CLINICAL STUDY PROTOCOL

A PHASE 2, OPEN-LABEL, SINGLE-ARM TRIAL OF TRASTUZUMAB DERUXTECAN IN HER2-POSITIVE, UNRESECTABLE OR METASTATIC GASTRIC OR GASTRO-ESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMA SUBJECTS WHO HAVE PROGRESSED ON OR AFTER A TRASTUZUMAB-CONTAINING REGIMEN

DS8201-A-U205

IND NUMBER 136179

EudraCT NUMBER 2019-001512-34

VERSION 2.0, 28 JULY 2020

DAIICHI SANKYO INC.

INVESTIGATOR AGREEMENT

A Phase 2, open-label, single-arm trial of trastuzumab deruxtecan in HER2-positive, unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Senior Director, Global Oncology R&D	
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

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

DOCUMENT HISTORY

Version Number	Version Date
1.0	23 April 2019

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 2.0 (dated 28 July 2020) vs. protocol Version 1.0 (dated 23 April 2019) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS8201-A-U205 clinical study protocol (Version 2.0) by section.

Amendment Rationale:

This amendment is primarily driven by the updated safety information and to incorporate Coronavirus disease 2019 (COVID-19) associated directives/guidance. Other minor changes are administrative and/or editorial.

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of subjects nor the scientific value of the study.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES

All locations (Section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.

Minor edits, such as update to language that does not alter original meaning, update to version numbering, formatting, change in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or change in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis	This section was updated	To align with clinical and safety changes
1.1.2.2. Clinical Experience in Gastric Cancer	This section was updated with the latest available efficacy results	To provide supporting evidence of increased clinical experience in gastric cancer
1.1.2.3.3. Interstitial Lung Disease/Pneumonitis	This section was updated	To align with the latest safety information
1.1.2.3.3.1. Left Ventricular Ejection Fraction Decrease	This section was updated	To align with the latest safety information
1.1.2.6. Clinical Pharmacokinetics	This section was updated	To provide the latest available pharmacokinetic (PK) data
2.3.3. Other Secondary Efficacy Endpoint(s)	The definitions of progression-free survival (PFS) and OS (overall survival) were updated	To align with the latest protocol template information
2.3.4	Cell-free RNA (cfRNA) was included for biomarker analysis	To include testing for cfRNA

Section # and Title	Description of Change	Brief Rationale
Exploratory Endpoints		
2.3.7 Health Economic and Outcomes Research Endpoints	"Health care resource utilization (hospitalization-related records)" was deleted from list of Health Economic and Outcomes Research (HEOR) endpoints based on patient-reported outcomes (PROs)	To remove an unrequired endpoint
Protocol Synopsis 3.1.1. Overview 3.2 Discussion of Study Design	The sample size was updated. The number of sites was updated to approximately 45. The countries, Australia and Israel were removed from the list of geographical sites.	To accommodate dropouts or losses to follow-up
Figure 3.1 Study Design Schema	The study design schema was updated.	To provide clarification
Protocol Synopsis 3.1.2. Duration of the Study	The duration of recruitment of subjects to the study was increased from 12-18 months to 18-24 months. The anticipated duration of the study was increased from 24-30 months to 30-36 months as countermeasure to minimize COVID-19 impact on patient recruitment.	To align with clinical changes
3.1.3. Duration of Subject Participation	This section was updated	To provide clarification
3.1.4. Definition of the End of the Study	This section was updated	To provide clarification
4. Study Population	This section was updated	To provide clarification
Protocol Synopsis 4.1. Inclusion Criteria	Criterion no. 5 was updated. Criteria nos. 10, 11, 12 and 13 were presented in a table as a single criterion no. 8. For criterion no. 10, the contraception period was changed to "7 months for female and 4 months for males" and the paragraph describing menopausal women on hormone replacement therapy was removed. Criterion no. 13 was added	To align with the latest safety information

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis 4.2 Exclusion Criteria	Criteria nos. 2, 5, 12, 14, 17 and 18 were updated. Criteria nos. 4 and 20 were deleted. Criteria nos. 19 and 24 were added.	To align with the latest safety information
Table 5.1 Management guidelines for Trastuzumab Deruxtecan	Modification guidelines for changes in troponin levels were removed.	To align with the latest safety information
5.1.5 Re-screening Procedures	This section was updated	To provide clarification
5.2.1. Description 5.2.3. Preparation	The description of determining dose based on body weight was updated	To provide clarification
5.2.6. Drug Accountability	This section was updated	To provide clearer instructions to the site
5.4. Dose Interruptions and Reductions	This section was updated	To provide clarification
5.4.1. Guidelines for Dose Modifications	This section was updated	To align with the latest safety information
Table 5.1 Management Guidelines	Guidelines for managing cardiac, pulmonary and hepatic toxicities were updated	To align with the latest safety information
5.6. Concomitant Medications, Treatments, and Procedures	This section was updated	To align with the latest safety information
6.1. Tissue Screening	This section was updated	To provide clarification
6.2. Screening (Day -28 to Day -1)	This section was updated.	To provide clarification and to align with the latest safety information
6.3 Treatment Period	This section was updated	To provide clarification and to align with the latest safety information
6.4	This section was updated	To provide clarification and

Section # and Title	Description of Change	Brief Rationale
End of treatment Visit		to align with the latest safety information
6.5.2. Long-term/Survival Follow-up (Every 3 Months ±14 Days)	This section was updated	To align with the latest safety information
6.6 Additional PK Assessments due to COVID-19 Infection Table 8.2 Schedule of PK Sample Collections in Case of Chloroquine and Hydroxychloroquine Treatment	This section and table were added	To monitor potential drug-drug interactions between investigational/study drug treatment and COVID-19 specific treatment
7. Efficacy Assessments	This section was updated	To provide clarification
7.2.1. Key Secondary Efficacy Endpoint	The definition of PFS was updated	To provide clarification
8.3.3. Immunogenicity (Anti-drug Antibodies)	The last paragraph in this section was updated	To clarify the anti-drug antibodies (ADA) testing
9. Safety Evaluation and Reporting	Several of the sub-sections in this section were updated	To align with the latest safety information
Protocol Synopsis 11.1 General Statistical Considerations 11.3. Study Population Data 11.4 Efficacy Analysis	Intent to treat (ITT) was changed to Full Analysis Set (FAS)	To accommodate a change in convention
11.6.1. Pharmacokinetic Analyses	This section was updated	To provide clarification.

