRF as an SAE and other relevant procedures must be followe d (see Section 9.5). Abnormal laboratory values (NCI-CTC AE Grade 3 or 4) occ urrin g durin g the clini ca l study will be followed until repeat test results return to normal (or base line), stabilize, or are no longer clini ca lly sign ificant.

9.9. Vital Signs

Vital sign meas urements will include systolic and diastolic blood pressure and pulse rate and body temperature. Additionally, SpO2 will be meas ured 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 eve nts. Standard ECG parameters will be measured, incl uding Hea rt rate, RR, PR, QT intervals, and QRS duration. All ECGs must be eva luated by the investigator or delegated physician for the presence of abnormalities

9.11. Physical Examinations

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

9.12. Other Examinations

ECOGPS

Cardiac Assessments

Either ECHO or MUGA scan will be performed as described in the schedule of events. LVEF will be measured by either ECHO or MUGA scan.

Ophthalmic Assessments

Ophthalmic assessments will include visual acuity testing, slit lamp examination and fundoscopy

Pulmonary Assessments

Pulmonary assessment will include CT or MRI of the chest, SpO2 and will be performed as described in scheduleof events. For more details please refer to Section 6 of the protocol.

An ILD AC will review all cases of potential ILD/pneumonitis on an ongoing basis. Description of the ILD AC is available in Section 9.3.2.1.

10. OTHER ASSESSMENTS

10.1. Patient Reported Outcomes

Patient reported outcomes (PRO) will be used in both groups of Primary Cohort to evaluate study treatment and comparator and will be measured on the same days as well as EOT. The impact of gastric cancer symptoms will be assessed based upon the FACT-Ga (Version 4.0) and EQ-5D-5L questionnaires (Section 17.5). FACT-Ga and EQ-5D-5L are completed on Day 1 before any tests/seeing Investigator, Day 15 (±1), the every 6 weeks from the beginning of the study (eg, Day 43 (±7), 85 (±7), 127 (±7), etc.), and EOT. EQ-5D-5L questionnaire to be completed first and then FACT-Ga questionnaire.

10.1.1. EQ-5D-SL

The EQ-5D-5L is a widely used generic health-related quality of life (QoL) instrument that allows for estimation of health utility.

The EQ-5D-5L is self-administered and consists of 2 parts, the EQ-5D-5L descriptive system, and the EQ Visual Analogue Scale (VAS) (Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version ofEQ-5D (EQ-5D-5L). Quality of Life Research.(2011) 20: 1727). The descriptivesystem comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5 digit number describing the respondent's health state. The numerals 1 to 5 have no arithmetic properties and should not be used as a cardinalscore.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, VAS with endpoints labeled ' the best health you can imagine' and ' the worst health you can imagine.' This information can be used as a quantitative measure of health as judged by the individual respondents.

10.1.2. FACT-Ga

The FACT-Ga is one of several instruments developed to assess QOL in patients with gastric cancer. The FACT-Ga is a 46-item Likert-scaled questionnaire, with response scores ranging from Oto 4. The response categories include ' Not at all', ' A little bit', 'Somewhat', 'Quite a bit' , and 'Very much' . Negatively worded items are reverse-scored so that all participants who experience a higher severity of symptoms receive a lower score (FACT-Ga: a new international measure of QOL in gastric cancer, Eremenco SL, Cashy J, Webster K, J Clin Oncol, 2004). The measure is based on the Functional Assessment of Cancer Therapy-General (FACT-G) (The Functional Assessment of Cancer Therapy scale: development and validation of the general measure, Cella DF, Tulsky DS, Gray G, J Clin Oncol, 1993), which is composed of four unidimensional factors (physical, social/family, emotional, and functional well-being), and includes a 19-item multidimensional ' Additional Concerns' subscale composed of items specifically pertaining to a wide range of symptoms related to gastrointestinal cancer.

10.1.3. Health Care Resource Utilization.

Time to SAE related hospitalization will be assessed for the Primary Cohort only. Each hospitalization event will prompt the completion, by the site, of a detailed hospitalization eCRF containing the following components:

1. Date of SAE related admission to hospital.
11. Date of SAE related discharge from hospital.
111. Primary reason for SAE related hospitalization.
1v. Discharge status from SAE related hospital (died, discharged home, discharged to home health care, discharged to nursing home care, discharged to long-term care, other).
v. Use of intensive care unit (ICU) services in hospital (Yes/No).
   a. If yes, date of admission to ICU.
   b. If yes, date of discharge from ICU.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The primary analysis for ORR and formal interim analysis for OS will be performed when all subjects have completed tumor assessment approximatelyat 24 weeks (or discontinued the study) in Primary Cohort. The final OS analysis will be performed when about 133 OS events are observed in Primary Cohort.

Summary statistics will be presented by cohort/treatment group. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum values (as well as geometric means and geometric coefficient of variation for Cmax and AUC PK parameters). Categorical variables will be summarized using frequency counts and percentages.

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

Analyses of ORR and DCR will be performed on the Response Evaluable Set. The other efficacy analyses will be performed on the full analysis set (FAS). Safety analyses will be performed using the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set. All other exploratory analyses will be performed based on the FAS and the availability ofassessments.

11.2. Analysis Sets

11.2.1. Full Analysis Set

TheFAS for the Primary Cohort will include all randomized subjects who received at least 1 dose of the study treatment. The FAS for the each of the Exploratory Cohorts will include all subjects who received at least 1 dose of the study treatment.

11.2.2. Response Evaluable Set

The Response Evaluable Set for the Primary Cohort will include all randomized subjects who received at least 1 dose of study drug and had measurable tumors based on central review at baseline. The Response Evaluable Set for the each of the Exploratory Cohorts will include all subjects who received at least 1 dose of the study treatment and had measurable tumors based on central review at baseline.

11.2.3. Safety Analysis Set

The Safety Analysis Sets for the Primary and each of the Exploratory Cohorts will include all subjects who received at least one dose of the study treatment. Subjects will be summarized according to treatment actually received.

11.2.4. Pharmacokinetic Set

The **PK** Analysis Sets for the Primary and each of the Exploratory Cohorts will include all subjects who received at least one dose of DS-820l a and had measura ble serum concentrations of DS-820la.

11.3. Study Population Data

Subject disposition will be summarized for the enrolled subjects in each cohort. The total number of subjects for each defined analysis set will also be tabulated for each cohort. The demographic and baseline characteristics will be summar ized descriptively for the FAS, Response Evaluable Set, and the Safety Analysis Set for each cohort. Study drug exposure, treatment duration, and comp liance with study therapy as well as prior and concomitant medications will be summarized us ing descriptive statistics for the Safety Analysis Set for each cohort.

11.4. Statistical Analyses

11.4.1. Efficacy Analyses

11.4.1.1. Primary Efficacy Analyses

The primary endpoint is ORR (the proportion of subjects who achieved a best overall response of CR or PR) assessed by independent central imaging facility review based on RECIST version 1.1. The primary efficacy analysis will be performed for the Response Evalua ble Set in the Primary Cohort. A Cochran-Mantel-Haenszel (CMH) test with region as a stratification factor will be used to compare ORR between the treatment groups. The primary efficacy analysis for ORR will be assessed for statistical significance at 2-sided alpha= 0.05.

The estimate of ORR and its 2-sided 95% exact CI will be provided for each cohort/treatment group. In addition, ORR by each fixed time point (eg, 3, 6, 9, 12 months) along with their 2-sided 95% exact Cls will be provided for each cohort/treatment group.

11.4.1.2. Secondary Efficacy Analyses

The secondary efficacy endpoints include OS, PFS, DoR, DCR (the proportion of subjects who achieved a best overall response of CR or PR or Stable Disease [SD]), TTF, and ORR assessed by independent central imaging facility review (for each Exploratory Cohort 1 and 2) and the investigator based on RECIST version 1.1.

OS is defined as the time from the date ofr andomization (the date of the registration for Exploratory Cohorts) to the date of death from any cause. If the death of a subject is not reported before the data cut-off for OS analysis, OS will be censored at the last contact date at which a subject was known to be alive.