Section # and Title	Description of Change	Brief Rationale
11.6.3. Biomarker Analyses	This section was updated	To provide clarification.
11.7.1 Adverse Event Analyses	The definition of treatment-emergent adverse event (TEAE) has been updated	To align with the latest safety information
Protocol Synopsis 11.8 Sample Size Determination	This section was updated	To provide clarification
Table 17.1 Schedule of Events	The table was updated	To provide clarification To align with the latest safety information
17.7 Instructions Related to COVID-19	This section was added	To provide management guidelines for COVID-19
Throughout the protocol	The words, “enrolled and enrollment” were replaced in most places by ‘first dose’ or ‘recruit(ment)’	To provide clarification and avoid confusion when describing the timing of events

PROTOCOL SYNOPSIS

EudraCT:	2019-001512-34
IND Number:	136179
Protocol Number:	DS8201-A-U205
Investigational Product:	Trastuzumab deruxtecan (also known as fam-trastuzumab deruxtecan)
Active Ingredient(s)/INN:	Trastuzumab deruxtecan consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA-1181a/ trastuzumab deruxtecan
Study Title:	A Phase 2, open-label, single-arm trial of trastuzumab deruxtecan in HER2-positive, unresectable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma subjects who have progressed on or after a trastuzumab-containing regimen
Study Phase:	Phase 2
Indication Under Investigation:	Unresectable or metastatic gastric or GEJ adenocarcinoma that has progressed on or after a trastuzumab-containing regimen
Study Objectives:	Primary objective: • To investigate the efficacy of trastuzumab deruxtecan based on the confirmed objective response rate (ORR) by independent central review by using Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 Secondary objectives: • To evaluate the efficacy of trastuzumab deruxtecan on progression-free survival (PFS), based on independent central review using RECIST v1.1. Other secondary objectives are: • To further evaluate the efficacy of trastuzumab deruxtecan by using the endpoint of OS • To further evaluate the efficacy of trastuzumab deruxtecan by using RECIST v1.1 for endpoints of PFS and ORR based on Investigator assessment, and duration of response (DoR) based on independent central review and Investigator assessment

	• To determine the pharmacokinetics (PK) of trastuzumab deruxtecan in serum • To further evaluate the safety of trastuzumab deruxtecan based on treatment-emergent adverse events (TEAEs) and anti-drug antibodies (ADAs) • To evaluate Health Economics and Outcomes Research (HEOR) endpoints based on patient-reported outcomes (PROs) Exploratory objectives: To evaluate the following: • Disease control rate (DCR), based on independent central review and Investigator assessment • Time to response, based on independent central review and Investigator assessment • Best percentage change in the sum of diameters of measurable tumors • Predictive, prognostic, and pharmacodynamics exploratory biomarkers in tissue samples and blood, and their association with disease status and/or response to treatment
Study Design:	This is an open-label, single-arm, multicenter Phase 2 study to evaluate the efficacy and safety of trastuzumab deruxtecan in unresectable or metastatic gastric cancer or GEJ previously treated with a trastuzumab-containing regimen. The sample size will be approximately 80subjects, recruited at approximately 45 study sites including but not limited to North America and the European Union (EU).
Study Duration:	Recruitment of subjects is planned to occur over approximately 18 to 24 months. Subjects will be treated until progression of disease or until withdrawal of treatment due to other reason. For each subject, there will be a 40-day (+7 days) Follow-up Visit after the last study drug administration or before starting new anticancer treatment, whichever comes first. This will be followed by Long-term/Survival Follow-up Visits every 12 weeks (±14 days) from the date of the 40-day (+7 days) Follow-up Visit, until death, withdrawal of consent, or loss to follow-up, whichever occurs first. Tumor assessment will be performed every 6 weeks (±7 days) from Cycle 1 Day 1 in the first year and every 12 weeks (±7 days) thereafter until objective disease progression (based on radiologic assessment) or until start of new anticancer treatment, if patient discontinues study treatment for any reason other than disease progression.

	The end of the study will occur when all subjects have either completed their last scheduled visit or died or withdrawn from study participation or move into another study or the Sponsor's decides to discontinue the study. This is anticipated to occur approximately 12 months after the last subject's first dose. The anticipated duration of the study is at least 30 to 36 months.
Study Sites and Location:	Approximately 45 sites possibly including but not limited to North America and the EU. Other countries may also be considered.
Subject Eligibility Criteria:	<u>Key Inclusion Criteria</u>: • Men or women ≥18 years old (Please follow local regulatory requirements if the legal age of consent for study participation is >18 years old.) • Has pathologically documented gastric or GEJ cancer that is: – Unresectable or metastatic – Centrally confirmed HER2-positive disease (immunohistochemistry [IHC]3+, IHC2+/in-situ hybridization [ISH]+) as determined according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines new tumor biopsy obtained after progression on or after a first-line trastuzumab-containing regimen. If a tumor biopsy was already collected after discontinuation of first-line treatment with a trastuzumab-containing regimen, it is acceptable to consider the biopsy to be a new biopsy for the purpose of this study, provided that there is sufficient tissue for exploratory biomarker studies. • Has experienced disease progression during or after first-line therapy with a trastuzumab-containing regimen (brand or approved biosimilar). – Note: Prior adjuvant therapy with a trastuzumab-containing regimen can be counted as a line of therapy if the subject progressed on or within 6 months of completing adjuvant therapy. • Has at least 1 measurable lesion per RECIST v1.1 as confirmed by the investigator review.

- Has left ventricular ejection fraction (LVEF) ≥50% within 28 days before first dose per echocardiogram (ECHO)/multigated acquisition (MUGA) scan.
- Has adequate organ function within 14 days before randomization, defined as:

Parameter	Laboratory value
Adequate bone marrow function	
Platelet count	≥ 100 000/mm^3 (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin	≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count (ANC)	≥ 1500/mm3 (granulocyte colony-stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment)
Adequate renal function	
Creatinine	Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation*
Adequate hepatic function	
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)	≤ 5 × the upper limit of normal (ULN)
Total bilirubin	≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
Serum Albumin	≥ 2.5 g/dL
Adequate blood clotting function	
International normalized ratio (INR) / Prothrombin time (PT) and activated partial	≤ 1.5 × ULN

thromboplastin time (aPTT)	

*Cockcroft-Gault equation:

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

- Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months for females and 4 months for males after the last dose of study drug.

Key Exclusion Criteria:

- Use of anticancer therapy after first-line treatment with a trastuzumab-containing regimen.
- Uncontrolled or significant cardiovascular disease, including any of the following:
  - History of myocardial infarction (MI) within 6 months of first dose
  - History of symptomatic congestive heart failure (New York Heart Association Class II to IV)
  - Troponin levels consistent with MI as defined according to the manufacturer within 28 days prior to first dose
  - Corrected QT interval (QTc) prolongation to >470 ms (females) or >450 ms (male) based on Screening triplicate 12-lead electrocardiogram (ECG)
- History of (non-infectious) interstitial lung disease (ILD)/ pneumonitis that required corticosteroid therapy or has current ILD /pneumonitis or is suspected to have such diseases by imaging during Screening.
- Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of the first dose, severe asthma, severe chronic obstructive pulmonary disease (COPD), restrictive lung disease, pleural effusion etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjogren's, sarcoidosis, etc.), or prior pneumonectomy.

	• Pleural effusion, ascites, or pericardial effusion that requires drainage, peritoneal shunt, or Cell-free and Concentrated Ascites Reinfusion Therapy (CART). (Drainage and Cell-free and CART are not allowed within 2 weeks prior to or during Screening.) • Spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. – Subjects with clinically inactive brain metastases may be included in the study. – Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study recruitment (1 week for stereotactic radiotherapy).
Dosage Form, Dose and Route of Administration:	Trastuzumab deruxtecan for injection 100 mg, Lyo-DP: a trastuzumab deruxtecan sterile lyophilized powder containing 100 mg of trastuzumab deruxtecan in a glass vial. The drug for intravenous (IV) infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight (BW) in a volume of 100 mL, by the study site pharmacist. The study drug will be administered as an IV infusion every 3 weeks (Q3W), initially for at least 90 minutes, and, if there is no infusion-related reaction (IRR), for at least 30 minutes thereafter. In case an IRR occurred at the first infusion, all subsequent infusions will be over at least 90 minutes. The starting dose of trastuzumab deruxtecan will be 6.4 mg/kg
Study Endpoints:	<u>Primary Endpoint (ie, primary outcome measure):</u> • Confirmed ORR, based on independent central review <u>Key Secondary Endpoint:</u> • PFS, based on independent central review <u>Other Secondary Endpoints</u> • PFS, based on Investigator assessment • ORR, based on Investigator assessment • OS

- DoR, based on independent central review and Investigator assessment

Exploratory Endpoints

- DCR, based on independent central review and Investigator assessment
- Time to response, based on independent central review and Investigator assessment
- Best percentage change in the sum of diameters of measurable tumors
- Serum extracellular domain of HER2 (HER2ECD)
- Biomarker analysis using cell-free deoxyribonucleic acid (cfDNA) and cell-free ribonucleic acid (cfRNA)

Health Economic and Outcomes Research Endpoints:

- European Organization for Research and Treatment of Cancer 5-dimension 5-level quality-of-life questionnaire (EORTC EQ-5D-5L)
- Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) questionnaire

Pharmacokinetic Endpoints:

- Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a
- Cmax, Tmax, AUClast, AUC21d, and, if appropriate, AUCinf, t1/2, CL, and Vss for each of the components

Safety Endpoints:

- Serious adverse events (SAEs)
- TEAEs
- Drug-related TEAEs
- Discontinuations due to adverse events (AEs)
- Adverse events of special interest (AESIs)
- Physical examination findings
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Vital sign measurements
- Standard clinical laboratory parameters

	• ECG parameters • ECHO/MUGA scan findings • ADAs
Planned Sample Size:	On the basis of historical data of current standard of care (SoC), western patients with second-line gastric or GEJ cancer have reported best ORR of ~27%. Seventy-two subjects provide a 90% power to achieve a lower limit of 95% confidence interval (CI) for the ORR that exceeds 27% (threshold) under the expected ORR of 45%. When potential dropouts are taken into consideration, approximately 80 subjects (planned sample size) will be recruited. The sample size computation was performed by using EAST v6.4.
Statistical Analyses:	Analysis Population: Full Analysis Set (FAS) will include all subjects who were recruited and have received at least 1 dose of the study drug. (This is the same as the Safety Analysis Set.) Response Evaluable Set will include recruited subjects who took at least 1 dose of trastuzumab deruxtecan, had measurable disease at baseline per independent central review, and had at least 1 postbaseline tumor assessment. Safety Analysis Set will include all recruited subjects who received at least 1 dose of study drug. PK Analysis Set will include all recruited subjects who received at least 1 dose of study drug and had measurable serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and/or MAAA-1181a. Primary Efficacy Analyses: The primary analyses will be on ORR (the sum of a best response of complete response (CR) rate and partial response (PR) rate) as assessed by independent central review based on RECIST v1.1. The estimate of ORR and its 2-sided 95% exact CI will be provided by using Clopper-Pearson method. The primary efficacy analysis will be performed on the basis of the ITT population and repeated on the Response Evaluable Set as a supportive analysis. Secondary Efficacy Analyses: • PFS, based on independent central review and Investigator assessments will be summarized separately with the median event time and its 95% CI using Brookmeyer and Crowley method.

- OS will be summarized with the median event time and the 95% CI.
- ORR, based on Investigator assessment will be analyzed in the similar approach as used for the primary endpoint.
- An additional secondary efficacy endpoint is DoR, based on independent central review and on Investigator assessment. This endpoint will be summarized with the median event time and its 95% CI using Brookmeyer and Crowley method.

Interim Analyses (optional):

There is no plan for an interim analysis.

Safety Analyses:

SAEs, TEAEs, drug-related TEAEs, AESIs, discontinuations due to AEs, physical examination findings, ECOG PS, vital sign measurements, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA scan findings, and ADAs. TEAEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.[44] Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Health Economic and Outcomes Research Analyses (optional):

The HEOR endpoints based on the following PRO questionnaires will be summarized: FACT-GA and EORTC EQ-5D-5L.

Pharmacokinetic Analyses:

Descriptive statistics will be provided for all serum concentration data (trastuzumab deruxtecan, total anti-HER2 antibody, and/or MAAA-1181a) at each time point and PK parameters.

The population-PK analysis to evaluate the effect of intrinsic and extrinsic factors of trastuzumab deruxtecan, and if appropriate, total anti-HER2 antibody, and MAAA-1181a will be characterized including available PK data from the other trastuzumab deruxtecan clinical trials.

After establishment of the population-PK model, a population-PK/pharmacodynamic model may be developed to evaluate the relationship between exposure and efficacy and toxicity. The results of the nonlinear mixed effects population-PK and population-PK/pharmacodynamic models may be reported separately from the clinical study report.