PFS is defined as the time from the date of randomization (the date of the registration for each of the Exploratory Cohorts) to the earlier of the dates of the first radiographic PD via independent central imaging facility review based on RECIST version l. l or death due to any cause. If the PD (eg, clinical diagnosis of PD) is not confirmed by central imaging, PFS will be censored at the last day of imaging assessment. Detailed censoring rules for PFS will be specified in the statistical analysis plan (SAP).

DoR is defined as the time from the date of the first objective response (CR or PR) to the date of the first disease progression or death due to any cause. DoR will be measured for respo nding subjects (CR or PR) only. Detailed censoring rules for DoR will be specified in the SAP.

TTF is defined as the time from the date ofr andomization (the date of the registration for Exploratory Cohorts) to the earliest date of the first radiographic PD, death due to any cause, or treatment discontinuation. Detailed censoring rules for TTF will be specified in the SAP.

OS and PFS will be compared between the treatment groups using stratified log-rank tests with region as a stratification factor in Primary Cohort. To control the family-wise type I error rate (FWER) for primary and secondary efficacy endpoints, a serial hierarchically ordered gatekeeping strategy will be applied. The tests will be performed in the followi ng order: ORR, OS. The sequence of tests will continue until the test does not meet the significancelevel of 2-sided alpha = 0.05. The testing procedure will follow the steps below:

1. Test the primary endpoint, ORR, at a 2-sided 5% significance level. If positive, continue to step 2; otherwise,stop.
2. Test OS (interim and final analyses) at an overall 2-sided 5% significance level.

The first analysis of OS will occur at the time of the primary analys is for ORR only if ORR meets the significance level of 2-sided alpha 0.05. The final analysis of OS will occur when about 133 OS events are observed in the Primary Cohort. A Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundary will be used to determine the significance level at the first and final analysis of OS. The HRs and their 95% CI will be estimated using stratifiedCox proportional hazardsregression models with region as a stratificationfactor. Kaplan-Meier estimates and survival curves will also be presented for each cohort/treatmentgroup.

OS , PFS , DoR , and TTF will be summarized with median event times and their 2-sided 95% CI for the median using Brookmeyer and Crowley methods for each cohort/treatment group. In addition, Kap lan-Meier estimates at each fixed time point (eg, 3, 6, 9, 12 months) along with their 2-sided 95% Cis will be provided for each cohort/treatment group.

DCR will be analyzed in the same manner as ORR analysis.

11.4.1.3. Exploratory Efficacy Analyses

11.4.1.3.1. Analyses of Exploratory Efficacy Endpoints

Duration of SD, time to response, time to SAE related hospitalization, best percent change in the sum of diameters of measurable tumors, and PFS based on investigator assessment will be evaluated and considered as exploratory efficacy endpoints.

Duration of SD is defined for subjects whose best response is SD as the time from the date of the first dose to the date of the first documentation of PD. Detailed censoring rules for duration of SD will be specified in the SAP.

Time to response is defined as the time from the date of the first dose to the date of the first documentation of objective response (CR or PR). Time to response will be measured for responding subjects (CR or PR) only.

Duration of SD, time to response, and time to SAE related hospitalization will be summarized with median event times and their 2-sided 95% CI for the median by cohort/treatment group using Kaplan-Meier methods.

Time to SAE related hospitalization, and PFS based on investigator assessment will be analyzed in the same manner as OS and PFS analyses.

Descriptive statistics for the best (minimum) percent change from baseline in the sum of diameters will be provided by cohort/treatment group. A waterfall plot of the best (minimum) percent change in the sum of diameters for each subject will be presentedfor each cohort/treatment group with vertical lines representing the sorted values of percent changes. A spider plot of the percent change in the sum of diameters for each subject will be also presented for each cohort/treatment group.

11.4.2. Pharmacokinetic /Pharmacodynamic/Biomarker Analyses

11.4.2.1. Pharmacokinetic Analyses

Serum concentrations for DS-820l a, total anti-HER2 antibody and MAAA-l 18la will be listed, plotted, and summarized using descriptive statistics by cohort/treatment arm at each time point. **PK** param ete rs will be listed and summarized using desc riptive stat istics by coho rt/treatment arm.

The population pharmacok.inetic (pop-PK) analysis to evaluate the effect of intrinsic and extrinsic factors of DS-8201a, and if appropriate, total anti-HER2 antibody and MAAA-1181a will be characterized, including available PK data from the Phase 1 (DS8201-A-Jl Ol) study. After establishment of the pop-PK model, a population pharmacokinetics/pharmacodynamics (pop-P K/PD) model will be developed to evaluate the relationship between exposure and efficacy and tox icity. The pop-PK and pop-PK/PD will be reported in a separate report from the clinical study report

11.4.2.2. Pharmacodynamic Analyses

Not applicable

11.4.2.3. Biomarker Analyses

Biomarkers will be listed and summarized using desc riptive stat istics.

11.4.2.4. Pharmacogenomic Analyses

Not applicable

11.4.3. Safety Analyses

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

Safety analysis will be performed using the Safety Analysis Set for each cohort and subjects will be analyzed according to their actual treatment received.

11.4.3.1. Adverse Event Analyses

A TEAE is defined as an AE that emerges during the treatment period (from date of first dose unti l the F/U visit after the last dose of the study drug), 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 related to the pre-treatment state, when the AE is continuous. TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and assigned grades based on version 4.03 of NCI-CTCAE . The number and percentage of subjects reporting TEAEs will be tabulated by System Organ Class (SOC), Preferred Term (PT), relationship to the study treatment, and the worst CTCAE grade. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by cohort/trea tment group, as well as TEAEs leading to disco ntinuation of the study treatments.

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

11.4.3.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline by cohort/treatment group at each scheduled time of evaluation, including the EOT visit, maximum post-treatment value, and minimum post-treatment value.

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

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

11.4.3.3. Vital Sign Analyses

Descriptive statistics will be provided by cohort/treatment group for the vital sign measurements and changes from baseline by scheduled time of evaluatio n, including the EOT visit and the maximum and minimum post-treatment values. All vital sign data will also be listed.

11.4.3.4. Electrocardiogram Analyses

Descriptive statistics will be provided by cohort/treatment group for ECG parameters and changes from baseline by scheduledtime of evaluation, includin g the EOT visit and the maximum post-treatment value. In add ition, the numb er and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc 450 ms, >450 to 80 ms, >480 ms to 500 ms, and >500 ms). The QT intervals will be corrected for hea1trate by Fridericia's f01mula ($QTcF = QT/[RR]'^{/3}$) ECG data will also be listed.

11.4.3.5. Anti-Drug Antibodies Analyses

A shift table, presenting the 2-way freq uency tabulation for base line and all sc hedule times, incl uding the EOT Visit, will be provided for each cohort/treatment group the incidence of ADA.

11.4.3.6. Other Safety Analyses

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

11.4.4. Other Analyses

11.4.4.1. Subgroup Analyses

Subgro up analyses for ORR, OS, PFS, DoR, and DCR will be performed. TEAEs will be also summarized by cohort/treatment group for eac h subgro up. Subgroups will include:

- Region (Japan, Korea)
- Lines of prior systemic therapy (2, 3, 24).
- Age (<65, 265 years).
- Sex (female, male).
- ECOG PS (0, 1).
- HER2 status (Primary Cohort: IHC 3+ or IHC 2+/ISH +)
- Primary tumor locat ion (Gastric/GE])
- Histological subt ype(Intestinal or Diffuse or Others)
- Number of metastatic sites (<2, 22)
- Previous total gastrectomy (Yes orNo)
- Prior adjuvant/ neoadjuvant therapy (Yes or No)
- Prior Ramcirumab contained treatment (Yes or No)
- Prior treatment with irinotecan or other topoisomerase I inhibitors (Yes or No)
- Most recently treatment with irinotecan or other topoisomerase I inhibitors (Yes or No)
- Prior treatment with checkpoint inhibitor or other immuno-o ncology therapy (Yes or No)
- Most recently treatment with trastuzumab or trastuzumab similar treatment including study drug (Yes or No)
- Presence of liver metastasis at baseline (Yes or No)
- Renal impairment at baseline (within normal range, and mild/moderate impairment)
- Physician's choice treatment (DS-820l a vs irinotecan or paclitaxel in physician's choice group)

In each subgroup defined above, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint.