Biomarker Analyses:

New tissue (taken after progression on or after first-line treatment with a trastuzumab-containing regimen) will be required for confirmation of

	HER2-positive disease (IHC3+ or IHC2+ and evidence of HER2 amplification by ISH), as well as exploratory biomarkers for eligibility assessment. A biopsy on treatment at the end of Cycle 3 prior to Cycle 4 Day 1 infusion (up to 7 days prior to start of Cycle 4) and at the end of treatment is required. At least 2 cores are requested but, if the risk of biopsy complications from a second biopsy is unacceptable (at the discretion of the Investigator), then a single biopsy core will suffice. Biomarkers will be summarized using descriptive statistics.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ASCO-CAP	American Society of Clinical Oncology – College of American Pathologists
AST	aspartate transaminase
AUC	areas under the plasma concentration-time curves
AUC21d	area under the plasma/serum concentration-time curve from time 0 to 21 days
AUCinf	area under the plasma/serum concentration-time curve from time 0 extrapolated to infinity
AUClast	area under the plasma concentration-time curve, from time 0 to last point with quantifiable concentration
BI	before infusion
BW	body weight
CART	Cell-free and Concentrated Ascites Reinfusion Therapy
cfDNA	cell-free deoxyribonucleic acid
cfRNA	cell-free ribonucleic acid
CI	confidence interval
CL	clearance
Cmax	maximum plasma/serum concentration
COVID-19	coronavirus disease 2019
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
DCO	data cutoff

ABBREVIATION	DEFINITION
DCR	disease control rate
DNA	deoxyribonucleic acid
DoR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	Electronic Data Capture
EIU	Exposure in Utero
EORTC EQ-5D-5L	European Organization for Research and Treatment of Cancer 5-dimension 5-level patient-reported outcome questionnaire
EOT	end of treatment
EQ-VAS	EuroQual quality-of-life visual analogue scale
EU	European Union
FACT-Ga	Functional Assessment of Cancer Therapy-Gastric
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FISH	fluorescent in-situ hybridization
GC	gastric cancer
GCP	Good Clinical Practice
GEJ	gastro-esophageal junction
HEOR	Health Economics and Outcomes Research
HER2	human epidermal growth factor receptor 2
HER2ECD	extracellular domain of human epidermal growth factor receptor 2
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form

ABBREVIATION	DEFINITION
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IHC	immunohistochemistry
ILD	interstitial lung disease
IQR	interquartile range
IRB	Institutional Review Board
IRR	infusion-related reaction
ISH	in-situ hybridization
ITT	intent to treat
IV	intravenous
LD	longest diameter
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NCI	National Cancer Institute
NL	new lesion
NSCLC	non-small cell lung cancer
NTL	non-target lesion
OATP	organic anion-transporting polypeptide
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response

ABBREVIATION	DEFINITION
PRO	patient-reported outcome
PT	preferred term
PTX	paclitaxel
QoL	quality-of-life
QTc	QT interval corrected for heart rate
Ram	ramucirumab
RECIST	Response Evaluation Criteria in Solid Tumors
RES	Response Evaluable Set
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	stable disease
SID	subject identification
SoC	standard of care
SOC	system organ class
SOP	standard operating procedure
SpO2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
t1/2	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TL	target lesion
Tmax	time of maximum plasma/serum concentration (Cmax)
ToGA	Trastuzumab for Gastric Cancer [study]
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
vs.	versus
V_{SS}	volume of distribution at steady-state
WBRT	whole brain radiotherapy
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

1.1.1. Overview of the Disease

Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths according to the most recent GLOBOCAN epidemiological estimates: in 2018, 1,605,735 (1,033,701 stomach, 572,034 esophageal) new cases were reported globally, representing 8.8% of all cancers.[1] Among all geographical regions in the world, the highest incidence of GC is observed in Eastern Asian countries, particularly in China (with nearly half of the world cases), Japan, and Korea.[1] In 2018, based on GLOBOCAN data, there were an estimated 763,483 new cases of GC in China (673,615 deaths due to GC); 135,565 new GC cases in Japan (50,539 deaths); and 6567 new GC cases in South Korea (4856 deaths). In comparison, 46,090 new cases (27,504 deaths) were reported in 2018 in the United States (US) and 186,097 new cases (47,228 deaths) in Europe. The GLOBOCAN estimates for the US are similar to those from the American Cancer Society, which estimated 43,530 patients newly diagnosed with GC in the US in 2018, with an estimated 27,650 deaths.[2,3]

Worldwide, GC is more frequent in men than in women. In Japan, it remains the most common type of cancer among men.[2] In Japan and South Korea, where screening is widely performed, early detection is often possible. However, in approximately 50% of patients, GC is diagnosed at an advanced stage, with a poor outcome.[2]

Human epidermal growth factor receptor 2 (HER2) gene amplification or protein expression has been associated with gastric and gastro-esophageal junction (GEJ) cancer, with authors reporting rates of HER2 amplification varying from 12% to 27% and HER2 overexpression of 9% to 23%.[2] The impact of HER2 status on survival outcomes in patients with GC remains unclear, with some analyses suggesting HER2 positivity is associated with a poor outcome,[4,5,6,7] while others did not demonstrate any prognostic significance to HER2 overexpression.[8,9,10] Nevertheless, the HER2 status in patients with GC has important clinical implications in the management of patients with advanced or metastatic disease, and HER2 testing is recommended for all patients with metastatic GC at the time of diagnosis.[2]

For patients with HER2 overexpressing locally advanced or metastatic gastric adenocarcinoma and a tumor score of 3+ by immunohistochemistry (IHC), or IHC 2+ and evidence of HER2 amplification by fluorescent in-situ hybridization (FISH), the addition of trastuzumab to first-line chemotherapy is now part of standard of care (SoC) after its efficacy was demonstrated in the Trastuzumab for Gastric Cancer (ToGA) trial.[11] In the ToGA trial, the addition of trastuzumab to chemotherapy resulted in significant improvement in median overall survival (OS) in the trastuzumab-plus-chemotherapy arm as compared to the chemotherapy-alone arm, with a 26% decrease in the death rate (hazard ratio [HR]: 0.74; 95% confidence interval [CI]: 0.60, 0.91; *P*-value = 0.0046). The median OS was 13.8 months (95% CI: 12, 16) in the trastuzumab-plus-chemotherapy arm versus (vs.) 11.1 months (95% CI: 10, 13) in the chemotherapy-alone arm, without a clinically meaningful difference in toxicity between arms. However, unlike the results seen in patients with breast cancer, pertuzumab (PERJETA®) did not increase benefit when added to the SoC in first-line HER2-positive GC patients.[12]

There is no established molecular-based patient-enriched treatment option for advanced GC in the second-line setting globally. After progression on first-line HER2-targeted systemic treatment, therapeutic options are limited and include cytotoxic systemic therapy, clinical trial or best supportive care (BSC). Chemotherapy may improve symptoms, survival, and quality-of-life (QoL) compared with BSC alone.[12]