11.4.4.2. Analyses of Exploratory HEOR Endpoints

HEOR endpoints (eg, EQ-5D-5L, FACT-Ga, health care resource utilization) will be summarized using standard methods of analysis for the corresponding questionnaires and descriptive statistics for the actual value and change from baseline will be computed for the summarized index scores for all subjects and by treatment group for the FAS in the Primary Cohort. Further details will be provided in the SAP.

11.5. Interim Analyses

One formal interim OS analysis will be conducted when all subjects have completed tumor assessment approximately at 24 weeks (or discontinued the st udy) in Primary Cohort assumi ng the OS events observed thus far do not reach the target number of OS events (i.e., 133 OS events in Primary Cohort). The interim OS will be tested only if ORR shows the statistical significance at 2-sided alpha = 0.05. The overall 2-sided alpha is to be controlled at 0.05 for the interim OS analysis and final OS analysis using the Lan-DeMets alpha-spending function with an O' Brien-Flemingboundary. The boundary used at the interim and final OS analysis depends on the actual number of observed deaths at the interim analysis.

11.6. Sample Size Determination

A total of approximately 220 (Primary Cohort: approximately 180, Exploratory Cohort 1: approximately 20, and Exploratory Cohort 2: approximately 20) will be enrolled.

Primary Cohort

Combined analysis of ORR from Phase 2 and 3 studies (a total of 13 studies) of second- or subsequent-line chemotherapyin patients with gastric cancer was conducted. [32] As a result, the combined ORR was 9.4% (95% confidence interval [CI]: l. l% to 17.7%).[33,34,35,36,37,38,39,40,41,42,43,44,45] The ORR in the physician's choice gro up was conservatively assumed to be 15%, which exceeded the above-mentioned combined mean estimate of ORR. The ORR in DS-820 la monotherapy group was also assumed to be 40%. The sample size of 180 subjects (120 subjects to DS-820la monotherapy group and 60 subjects to the physician's choice group) provides a 92.9% power to detect this magnitude of difference using a Fisher's exact test at 2-sided alpha = 0.05 level of significance.

Approximately 133 OS events will be needed to detect a HR of 0.61 for OS (a 64% improvement in median OS from 5.5 months in the physician's choice group to 9.0 months in DS-820 la monotherapy group) with an 2-sided alpha = 0.05 level of significanceand 80% power. The sample size of 180 subjects also provides an 80.8% power to detect this magnitude of OS difference, assuming a 10-month long enrollment period and a 12-month follow-up period after the last subject is randomized.

Exploratory Cohort *(l* and 2)

The probability that more than 4 responders out of 20 subjects (ORR >20%) are observed will be less than 20% under the lower reference value of ORR= 15%, but more than 75% under the expected ORR =30%.

The power computation is performed using the POWER procedure of SAS® Vers io n 9.3.

11.7. Statistical Analysis Process

The clinical study will be analyzed by Daiichi Sankyo or its agent/CRO followed by this protoco l, and the SAP which will demonstrate all methodologies and disp lays/shells for statistical analyses.

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

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

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

12. DATA INTEGRITY AND QUALITY ASSURANCE

For the purpose of monitoring and auditing by Daiichi Sankyo and inspection by the regulatory authoriti es and/or the IRB, the study site should provide direct access to all documents and records related to this study, includin g the source documents. To verify the proper conduct of the study and the absolute reliability of the study data, Daiichi Sankyo should perform monitoring and auditing by reviewing the source documents and other relevant documents directly. Daiichi Sankyo should arrange the procedures for direct access to these documents in advancewith the investigator. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important for evaluation of a clinical study.

12.1. Monitoring and Inspections

Daiichi Sankyo or CRO monitor and the regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities, and upon reque st, inspecting the various record s of the study (eg, CRFs, source data, and other pertinent documents).

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

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

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

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

12.2. Data Collection

An eCRF must be completed for each subject who signs an ICF (including a separate tissue screening ICF). The investigator, sub-investigator, or study site staff will enter the data in the CRF in accordance with the CRF Completion Guidelines that are provided by Daiichi Sankyo.

CRF completion should be kept cmTentto enable the monitor to review the subject's status throughout the course of the study. CRFs will be completed, reviewed, and e-signed by the investigator.

The investigator e-signs according to the study data flow.

Any clinical data entered in the CRF will be subject to these data management procedures and will be included in the final study data sets according to CDISC standards.

Daiichi Sankyo or a designee will supply eCRFs. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the EDC software's "audit trail."

Data for all study visits will be recorded on the eCRF for subjects who have received the 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 the study drug. Further data, such as AEs, will not be collected from subjects once they are considered screening failures or have decided to withdraw prior to receiving the study drug.

Data will be electronically recorded using the EDC {Table 12.l) system, which enables the preparation of eCRF. The CRF and audit trail will be prepared using the EDC system. The signed eCRF will be treated as an original report. The EDC system should be validated before use.

Table 12.1: EDC System

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

12.3. Data Management

Each subject will be identified in the database by a unique subject ID as defined by Daiichi Sankyo.

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Manage ment review will be performed on subject data according to specifications given to Daiichi Sankyo or CRO. Data will be vetted both electronically and manua lly for CRFs and the data will be electronically vetted by programmed data rules within the applicatio n. Queries generate d by rules and raised by reviewers will be generate d within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

Data received from external sources such as ce ntral labs will be reconciled with 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 using the latest version of the World Health Organization Drug Dictio nary.

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.

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

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

Investigators will maintain a confidential site subj ect identifier list. This confidential list of names of all subjects allocated to study numbers when enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

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

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

12.5. Record Keeping

The investigator and study staff are responsible to maintain a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives of Daiichi Sankyo and/or the applicable regulatory authorities . Essent ial documents contained in the Trial Master File include:

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

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

All study-relatedessential documentation will be retained by the institution for at least 15 years after completion of the study (for a longer period if needed to comply with other applicable requirement s), or until the institution is instructed otherwise by Daiichi Sankyo. It is the responsibility of Daiichi Sankyo to inform the investigator/institution when these documents no longer need to be retained.

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

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

Daiichi Sankyo 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 upo n by the parties.

14. PUBLICATION POLICY

[redacted]

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

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

- Japanese Ministry of Health, Labour and Welfare Ordinance No. 28 of27 March, 1997 and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics of25 November, 2014;
- Other applicable local regulations.

15.2. Subject Confidentiality

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

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

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

15.3. Informed Consent

Before a subject participates 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-specificprocedures or any study drugs are administered. Subjects must be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and must have adequate time to decide whether or not to participate in the study. The written ICF must be prepared in the local language(s) of the potential subject pop ulation.

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

The subject' s written infmmed consent must be documented in the subject' s medical records. The ICF must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to the subject. The date and time (if applicable) when informed consent was given must be recorded in the CRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness must be present during the entire informed consent discussion . This witness must sign the ICF after the subject has consented to the subject's pa1ticipation and if possible, sign the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequate ly exp lained to and apparently understood by the subject and that informed consent was freely given bythe subject.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) are provided in the Daiichi Sankyo's ICF template for the investigator to prepare the documents to be used at his or her study site. Updates to applicable forms will be communicate d in writing by Daiichi Sankyo.

15.4. Informed Consent for Pharmacogenomic Analysis

Before obtaining samples for pharmacogenomic analysis, the investigator is responsible for obtaining freely given consent, in writing, from the subject, after giving an explanation of the pharmacogenomic analysis in intelligible terms. Before obtaining the informed consent, the investigator should provide the subjects with adequate time to have the opportunity to inquire abo ut the detail s of the study, and should answer all questions properly. This analysis is an optional analysis for whom agreed to join clinical study, and another written informed consent document is prepared, separately from informed consent for clinical study.

15.5. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any written instruction s 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 qualificat ions must be submitted to the EC or IRB for ethical review and approval according to the local regulations, prior to the study start. The written approval must 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.

Daiichi Sankyo will appoint a Coordinating Investigator. The Coordinating Investigator will be responsible for testifying to the accuracy of the description of the study conduct.

The investigator and/or Daiichi Sankyo must subm it and, where necessary, obtain approval from the EC or IRB for all subse quent protocol amendments and changes to the ICF. The investigator must notify the EC or IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from Daiichi Sankyo/CRO, in accordance with local procedures.

As required by local regulations, the Daiichi Sankyo's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure that all legal aspects are covered, and that approval from the appropriate regulatory bodies has been obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to the regulatory authorities and that these changes are implemented only after approval by the relevant regulatory bodies, as required.

In the event of any prohibition or restrictions imposed (eg, clinical hold) by any applicable Regulatory Authority(ies) in any area of the world, or if the investigator is aware of any new information that may influence the evaluation of the benefits and risks of the study drug, Daiichi Sankyo should be informed immediately.

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

15.6. Protocol Deviations

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

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate an immediate hazard(s) to the subject. Daiichi Sankyo 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 an incorrect dose or study treatment, and had at least **1** administration of study drug, data should be collected for safety purposes.

If applicable, the investigator must notify the EC or IRB of deviations from the protocol in accordance with local procedures.

15.7. 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, Daiichi Sankyo will inform all investigators involved in the clinical study, ECs/lRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The investigator should immediately inform the subjects whenever new information becomes available that may be relevant to the subjects' consent or may influence the subjects' willingness to continue pa1ticipation in the study. The communication should be documented on the 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 investigatorshouldobtain written informed consent to continue participation with the

revised written information even if subjects have already been informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject must sign and date the revised ICF.

15.8. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by Daiichi Sankyo or the CRO.

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 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.

15.9. Study Termination

In case any of the following conditions apply, and Daiichi Sankyo judges that it is difficult to continue the study, Daiichi Sankyo will prematurely terminate or suspend the study. Daiichi Sankyo should then decide whether or not to terminate or suspend the study, and document the decision.

1. In case new safety information or SAE information on the study drug is obtained.
2. In case of a significant GCP violation or protocol deviation on the part of Daiichi Sankyo, study site, or the investigator.
3. In case other new information is obtained during the study.

If the study is prematurely terminated or suspended by Daiichi Sankyo in consultation with the medical advisor, Daiichi Sankyo must promptly inform the investigators/study sites of the termination or suspension and the reason(s) for the termination or suspension in written form. The IRB should also be informed promptly and provided reason(s) for the termination or suspension by Daiichi Sankyo or by the investigator/study site, as specified by the applicable regulatory requirement(s).

If the study is terminated or suspended, for whatever reason, the investigator must promptly inform the subjects and take appropriate measures (eg, conducting examinations) to ensure the safety of the subjects.

15.10. Steering Committee

A steering committee will be established for this study. Details on the membership, responsibilities, and working procedures of the committee will be described in its own charter.

15.11. Data and Safety Monitoring Board

Not applicable

15.12. Address List

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

15.12.1. Sponsor

Daiichi Sankyo Co., Ltd
3-5-1, Nihonbashi-honcho.Chuo-ku, Tokyo I03-8426 Japan

15.12.2. Medical Officer / External Medical Monitor/ Internal Medical Monitor

Medical Officer / External Medical Monitor:

PD

Natio nal Cancer Center Hospital East
6-5-1, Kashiwanoha. Kashiwa-shi, Chiba-ken, 277-8577 Japan
PD
PD

Internal Medical Monitor:

PD
PD

15.12.3. Coordina ting Investigator

PPD

The Cancer Institute Hospital of Japanese Foundation for Cancer Research
3-8-31, Ariake, Koto-ku, Tokyo 135-8550, Japan
PD

15.12.4. Sponsor's Clinical Study Lead

PPD
PPD

15.12.5. Spon sor's Clinical Operations Delivery Lead

PPD
PPD

15.12.6. Spon sor's Safe ty Contacts

PD

PD

PPD
PPD

15.12.7. ARO

Not applicab le

15.12.8. CROs

CMIC Co., Ltd. (Japan)
1-1-1, Shibaura, Minato-ku, Tokyo, 105-0023, Japa-
PD

CMIC Korea Co., Ltd. (Korea)
lOF, 129, Teheran-ro, Gangnarn-gu, Seoul, Republi c of Korea (06133)
PD

DAIICHI SANKYO RD NOVARE CO., LTD.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japan
PD

15.12.9. EDC Vendor

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

15.12.10. EDC System Support

Fujitsu Limited
TOKYU REIT Kamata Building 5-13-23, Kamata, Ota-ku, To kyo 144-0052 Japan
PD

15.12.11. IXRS Vendor

Almac group
25 Fretz Road Souderton, PA 18964
PU

15.12.12. Central Laboratory

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214
PPD

Guardant Health, Inc.
505 Penobscot Drive
Redwood City, CA 94063 U.S.A.
PD

Daiichi Sankyo RD Novare Co., Ltd.
1-16-13 Kitakasai, Edogawa, Tokyo 134-8630, JAPAN
PD

15.12.13. Central Imaging

Bioclinica Inc.
211 Carnegie Center, Princeton, NJ 08540
PD

15.12.14. Bioanalytical Laboratory (Pharmacokinetics and Anti-Drug Antibodies)

PPD
2244 Dabney Road
Richmond VA 23230, USA
PD

15.12.15. Sponsor's Biostatistician

PD

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

15.12.16. Data Safety Monitoring Board

CMIC Co., Ltd. Academia Clinical Research Division
Osaka branch, Nakanoshima Central Tower, 2-2-7 Nakanoshima, Kita-ku
Osaka 530-0005, Japan
po

16. REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr, accessed on 09/05/2015.
2. Park JM, Kim YH. Current approaches to gastric cancer in Korea. Gastrointest Cancer Res. 2008;2(3):137-44.
3. Inoue M, Tsugane S. Ep idemio logy of gastr ic cancer in Japan. Postgrad Med J. 2005;81(957):419-24.
4. Minashi K, Hironaka S. Advances in secondary chemotherapy for gastric cancer. Gan To Kagaku Ryoho. 2015;42(4):398-402.
5. Park DI, Yun JW, Park JH, et al. HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci 2006;51(8):1371-9.
6. Kim KC, Koh YW, Chang HM, et al. Evaluation ofHER2 protein expression in gastric carcinomas: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. Ann Surg Oncol. 2011;18(10):2833-40.
7. Cho EY, Park K, Do I, et al. Heterogeneity ofERBB2 in gastric carcinomas: a study of tissue microarray and matched primary and metastatic carcinomas. Mod Pathol. 2013;26(5):677-84.
8. Shan L, Ying J, Lu N. HER2 expression and relevant clinicopathological features in gastric and gastroesophagealjunction adenocarcinoma in a Chinese population. Diagn Pathol. 2013;8:76-82.
9. Yano T, Doi T, Ohtsu A, et al. Comparison ofHER2 gene amplication assessed by fluoresce nce in s itu hybridization and HER2 protein expression assessed by immunohistochemistry in gastric cancer. Oncol Rep. 2006;15(1): 65-71.
10. Yoon HH, Shi Q, Sukov WR, et al. Assoc iation of HER2/ErbB2 expression and gene amplication with pathological features and prognosis in esophageal adenocarcinomas. Clin Cancer Res. 2012;18(2):546-54.
11. Yan M, Parker BA, Schwab R, et al. HER2 aberrations in cancer: implications for therapy. Cancer Treat Rev. 2014;40(6):770-80.
12. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines Version 4 (May, 2014).
13. Japanese Gastric Cancer Association. Preliminary Figures for Ramucirumab, Japanese gastric cancer treatment guidelines Version 4 (October, 2015).
14. Nishimura T, Iwasa S, Nagashima K, et al. lrinotecan monotherapy as third-line treatment for advanced gastric cancer refractory to fluorop yrimidine s, platinum, and taxanes. Gastric Cancer. 2017;20(4):655-662.
15. Shimoyama R, Yasui H, Boku N, et al. Weekly paclitaxel for heavily treated advanced or recurrent gastric cancer refractory to fluoro uracil, irinotecan, and cisplatin. Gastric Cancer. 2009;12(4):206-11.

16. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017; 390: 2461-2471

17. Seyoung S, Min-HR, Ji YA, et al. Loss of HER2 positivity after anti-HER2 chemotherapyin HER2-positive gastric cancer patients: Results of GASTric cancer HER2 reassessment study 3 (GASTHER3) [abstract]. J Clin Oncol. 2017;35(Suppl 4):27.

18. Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. J ClinOncol. 2006;24(27):4441-7.

19. Cheverton **P,** Friess **H,** Andras C, et al. Phase III results of exatecan (DX-8951£) versus gemc itabine (Gem) in chemotherapy-naivepatients with advanced pancreatic cancer (APC) [abstract]. J Clin Oncol. 2004;22(Suppl 14):4005.

20. De Jager R, Cheverton P, Tamanoi K, et al. DX-895lf: summary of phase I clinical trials. Ann NY Acad Sci. 2000;922:260-73.

21. Ogitani Y, Aida T, Hagihara K, et al. DS-820 la, a nove l HER2-targeting ADC with a novel DNA topoiso merase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DMl. Clin Cancer Res. 2016;22(20):5097-108.

22. Ogitani Y, Hagihara K, Oitate **M,** et al. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. Cancer Sci. 2016;107(7):1039-46.

23. Archer SG, Eliopoulos A, Spandidos D, et al. Expression of ras p21, p53 and c-erbB-2 in advanced breast cancer and response to first line hormonal therapy. Br J Cancer. 1995;72(5):1259-66.

24. Esteva FJ, Guo H, Zhang S, et al. PTEN , PIK3CA, p-AKT, and p-p70S6K status: association with trastuzumab response and survival in patients with HER2-positive metastatic breast cancer. Am J Pathol. 2010;177(4):1647-56.

25. Ross JS, SlodkowskaEA, Symmans WF, et al. The HER-2 receptor and breast cancer: ten years of targeted anti-HER-2 therapy and personalized medicine. Oncologist. 2009;14(4):320-68.

26. Hofmann M, Stoss 0, Shi D, et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008;52(7):797-805.

27. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008;19(9):1523-9.

28. Harder J, Ihorst G, Heinemann V, et al. Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer. Br J Cancer. 2012;106(6):1033-8.

29. Yoshizawa A, Sumiyoshi S, Sonobe M, et al. HER2 status in lung adenocarcinoma: a comparison of immunohistochemistry, fluorescence in situ hybridization (FISH), dual-ISH, and gene mutations. Lung Cancer. 2014;85(3) :373-8 .

30. Blok EJ, Kuppen PJ, van Leeuwen JE, et al. Cytoplasmic overexpression ofHER2: a key factor in colorectal cancer. Clin Med Insights Oncol. 2013;7:41-51.

31. Verri E, Guglielmini P, Puntoni M, et al. HER2/neu oncoprotein overexpression in epithelial ovarian cancer: evaluation of its prevalence and prognostic significance. Clinical study. Oncology. 2005;68(2-3):154-61.

32. Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions, 3rd edition. John Wiley & Sons, Inc. New Jersey; 2003. p. 209-26.

33. Hartmann JT, Pintoffl JP, Al-Batran SE, et al. Mitomycin C plus infusional 5-fluoro uracil in platinum-refractory gastric adenocarcinoma: an extended multicenter phase II study. Onkologie. 2007;30(5):235-40.

34. Zhang XT, Li J, Bai Y, et al. A phase II study of triweekly paclitaxel and capecitabine combination therapy in patients with fluoropyrimidine-platinum-resistant metastatic gastric adenocarcinoma. J Cancer Res Ther. 2013;9 Suppl:S153-7.

35. Bang YJ, Im SA, Lee KW, et al. Randomized, Double-blind phase II trial with prospective classification by ATM protein level to evaluate the efficacy and tolerability of olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer. J Clin Oncol. 2015;33(33):3858-65.

36. Tanabe K, Fujii M, Nishikawa K, et al. Phase II/III study of second-line chemotherapy comparing irinotecan-alone with S-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with S-1 (JACCRO GC-05). Ann Oncol. 2015;26(9):1916-22.

37. Wainberg ZA, Soares HP, Patel R, et al. Phase II trial of everolimus in patients with refractory metastatic adenocarcinoma of the esophagus, gastroesophageal junction and stomach: possible role for predictive biomarkers. Cancer Chemother Pharmacol. 2015;76(1):61-7.

38. Zheng Y, Fang W, Mao C, et al. Biweekly S-1 plus paclitaxel (SPA) as second-line chemotherapy after failure from fluoropyrimidine and platinum in advanced gastric cancer: a phase II study. Cancer Chemother Pharmacol. 2014;74(3):503-9.

39. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31-9.

40. Martin-Richard M, Gallego R, Pericay C, et al. Multicenter phase II study of oxaliplatin and sorafenib in advanced gastric adenocarcinoma after failure of cisplatin and fluoropyrimidine treatment. A GEMCAD study. Invest New Drugs. 2013;31(6):1573-9.

41. Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previo usly treated advanced gastric cancer: results of the randomized, do uble-bl ind phase III GRANITE- I study. J Clin Oncol. 2013;31(31):3935-43.

42. Kato K, Chin K, Yoshikawa T, et al. Phase II study ofNK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer. Invest New Drugs. 2012;30(4):1621-7.

43. Kim SG, Oh SY, Kwon HC, et al. A Phase II study of irinotecan with bi-weekly, low-dose leucovorin and bolus and continuous infusion 5-fiuorouracil (modified FOLFIRI) as salvagetherapy for patients with advanced or metastatic gastric cancer. Jpn J Clin Oncol. 2007;37(10):744-9.

44. Barone C, Basso M, Schinzari G, et al. Docetaxel and oxaliplatin combination in second-line treatment of patients with advanced gastric cancer. Gastric Cancer. 2007;10(2):104-11.

45. Lim JY, Cho JY, Paik YH, et al. Salvage chemotherapy with docetaxel and epirubicin for advanced/metastatic gastric cancer. Oncology. 2007;73(1-2):2-8.

17. APPENDICES

17.1. Cockcroft-GaultEquation

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

Conventional- serum creatinine in mg/dL:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age(in years)}] \times \text{weight (in kg)}}{\text{sennn creatinine (in mgldL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age(in years)}] \times \text{weight (in kg)}}{\text{sen.nu crea tinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units (SI) - serum creatinine in pmol/L:

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in year s)}] \times \text{weight (in kg)}}{\text{sennn creatinine (in µrnoVL)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{sennn creatinine (in µmoVL)} \times 72 \times 0.0\,113} \times 0.85$$

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

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

Table 17.1: Eastern Cooperative Oncology Group Performance Status Scale

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

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

17.3. Response Evaluation Criteria in Solid Tumors, Version 1.1

17.3.1. Measurability of Tumor at Baseline

17.3.1.1. Definitions

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

17.3.1.1.1. Measurable

- Tumor les ions: Must be accurately measured in at least **1** dimension (Longest diameter in the plane of measurement is to be recorded. Lymph nodes should be meas ured by the shortest diameter.) 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 accura tely measured with calipers should be recorded as non-measura ble)
  - 20 mm by chest X-ray (however lesion measurement by CT scan is preferable).
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 2:15 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 nodemeasurement.