Preferred regimens in second-line therapy for metastatic or locally advanced GC based on the National Comprehensive Cancer Network (NCCN) guidelines include ramucirumab (Ram)[41] and paclitaxel (PTX)[43] as single agents or in combination, as well as irinotecan and docetaxel as single agents. Fluorouracil and irinotecan may also be considered as a second-line option provided they were not used in first line.[2]

Overall, the prognosis of patients who failed first-line therapy is poor, with median survival ranging approximately from 5.0 to 9.0 months based on published studies. In the Phase 3 WJOG4007 study comparing treatment with weekly PTX (n = 108) and biweekly irinotecan (n = 111) in patients with advanced GC refractory to treatment with fluoropyrimidine plus platinum, there was no statistically significant difference between the 2 treatment arms with regard to median OS.[13] The median OS was 9.5 months in the PTX arm and 8.4 months in the irinotecan arm (HR = 1.13 [95% CI: 0.86, 1.49]; *P*-value = 0.38). The median progression-free survival (PFS) was 3.6 months in the PTX arm and 2.3 months in the irinotecan arm (HR = 1.14 [95% CI: 0.88, 1.49]; *P*-value = 0.33); and the objective response rate (ORR) was 20.9% in the PTX arm and 13.6% in the irinotecan arm (*P*-value = 0.24).

Ramucirumab, a vascular endothelial growth factor receptor 2 (VEGFR 2) antibody of the family of VEGFR receptor tyrosine kinases involved in angiogenesis, was approved by the Food and Drug Administration (FDA) for the treatment of patients with advanced gastric or GEJ cancer refractory to, or progressive following, first-line therapy with platinum- or fluoropyrimidine-based chemotherapy, based on the results of 2 randomized Phase 3 trials, REGARD (Ram vs. placebo) and RAINBOW (Ram + PTX vs. PTX-alone).[14,15 41]

In the REGARD trial, 355 patients with advanced gastric or GEJ cancer that had progressed after first-line therapy were randomized to Ram or placebo.[14] The median OS was 5.2 months in patients on Ram vs. 3.8 months in patients on placebo (*P*-value = 0.047). A higher proportion of patients on Ram experienced hypertension compared to patients on placebo (16% vs. 8%).

In the RAINBOW trial (665 patients), combination therapy with Ram + PTX resulted in a statistically significant longer median OS as compared with PTX-alone (9.6 months vs. 7.4 months; *P*-value < 0.0001); a median PFS of 4.4 months (Ram + PTX) vs. 2.9 months (PTX-alone); and a statistically significant difference in ORR in favor of the Ram + PTX combination vs. PTX-alone (28% vs. 16%, respectively; *P*-value = 0.0001).[15] Neutropenia and hypertension were more frequent in the Ram + PTX combination arm than in the PTX-alone arm.

Subgroup analyses by region were conducted in Western (n = 398) and Japanese (n = 140) patients enrolled in the RAINBOW trial.[16] In the Western population, the median OS was 8.6 months (interquartile range [IQR]: 4.7, 13.6) in the Ram + PTX arm (n = 198) vs. 5.9 months (IQR: 3.1, 11.0) in the PTX-alone (n = 200) arm (HR: 0.73 [95% CI: 0.58, 0.91]; *P*-value = 0.0050 [stratified]). The median PFS was 4.2 months in the Ram + PTX arm vs. 2.8 months in the PTX-alone arm (HR: 0.631 [95% CI: 0.506, 0.786]; *P*-value < 0.0001

[stratified]); and the ORR was 26.8% (95% CI: 21.1, 33.3) in the Ram + PTX arm vs. 13.0% (95% CI: 9.0, 18.4) in the PTX-alone arm (*P*-value = 0.0004).

In further studies in patients with advanced GC in second-line therapy conducted to date, potential chemotherapeutic regimens failed to improve the clinical outcomes over existing second-line options.[17,18]

In the GATSBY study, a randomized, open-label, adaptive, Phase 2/3 study of trastuzumab emtansine vs. taxane (docetaxel or PTX) as second-line therapy in patients with unresectable, locally advanced or metastatic HER2-positive GC including GEJ cancer, trastuzumab emtansine was not superior to taxane.[18] The median OS was 7.9 months (95% CI: 6.7, 9.5) with trastuzumab emtansine (2.4 mg/kg weekly) vs. 8.6 months (95% CI: 7.1, 11.2) with taxane (HR: 1.15 [95% CI: 0.87, 1.51]; *P*-value = 0.86). Treatment with trastuzumab emtansine resulted in fewer patients with ≥ Grade 3 adverse events (AEs) than with taxane, with a similar proportion of patients with serious AEs (SAEs), AEs resulting in death, and AEs leading to treatment discontinuation in both treatment arms.

Similarly, in the Ty-TAN study, a randomized, Phase 3 study of lapatinib (an anti-HER2 agent) plus PTX vs. PTX-alone in Asian patients with advanced GC in second-line therapy, the addition of lapatinib to the standard PTX regimen did not result in a statistically significant difference in clinical outcomes. The median OS was 11.0 months in the lapatinib-plus-PTX arm vs. 8.9 months in the PTX-alone arm (*P*-value = 0.0144), with no significant difference between arms in median PFS (5.4 and 4.4 months, respectively). The ORR was higher in the lapatinib-plus-PTX arm than in the PTX-alone arm (odds ratio: 3.85; *P*-value < 0.001).

Therefore, unlike treatments for breast cancer, trastuzumab emtansine and lapatinib have not been approved in GC, and there is no established HER2-targeting drug for GC after treatment with a trastuzumab-containing regimen.

In September 2017, the FDA granted accelerated approval to pembrolizumab for the treatment of patients with programmed cell death ligand 1 (PD-L1)-positive recurrent or advanced gastric or GEJ cancer who have received 2 or more lines of chemotherapy, including fluoropyrimidine- and platinum-containing chemotherapy, and if appropriate, HER2/neu-targeted therapy. However, the Phase 3 study of pembrolizumab vs. PTX as second-line therapy in 592 patients with advanced PD-L1-positive gastric or GEJ adenocarcinoma who progressed on first-line therapy with platinum and fluoropyrimidine doublet therapy (KEYNOTE-061 trial) failed to show an improvement in OS and PFS vs. PTX alone.[19]

In summary, patients with advanced GC who fail first-line chemotherapy (with or without trastuzumab) have a poor survival outcome and limited therapeutic options. There is a significant unmet medical need in this patient population, and a molecular-based approach is required.