17.3.1.1.2. Non-Measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 2'.:10 to <15 mm short axis), as well as truly non-measura ble lesions. Lesions considered truly non-measura ble include: leptomeningeal disease, ascites, pleural or pericardia! effusion, inflammatory breast disease, lymphangiticinvolvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurab le by reproducible imaging techniques.

17.3.1.1.3. Special Considerations Regarding Lesion Measurability

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

17.3.1.1.3.1. Bone Lesions

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

17.3.1.1.3.2. Cystic Lesions

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

17.3.1.1.3.3. Lesions with Prior Local Treatment

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

17.3.1.2. Specifications by Methods of Measurements

17.3.1.2.1. Measurement of Lesions

All measuremen ts should be recorded in metric notatio n, using cal ipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and NEVER more than 28 days of the first dose of study drug administration.

17.3.1.2.2. Method of Assessment

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

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

17.3.2. Tumor Response Evaluation

17.3.2.1. Assessment of Overall Tumor Burden and Measurable Disease

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

In this study, only subjects with measurab le disease at baseline should be included in the study.

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

Target lesions are all measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, 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 respect ively will be recorded).

Target lesions should be se lected 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, pathologica l nodes which are defined as measurable and may be identified as target les ions must meet the criterion of a sh01i axis of 2':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 x 30 mm has a short axis of 20 mm and qualifi es as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with sho1i axis 2':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 diam eter s will be used as reference to further characterise any objective tumor regression in the measura ble dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes sho uld 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 "unequivocalprogression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

17.3.2.3. Response Criteria

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

17.3.2.3.1. Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < l 0 mm.

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

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 demon strate an absolute increase of at least 5 mm (Note: the appearance of 1 or more new lesions is also considered progression). If investigator makes a clinical diagnosis that there has been progression, imaging examinations should be performed as promptly as possible, and effo rt should be made to obtain an imagebased assessment of PD.

SD: Neither sufficie nt shrink age to qualify for PR nor sufficient increase to qualify for **PD,** taking as reference the smallest sum diameters while on study.

17.3.2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured **in** the same anatom ica l p lane 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 impo1tant 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 O 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 surround ed by fat such as in the retroperitoneum ; ho wever,if a lymph node is believed to be present and is faintly seen but too small to meas ure, 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 erro r. 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 "frag ment," the longestdiameters ofthe fragmented portions should be added together to calculate the target les ion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

17.3.2.3.3. Evaluation of Non-target Lesions

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

CR: Disappearanceof 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). Overall tumor burden increases significantly enough to require a change in therapy.

If investigator makes a clinical diagnosis that there has been progression, imaging examinations should be performed as promptly as possible, and effort should be made to obtain an imagebased assessment of PD.

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

The concept of progression of non-target disease requires additional exp lanation 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 substa ntial 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 suf ficient to qualit y for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

17.3.2.3.5. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning tec hnique, 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 pa1ticularly imp01iant when the subject' s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be repo1ted on a CT scan rep01i as a " new" cystic lesion, which it is not.

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

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

17.3.2.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the EOT. Confirmatory measurement for CR, PR, or SD in Primary Cohort is not required. In Exploratory Cohort l and 2, confirm ato ry measureme nt for CR, PR, or SD is required in the study.

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

17.3.2.4.1. Time Point Response

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

Table 17.2: Overall Response: Subjects with Target (±Non-target) Disease

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

CR = Complete Response, PR= Partial Response, SD = Stable Disease, PD= Progressive Disease, and NE = Not Evaluable.

17.3.2.4.2. Missing Assessments and Inevaluable Designation

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

17.3.2.4.3. Best Overall Response: All Time Points

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

As for Primary Cohort, confirmation is not needed. But, as for Exploratory Cohorts 1 and 2 is needed. 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 SD). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, 6 weeks (±7 days). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

17.3.2.4.4. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "norm al " size (<l 0 mm), they may still have a meas urement reported on scans. This measurements hould 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 "symptomaticdeterioration." Every eff01t should be made to document objective progression eve n 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 dete rmined 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. lf at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progress ion was suspecte d.

17.3.2.5. Frequency of Tumor Re-evaluation

In this study, tumor measure ment will be conducted every 6 weeks (±7 days) after Day 1 of Cycle 1 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 suspecte d sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. How ever, 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. lf no clinical symptoms are observed, brain CT or MRI is not mandatory during st udy period. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

17.4. New York Heart Association Functional Classification

Table 17.3: New York Heart Association Functional Classification

Functio11a l Ca p acity	*O bj ective Assess m e nt*
***Class** I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina/ pain.*	***A.** No objective evidence of cardiovascular disease.*
***Class JI.** Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina/ pain.*	***B.** Objective evidence of minimal cardiovascular disease.*
***Class Ill.** Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or angina/ pain.*	***C.** Objective evidence of moderately severe cardiovascular disease.*
*Class **JV.** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the angina! syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.*	***D.** Objective evidence of severe cardiovascular disease.*

Source: American Heart Association, Inc. Classification of Functional Capacity and Objective Assessment. Available from:
http://my.americanheart.org/profess ional/Statemen tsG uide lines/B yPublicationDate/PreviousYears/Classifica tion-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

17.5. Quality of Life Questionnaires

17.5.1. FACT-G

f ΛCT-Ga (Version 4)

Below is a lis t of statemen ts that other people witb your illness bavc said are important. **Please** cir cle or ma r k one nu mber Iler line to indi ca te yo ur respons e as it a pplies to t he nast 7 da ys.

	PHYSICAL WELL-BEING	Nol Ill1111	A lillle bit	om e•	Quite n bit	Ver) mu ch
"	I have a lack of energy	0		2	3	-l
CI1"!	1have nausea	0		2	3	4
GP-\	Because of my physical condition, I hnvc trouble meeting the needs of my family	0		2	3	4
C,, ,	1 have pain	0		2	3	4
(Ip>\	I am bothered by side effects of treatment	0		2	3	4
''''	I feel ill	0		2	3	4
'', ,,	1am forced 10 spend time in bed	0		2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
,,,·'	1feel close to my friends	0		2	3	4
,····	1gel emotional support from rny family	0		2	3	4
''''	Iget support frommy friends	0		2	3	4
'''''	ly family has accepted my illness	0		2	3	4
,····	1am satisfied with fomily communication about my illness	0		2	3	4
c.v. .	I feel close to my partner (or the person who is my main support)	0		2	3	4
1)1	*!l<!ganlless ofyourcwre/11level of:,·e.rnal acrlrfly, please answer tlr ll followln[!. q1112srl011.lfyo11 prefer 1101ro a11swer Ir. please mark111/s box* D *and o ro r/Je ne .rrseer/on.*					
'''''	I am satisfied with my sex life	0		2	3	4

FACT-Ga (Ve rsion 4)

Pl eas e ci r cl e o r m a r k o ne nu m b er pe r li ne to ind ica te yo ur re spo nse as it a p11lies to the pa st 7 da vs.

EMOT IO NAL W ELL-BE ING	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel sad	0		2	3	4
I am satisfied with how I am coping with my illness.	0		2	3	4
I am hopeful hope in the fight against my illness	0		2	3	4
I feel nervous	0		2	3	4
I worry about dying	0		2	3	4
I worry that my condition will get worse	0		2	3	4

FUNCTIONAL WELL-BEING	Not at all	A lit tle bit	So me-what	Quite a bit	Very much
I am able10 work (include work at home)	0		2	3	4
My work (include work at home) is fulfilling	0		2	3	4
I am able to enjoy life	0		2	3	4
I have accepted my illness	0		2	3	4
I am sleeping well	0		2	3	4
I am enjoying the things I usually do for fun	0		2	3	4
I am content with the quality of my life right now.	0		2	3	4

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FACT-Ga (Version 4)

Please circle or mark one numb er per line to indicate your response as it alJplies to the past 7 davs.

	ADDITIONAL CONCERNS	Not at all	A lit1le bit	Some-what	Quite a bit	Ve , mu ch
c,	I am losing weight	0		2	3	4
"'|	I havea loss of appetite	0		2	3	4
('a'.!	I am bothered by reflux or heartburn	0		2	3	4
H.'1	*I* a m able to eat the foods that I like	0		2	3	4
.....	T have discomfort or pain when I eat	0		2	3	4
""	I have a feeling of fullness or heaviness in my stomach area	0		2	3	4
c 1	I have swelling or cramps in my stomach area	0		2	3	4
Go , 1	I have rrouble swallowing food	0		2	3	4
""	I a m bothered by a change in my eating habits	0		2	3	4
• •	I am able to enjoy meals with family or friends	0		2	3	4
Go 19	My digestive problems interfere with my usual activities	0		2	3	4
c••	T a void going out to eat because of my illness	0		2	3	4
"""	I *have* stomachproblems that worry me	0		2	3	4
"'"	I havediscomfort or pain in my stomach area	0		2	3	4
c.. u	ram bothered by gas (natulence)	0		2	3	4
cs	I have diarrhea (diarrhoea)	0		2	3	4
"'I	I feel tired	0		2	3	4
••	I feel weak all over	0		2	3	4
"""	Beca use of my illness, I have difficulty planning for the future	0		2	3	4

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17.5.2. EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about **D**
I have slight problems in walking about **D**
I have moderate problems in walking about **D**
I have severe problems in walking about **D**
I am unable to walk about **D**

SELF-CARE

I have no problems washing or dressing myself **D**
I have slight problems washing or dressing myself **D**
I have moderate problems washing or dressing myself **D**
I have severe problems washing or dressing myself **D**
I am unable to wash or dress myself **D**

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities **D**
I have slight problems doing my usual activities **D**
I have moderate problems doing my usual activities **D**
I have severe problems doing my usual activities **D**
I am unable to do my usual activities **D**

PAIN / DISCOMFORT

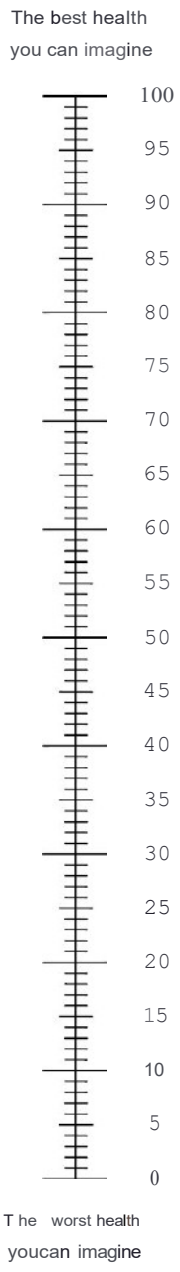
I have no pain or discomfort **D**
I have slight pain or discomfort **D**
I have moderate pain or discomfort □
I have severe pain or discomfort D
I have extreme pain or discomfort □

ANXIETY / DEPRESSION

I am not anxious or depressed **D**
I am slightly anxious or depressed **D**
I am moderately anxious or depressed D
I am severely anxious or depressed **D**
I am extremely anxious or depressed **D**

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from Oto 100.
- 100 means the best health you can imagine.
  0 means the worst health you canimagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY= D



17.6. Instructions Related to SARS-CoV-2

Due to the potential impact of SARS-CoV-2, ie COVID-19, on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspecte d SARS-CoV-2 while being treated with DS-820l a. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 4.03 general grading criteria to evaluate SARS-CoV-2** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

17.6.1. Dose Modification Criteria for Suspected or Confirmed SARS-CoV-2

If SARS-CoV-2 infection is suspected, interrupt DS-820 l a and rule out SARS-CoV-2 per local guidance.

- If SARS-CoV-2 is ruled out, follow study protocol.
- If SARS-CoV-2 is confirmed or is still suspected after eva luation fo llow dose modification as outlined in Tab le 17.4 below and manage SARS-CoV-2 per local guidance until recovery of SARS-CoV-2. SARS-CoV-2 recovery is defined as no signs/symptoms of SARS-CoV-2, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

Table 17.4: SARS-CoV-2Dose Modification Criteria

SARS-CoV-2 Worst Toxicity NCI-CTCAE Version 4.03 Grade	Schedule Modification for DS-8201a
Grade 1	Resume study drug at the same dosea
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved" Reduce by 1 dose level if chest CT findings are nearly resolved
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved Discontinue study drug if chest CT findings are **not** complete ly resolved
Grade 4	Discontinue study drug

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

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

In addition to the recommendations outlined in Table 17.4, investigators may consider dose modifications of the study drng according to the subject' s condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline

17.6.2. Prior and Concomitant Medications- Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 5.5.3).
  - If treatment is absolutely required for SARS-CoV-2, DS-820la must be interrupted.
  - If administered, then a washout period ofno lessthan 14 days is required before resumption ofDS-8201a.

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

Additional PK serum samples should be collected, if chloroquine or hydroxychloroquine is administered for SARS-CoV-2 infection, at the time points specified in the Schedule of Events (Table 8.3).

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

17.6.4. SARS-CoV-2 Assessment(s)

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

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

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

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

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

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

18. SCHEDULE OF EVENTS

18.1. Schedule of Events for Subjects Receiving DS-8201a

This safety monitoring is also applied if suspected ILD/pneumonitis occurs at EOT and during Follow-up.

	Tissue Screen	SC R	Cycle I					Cycle 2			Cycle 3					Cycle 4 and subsequent cycles Day 1		EOT (a)	F/U (b)	Q3M F/U (±14 days)
			Day I		Day 8	Day 15	Day 22	Day I		Day 22	Day I		Day 8	Day 15	Day 22					
			Bl	EOI	(± 1 day)	(± 1 day)	(±2 days)	Bl	EOI	(±2 days)	Bl	EOI	(±3 days)	(±3 days)	(±2 days)	Bl	EOI			
Informed Consent	●	●																		
Tumor sample for tissue screenin"	●																			
Fresh biopsy tumor sample for HER2 Status, RNA expression, addional biomaker assessment (c)		●																●		
Administer DS-820 la (d)			●					●			●					●				
Contact IXRS (e)	●	●	●					●			●					●		●		
Medical history /Primary Cancer historv/Demograohic		●																		
Vital Signs		• ct)	• cg	●	●	●		• cg	'		• <g)	●				• cg)		●	●	
Physical Examination		• cQ	• cg					• <g			• <g)					• cgl		●	●	
SpO 2		• cQ	• cg					• cg			• <g)					• cg		●	●	
H e ight		• cQ																		
Weight, ECOG PS		• ct)	. (g)					• cg			• <g)					• cg)		●	●	
Laboratory Tests		• cQ	• cg		●	●		• <g			. (g)					• cgl		●	●	

	Tissue Screen	SCR	Cycle 1					Cycle 2			Cycle 3					Cycle 4 and subsequent cycles Day I		EOT (a)	F/U (b)	Q3M F/U (±14 days)
			Day I		Day 8	Day IS	Day 22	Day 1		Day 22	Day I		Day 8	Day IS	Day 22					
			BI	EOI	(±1 day)	(±1 day)	(±2 days)	Bl	EOI	(±2 days)	BI	EOI	(±3 days)	(±3 days)	(±2 days)	BI	EOI			
Tro p on in(h)		• <l)		●					●			●						• (h>		
Blood Samples for cfDNA			• <g													• <g,i)		●		
Pharmacogenomics Blood Sample			. (j)																	
PK Blood Sample (x)			. (k	e (l,m)	●	●	e (n)	• 0c)	• 0>	e (o)	e (k)	e (l,m)	●	●	e (n)	e (k)	. (l)			
ADA Blood Sample			e (o)					e (o)								e (o)			●	. (p)
Blood Sample for HER2ECD(y)			. (g)								• <gq,)					• <g,v		●		
Urinalysis		• <l)																		
EC HO o r MUGA (L VEF) (r)		e (s)														• <t)		●		
12-lead ECG in triplicate (u)		• <l)	. (g)					• <gl			• <g)					. (g)		●		
Ophthalmologic Assessments(v)		e (s)						e (v)												
Pregnancy Test		• <l)																●		
EQ-5 D-SL, FACT-Ga(w)			e (w)															●		
Tumor Assessment		• CS)	E very 6 weeks (±7 days)from Cycle I Day I until PD, starting new anticancer treatment, or withdrawal of consent by subject regardless of Post Treatment Follow-up period															●		
Concomitant Medications		●																		
AEs		●																		
Survival Follow-up																				●