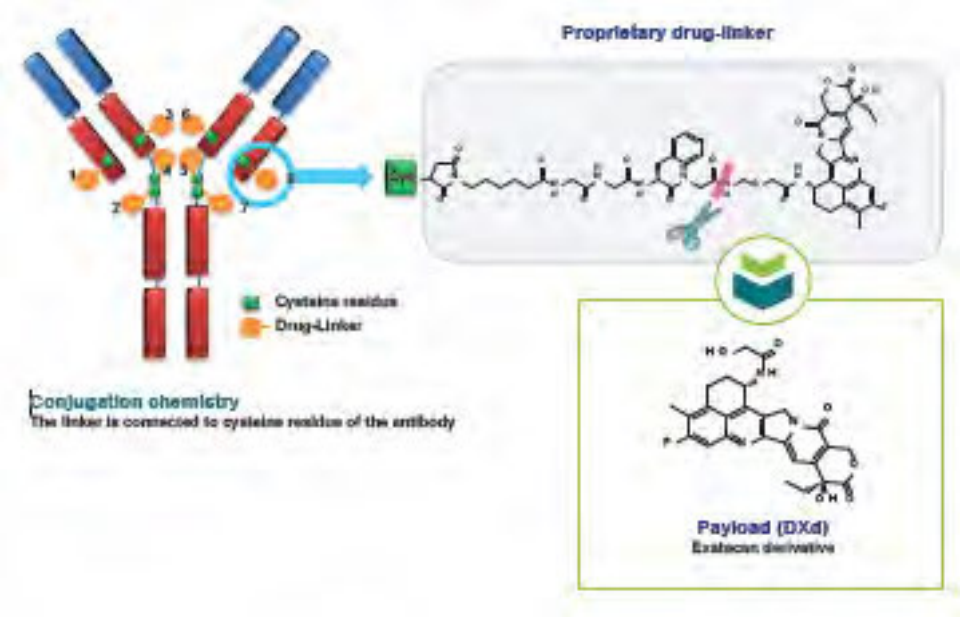
1.1.2. The Investigational Product: Trastuzumab Deruxtecan

1.1.2.1. Description

Trastuzumab deruxtecan (, also known as fam-trastuzumab deruxtecan) is a novel HER2-targeting antibody-drug conjugate (ADC) composed of an antibody component, MAAL-9001, covalently conjugated to a drug component, MAAA-1181a, through an enzyme-cleavable

maleimide tetrapeptide linker, MAAA-1162a. The antibody component, MAAL-9001, is a recombinant humanized anti-human HER2 immunoglobulin G1 monoclonal antibody with the same amino acid sequence as trastuzumab. The drug component, MAAA-1181a, an exatecan derivative, is a novel topoisomerase I inhibitor permeable to the cell membrane and more potent than SN-38, the active metabolite of irinotecan.[20, 21] Trastuzumab deruxtecan has a high drug-to-antibody ratio (approximately 8) when compared with trastuzumab emtansine (Figure 1.1).

Figure 1.1: Trastuzumab Deruxtecan Structure



In studies of mechanism of action, trastuzumab deruxtecan was shown to induce HER2-mediated inhibition of Akt phosphorylation and to exhibit antibody-dependent cellular cytotoxic activities. After binding to the HER2 receptor, trastuzumab deruxtecan is internalized in tumor cells, cleaved by lysosomal enzymes, and releases MAAA-1181a in the cytoplasm. The released drug MAAA-1181a inhibits topoisomerase I, causing deoxyribonucleic acid (DNA) damage and leading to apoptosis of the target cells. Thus, trastuzumab deruxtecan exhibits HER2-specific cell growth inhibition and antitumor activity via a novel mechanism of action that combines the pharmacological activities of MAAL-9001, the antibody component, with those of MAAA-1181a, the drug component.

In preclinical studies, trastuzumab deruxtecan has shown antitumor activity in a broad spectrum of tumor types across a range of high and low HER2-expressing tumors.[20]

1.1.2.2. Clinical Experience in Gastric Cancer

Encouraging findings from the dose-escalation part of an ongoing, first-in-human, 2-part, open-label, Phase 1 trial of trastuzumab deruxtecan (Study DS8201-A-J101) conducted in heavily-pretreated subjects with breast or gastric and GEJ carcinomas refractory to standard therapy, regardless of HER2 status, showed trastuzumab deruxtecan had antitumor activity even in low HER2-expressing tumors. The maximum tolerated dose in the dose-escalation phase was not reached.[22] Based on the Part 1 results of the study, doses of 5.4 mg/kg and 6.4 mg/kg were

selected for the dose-expansion phase of the study; a dose of 6.4 mg/kg was finally selected for Phase 2 and subsequent studies in HER2-positive GC patients.

These promising findings from dose-escalation were replicated at the interim analysis of the dose-expansion part of the study, which included a cohort of subjects with advanced HER2-positive GC previously treated with trastuzumab (cohort 2b).[23]

The efficacy results for all subjects with HER2-positive gastric/GEJ cancer as of the data cutoff date of 01 Feb 2019, are summarized in Table 1.1.

Median duration of follow-up was 8.3 months (range: 1.4 months to 34.1 months).

In the Enrolled Analysis Set, a confirmed ORR by ICR of 29.5% (95% CI: 16.8 to 45.2) was observed in subjects with gastric/GEJ cancer at doses of 5.4 mg/kg (26.3% [95% CI: 9.1 to 51.2]) or 6.4 mg/kg (32.0% [95% CI: 14.9 to 53.5]). In all subjects with gastric/GEJ cancer, 13 subjects had BORs of complete response (CR) (1 [2.3%] subject) or PR (12 [27.3%] subjects).

The median time to response was 1.7 months (95% CI: 1.4 to 2.8), which corresponded to the first postbaseline scan. Among subjects who did not achieve a response, the majority still showed tumor regression with best response of stable disease.

The median confirmed DoR based on ICR (calculated using the KM method) was 5.8 months in subjects with HER2-positive gastric/GEJ cancer who received 1 of the doses of 5.4 mg/kg or 6.4 mg/kg. Of the 13 subjects with confirmed response by ICR assessment who received 5.4 mg/kg or 6.4 mg/kg, 8 (61.5%) subjects had progressed and none had died as of the data cutoff. Based on the KM estimate of confirmed CR/PR by ICR assessment, the estimated proportion of subjects remaining in response was 44.0% at 6 months and 22.0% at 12 months and 18 months.

At the time of the data cutoff, 30 of 44 (68.2%) subjects had PD based on ICR assessment and/or death. The median PFS by ICR was 5.4 months (95% CI: 4.1 to 8.5) in all subjects with HER2 positive gastric/GEJ cancer at doses of 5.4 mg/kg or 6.4 mg/kg.

At the time of data cutoff, 18 of 44 (40.9%) subjects in the Enrolled Analysis Set had died. The median OS was 20.2 months in all subjects with HER2-positive gastric/GEJ cancer at doses of 5.4 mg/kg or 6.4 mg/kg. Based on the KM analysis, the estimated proportion of subjects alive were 79.3% at 6 months, 58.0% at 12 months and 18 months, and 41.0% at 24 months.

Overall, 41 of 44 (93.2%) subjects with HER2-positive gastric/GEJ cancer at doses of 5.4 mg/kg or 6.4 mg/kg had baseline and postbaseline tumor assessments by ICR. The mean tumor shrinkage of target lesions was -27.22% (33.525). Most subjects had tumor shrinkage by ICR (75.6% [31/41]), all of which occurred at the first postbaseline tumor assessment.

Similarly, a dose of 6.4 mg/kg is the recommended dose for HER2-positive gastric cancer (GC) in the DS8201 A-J202 study and the planned dose for further clinical studies in HER2-positive GC.

Further information on the efficacy and safety of trastuzumab deruxtecan in ongoing studies to date is available in the latest version of the Investigator's Brochure (IB)[21] .

Table 1.1: Efficacy Results in HER2-Positive Gastric/Gastro-esophageal Junction Cancer in Study DS8201-A-J101 (Enrolled Analysis Set)

Efficacy Variable	HER2-Positive Gastric/GEJ Cancer		
	5.4 mg/kg (N = 19)	6.4 mg/kg (N = 25)	Total (N = 44)
Confirmed ORR, n (%) (95% CI[a])			
ORR by ICR	5 (26.3) (9.1, 51.2)	8 (32.0) (14.9, 53.5)	13 (29.5) (16.8, 45.2)
ORR by investigator	6 (31.6) (12.6, 56.6)	13 (52.0) (31.3, 72.2)	19 (43.2) (28.3, 59.0)
ORR by ICR in response evaluable set, n/N	5/18 (27.8) (9.7, 53.5)	8/23 (34.8) (16.4, 57.3)	13/41 (31.7) (18.1, 48.1)
Confirmed best overall response by ICR, n (%)			
CR	0	1 (4.0)	1 (2.3)
PR	5 (26.3)	7 (28.0)	12 (27.3)
Stable disease	10 (52.6)	14 (56.0)	24 (54.5)
PD	4 (21.1)	3 (12.0)	7 (15.9)
NE	0	0	0
Confirmed best overall response by investigator, n (%)			
CR	0	0	0
PR	6 (31.6)	13 (52.0)	19 (43.2)
Stable disease	10 (52.6)	7 (28.0)	17 (38.6)
PD	3 (15.8)	5 (20.0)	8 (18.2)
NE	0	0	0
Confirmed DoR, median[b] (95% CI) (months)			
DoR by ICR	5.6 (2.9, -)	6.9 (3.5, -)	5.8 (3.5, -)
DoR by investigator	7.1 (3.0, -)	7.0 (3.9, 12.2)	7.1 (4.7, 12.2)
Confirmed DCR,[c] n (%) (95% CI[a])			
DCR by ICR	15 (78.9) (54.4, 93.9)	22 (88.0) (68.8, 97.5)	37 (84.1) (69.9, 93.4)
DCR by investigator	16 (84.2) (60.4, 96.6)	20 (80.0) (59.3, 93.2)	36 (81.8) (67.3, 91.8)
Time to response by ICR, median[b] (95% CI) (months)	1.6 (1.2, 3.1)	2.2 (1.4, 2.9)	1.7 (1.4, 2.8)
Duration of confirmed stable disease by ICR, median[b] (95% CI) (months)	4.3 (2.5, 11.4)	6.6 (2.6, 11.2)	4.4 (4.1, 11.0)
PFS			
PFS by ICR			
Events, n (%)	15 (78.9)	15 (60.0)	30 (68.2)
Median[b] (95% CI) (months)	4.3 (2.6, 8.6)	8.2 (4.2, 11.0)	5.4 (4.1, 8.5)
PFS by investigator			
Events, n (%)	15 (78.9)	21 (84.0)	36 (81.8)
Median[b] (95% CI) (months)	4.4 (2.5, 5.9)	6.6 (2.8, 8.4)	5.6 (3.0, 8.4)

Efficacy Variable	HER2-Positive Gastric/GEJ Cancer		
	5.4 mg/kg (N = 19)	6.4 mg/kg (N = 25)	Total (N = 44)
Overall survival			
Events, n (%)	9 (47.4)	9 (36.0)	18 (40.9)
Median[b] (95% CI) (months)	18.9 (5.7, -)	26.2 (10.0, -)	20.2 (10.0, -)
Survival at 6 months, % (95% CI[d])	77.0 (49.7, 90.7)	81.3 (57.6, 92.6)	79.3 (62.8, 89.1)
Survival at 12 months, % (95% CI[d])	54.0 (25.8, 75.6)	61.3 (34.2, 80.1)	58.0 (38.7, 73.2)
Survival at 18 months, % (95% CI[d])	54.0 (25.8, 75.6)	61.3 (34.2, 80.1)	58.0 (38.7, 73.2)
Survival at 24 months, % (95% CI[d])	33.8 (9.8, 60.2)	51.1 (23.0, 73.6)	41.0 (20.8, 60.3)

CI = confidence interval; CR = complete response; DCR = disease control rate; DoR = duration of response; GEJ = gastro-esophageal junction; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; NE = non-evaluable; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response

[a] 95% exact binomial CI.

[b] Median is from Kaplan-Meier estimate. CI for median was computed using the Brookmeyer-Crowley method.

[c] DCR was calculated as the proportion of subjects demonstrating CR, PR, or stable disease for a minimum of 6 weeks (±1 week) from the first dosing date.

[d] CI for the rate at a fixed time point was computed by applying asymptotic normality to the log-log transformation of the rate.

Dashes (-) represent data that are not estimable

The range includes the censored observations where using "+" after the value indicates censoring. Months were days × 12 / 365.25.

Part 1 (5.4 mg/kg and 6.4 mg/kg) and Part 2 subjects are included.

Data cutoff date: 01 Feb 2019.

Source: Preliminary data as of 01 Feb 2019.

1.1.2.3. Safety Information

1.1.2.3.1. Nonclinical Safety Information

In telemetered male cynomolgus monkeys treated with single IV doses of trastuzumab deruxtecan, no effects on the cardiovascular, respiratory, or central nervous systems (CNS) 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-1181d, monohydrate of MAAA-1181a, MAAA 1181d did not inhibit the hERG channel current at concentrations of up to 10 µmol/L (approximately 5000 ng/mL).