SCR: screening, F/U: follow-up, BI: before infusion, EOI: end of infusion, EOT: end of treatment
a The date when the investigator decides to discontinue study treatment (+7 days)
b 40 days (+7 days) after the last study drug administration or before startingnew anticancer treatment, whichever comes first

c The subject who has a tumor amenable to biopsy undergo a fresh tumor biopsy. If not amenable, the investigator must document why not amenable. If fresh tumor has been already submitted for this study and no chemotherapy or immunotherapy was conducted, re-submission is not necessary.
d DS-820la is to be administered every 3 weeks (Cycle allowance is ±3 days) unless discontinuation criteria are required.
e Eligible subjects will be registered using IXRS. The subject is recorded as ineligible in the IXRS if a screen failure
f Within 14 days before registration
g Within 3 daysbefore administration
h Collect blood samples for troponin (preferably high-sensitivity troponin-T) at Screening, EOT and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis (Refer to section 6.2.4).
i Samples will be collected at BI on Day 1 of Cycle 1, Cycle 4, and EOT for ctDNA in plasma
j Participation in this part of the study is optional for all subjects.
k Within 8 hours BI on Day l of each cycle until Cycle 4 and then every 2 cycles until Cycle 8 (eg, Cycle l, 2, 3, 4, 6, 8).
1 Within 15 minutes ofEOI on Day 1 of each cycle until Cycle 4 (eg, Cycle 1, 2, 3 and 4) and then on Day 1 of Cycle 6 and Cycle 8.
m4 h and 7 h after the start of administration(±15 minutes)
n If treatment of the next cycle is delayed for 3 days or longer, or the subject is discontinued, collect a PK blood sample on this day (±2 days)
o Within 8 hours BI on Day 1 of Cycle l, 2 and 4, and then every 4 cycles
p For subjects with positive ADA at the F/U visit, additional serum ADA samples may be collected every 3 months (±14 days) up to l year after the last dose of the study drug, or until the ADA becomes negative, or until the ADA titer becomes less than the baseline (applicable when pre-existing ADA was observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
q Before administration at every 2 cycles from Cycle 3 (eg, Cycle 3, 5, 7, 9...)
r If meet dose reduction criteria, additional test is required within 3 weeks
s Within 28 days before registration.
t ECHO or MUGA scan assessments (note: the same test must be used for the subject throughout the study) will be performed at Screening and Day l of Cycle 5 and then every 4 cycles (±7 days) (eg, Cycle 5, 9, 13...)
u ECG will be taken in triplicate in close succession at screening. Subsequent ECGs in triplicate will be performed at Day l of Cycle 5 and then every 4 cycles (±7 days) (eg, Cycle 5, 9, 13...), EOT and if an abnormality is noted. ECGs will be taken while in a supine/semi-recumbent position.
v Ophthalmologic assessments will be performed at Screening and EOT and as clinically indicated
wTo be completed on Day 1 before any tests/seeing Investigator, Day 15 (±1), the every 6 weeks from the beginning of the study (eg, Day 43 (±7), 85 (±7), 127 (±7), etc.), and EOT. EQ-5D-5L questionnaire to be completed first and then FACT-Ga questionnaire. PRO could be collected in only Primary Cohort.
x: In case of administration of chloroquine/hydroxychloroquine, perform PK sampling according to the following schedule: pre-dose on Day I of chloroquine/hydroxychloroquine administration,pre-dose on Day 3 or Day 4 (within 4 hours), end of chloroquine/hydroxychloroquine treatment (within 4 hours), and after washout period pre-dose on the day of restarting study treatment (within 8 hours)
y: A portion ofHER2ECD blood sample from each subject who provides consent will be used for future central lab analysis for SARS-CoV-2 testing. SARS-CoV-2 testing will be conducted every 4 cycles from Cycle 5 (Cycles 5, 9, 13, etc) and EOT.

For suspected ILD/pneumonitis, treatment with study drug should be interruptedpending evaluation. Evaluations should include:
- high resolution CT
- pulmonologist consultation(Infectious Disease consultationas clinically indicated)
- blood culture and CBC. Other blood tests could be considered as needed

- consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- pulmonary function tests and pulse oximetry (Sp02)
- arterial blood gases if clinically indicated
- one blood sample collection for PK and analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

18.2. Schedule of Events for Subjects Receiving the physician's choice treatment

This safety monitoring is also applied if suspected ILD/pneumonitis occur at EOT and during Follow-up.

	Tissue Screen	SC R	Treatment Period	EOT (a)	F/ U (b)	QJM F/U (±14 days)
Informed Consent	●	●				
Tumor sample for tissue screening						
Fresh biopsy tumor sample for HER2 Status, RNA expression, addional biomaker assessment (c)		●				
Contact IXRS (d)	●	●	●	●		
Administer the physician' s choice treatment		●	e (e)			
Medic.al history!Primary Cancer history/Demographic						
Height		e (f)				
Vital Signs		. (f)	At administration of physician's choice treatment	●	●	
Physical Examination						
SpO2					●	
Weight, ECOG PS					●	
Laboratory Tests					●	
12-lead ECG in triplicate (g)						
Urinalysis		• <f)				
Tropon in		• <f)		e (h)		
Pregnancy Test		• <f)				
ECHO or MUGA (LVEF)		• <i)				
Ophthalmo logic Assessments		• <i)				
EQ - 5 D- S L, FACT-Ga			• u)	• u)		
Tumor Assessment		• <i)	Every 6 weeks (±7 days) from the day of fisrt dosing until PD, starting new anticancer treatment, or withdrawal of consent by subject regardless of Post Treatment Follow-up period	●		
Concomitant Medications						

	Tissue Screen	SCR	Treatment Period	EOT(a)	F/U (b)	QJM F/U (±14 days)
AEs			●			
Survival Follow-up						●

SCR: screening, F/U: follow-up, BI: before infusion, EOI: end of infusion, EOT: end of treatment
a The date when the investigator decides to discontinue study treatment (+7 days)
b 40 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first
c The subject who has a tumor amenable to biopsy undergo a fresh tumor biopsy. If not amenable, the investigator must document why not amenable. If fresh tumor has been already submitted for this study and no chemotherapy or immunotherapy was conducted, re-submission is not necessary.
d Eligible subjects will be registered using IXRS. The subject is recorded as ineligible in the IXRS if a screen failure.
e Subjects receive the physician's choice treatment irinotecan monotherapy or paclitaxel monotherapy
f Within 14 days before registration
g ECG will be taken in triplicate in close succession at screening, EOT, and if an abnormality is noted. ECGs will be taken while in a supine/semi-recumbent position.
h Collect blood samples for troponin (preferably high-sensitivity troponin-T) at Screening, EOT and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis (Refer to section 6.2.4).
i Within 28 days before registration.
j To be completed on Day 1 before any tests/seeing Investigator, Day 15 (±1), the every 6 weeks from the beginning of the study (eg, Day 43 (±7), 85 (±7), 127 (±7), etc.), and EOT. EQ-5D-5L questionnaire to be completed first and then FACT-Ga questionnaire.

For suspected ILD/pneumonitis, treatment with study drug should be interrupted pending evaluation. Evaluations should include:
- high resolution CT
- pulmonologist consultation (Infectious Disease consultation as clinically indicated)
- blood culture and CBC. Other blood tests could be considered as needed
- consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- pulmonary function tests and pulse oximetry (SpO_2)
- arterial blood gases if clinically indicated

Other tests could be considered, as needed.