1.1.2.3.2. Clinical Safety Information

As of 08 Jun 2019, 3 clinical studies (Studies DS8201-A-J102, DS8201-A-A103, and DS8201-A-A104) were completed, and 9 clinical studies (Studies DS8201-A-J101, DS8201-A-U201, DS8201-A-J202, DS8201-A-J203, DS8201-A-U204, DS8201-A-U105, DS8201-A-U301, DS8201-A-U302, and DS8201-A-U303) were ongoing, with an estimated 1036 subjects exposed.

Further information on the safety of trastuzumab deruxtecan in ongoing studies to date is available in the latest version of the IB[21].

DS8201-A-J101 study

As of the data cutoff date of 01 Feb 2019, there were 289 subjects in total who received at least 1 dose of trastuzumab deruxtecan (27 subjects during the Dose Escalation Phase [Part 1] and 262 subjects during the Dose Expansion Phase [Part 2]) across all tumor types and doses. Median duration of treatment across all tumor types and doses is 7.4 months, and 25.3% of subjects had ≥12 months of treatment. Across tumor types by dose, the median duration of treatment was similar between 5.4 mg/kg (7.1 months) and 6.4 mg/kg (7.8 months). Median duration of treatment was longest in HER2-positive breast cancer (8.5 months in subjects dosed with 5.4 mg/kg and 9.0 months in subjects dosed with 6.4 mg/kg).

No dose limiting toxicity (DLT) was reported, and the maximum tolerated dose (MTD) was not reached in the Dose Escalation Phase.

A total of 288 (99.7%) subjects experienced at least 1 TEAE, with most of the common TEAEs being gastrointestinal or hematological in nature.

- Gastrointestinal: Nausea was most frequently reported, was predominantly Grade 1 or Grade 2, occurred early in the treatment (the majority occurring in the first 1 to 3 cycles), and was manageable under routine clinical practice. The median time to event onset was 3.0 days for nausea, 11.0 days for vomiting, and 26.5 days for diarrhea.
- Hematological: Events were predominantly Grade 1 or Grade 2, occurred early in treatment (the majority occurring in the first 1 to 3 cycles), and were manageable under routine clinical practice. Platelet count decrease (grouped term for preferred terms [PTs] platelet count decreased and thrombocytopenia) was commonly seen, with 11.8% of subjects having events of Grade 3 or above. The median time to onset was 9.0 days for platelet count decrease, 41.0 days for neutrophil count decrease (grouped term including PTs of neutropenia and neutrophil count decreased), and 30.5 days for anemia (grouped term including PTs of anaemia, hemoglobin decreased, and red blood cell count decreased). The time to onset for febrile neutropenia ranged from 11 days to 326 days.

DS8201-A-U201 study

As of the data cutoff date of 21 Mar 2019, there were 253 subjects in the 5.4-mg/kg, 6.4-mg/kg, and 7.4-mg/kg dose cohorts who received at least 1 dose of trastuzumab deruxtecan. The safety evaluation for this study mainly focuses on the 184 subjects in Parts 1, 2a, and 2b who received the recommended dose of trastuzumab deruxtecan at 5.4 mg/kg (overall 5.4-mg/kg dose cohort hereafter).

The overall median treatment duration (interval between last dose and first dose) was 7.0 months. In the overall 5.4-mg/kg dose cohort, the median treatment duration was 6.9 months.

Overall, most subjects (252 of 253 [99.6%] subjects) experienced at least 1 TEAE, with 250 (98.8%) subjects having at least 1 drug-related TEAE based on the investigator's assessment.

Further information on the safety of trastuzumab deruxtecan in ongoing studies to date is available in the latest version of the IB[21].

1.1.2.3.3. Interstitial Lung Disease/Pneumonitis

Based on the cumulative review of the safety data including available nonclinical, clinical, epidemiologic information, and scientific literature (published and unpublished), and taking into consideration biological plausibility, ILD/pneumonitis, which was previously classified as an important potential risk was reclassified as an important identified risk.

For latest clinical data, refer to IB.

An independent ILD Adjudication Committee for the trastuzumab deruxtecan program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This 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 (AEs) reported by using selected 42 Preferred Terms [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure.

1.1.2.3.3.1. Left Ventricular Ejection Fraction Decrease

Based on the cumulative review of the safety data including available nonclinical, clinical, epidemiologic information, scientific literature (published and unpublished) including literature from products in the same class, left ventricular ejection fraction (LVEF) decrease is considered to be important potential risk associated with trastuzumab deruxtecan.

For latest clinical data, refer to the IB[21].

1.1.2.3.4. Anemia, Neutrophil Count Decrease (including febrile neutropenia), and Platelet Count Decrease

Anemia, neutrophil count decrease (including febrile neutropenia), and platelet count decrease are considered to be important identified risks, based on available preclinical, clinical, and literature review of products of similar class.

For latest clinical data, refer to the IB[21].

1.1.2.4. Intended Use Under Investigation

This study will investigate the efficacy of trastuzumab deruxtecan in subjects with HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma that has progressed on or after a prior trastuzumab-containing regimen when treated in an advanced setting.

1.1.2.5. Comparator Regimen

Not applicable

1.1.2.6. Clinical Pharmacokinetics

As of 08 Jun 2019, PK data were available for 3 completed clinical studies for trastuzumab deruxtecan (Studies DS8201 A J102, DS8201-A-A103, and DS8201 A A104), and preliminary PK data were also available for 2 ongoing clinical studies (Studies DS8201-A-J101 and DS820-A-U201). PK data for the ongoing studies are provided as follows. (Please refer to the IB[21] for PK data from the completed studies).

DS8201-A-J101 (Ongoing)

Preliminary PK data from the Dose Escalation part of the study as of 01 Feb 2019 show that the trastuzumab deruxtecan Cmax was dose proportional across the dose range of 0.8 mg/kg to 8.0 mg/kg. The area under the serum concentration-time curve up to the last quantifiable time (AUClast) increased greater than dose proportionally from 0.8 mg/kg to 3.2 mg/kg and then increased dose proportionally from 3.2 mg/kg and above. The total anti-HER2 antibody exposure was similar to trastuzumab deruxtecan. On a molar basis, the trastuzumab deruxtecan exposures at the 5.4-mg/kg dose were approximately 39-fold to 44-fold higher than those for MAAA 1181a.

Preliminary PK data from the Dose Expansion part of the study as of 01 Feb 2019 showed that the trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a exposures were similar between HER2-positive and HER2-low breast cancer. The trastuzumab deruxtecan and total anti-HER2 antibody exposures appeared to be numerically lower in HER2-positive GEJ cancer than in breast cancer. MAAA-1181a exposures were consistent across all tumor types evaluated.

DS8201-A-U201 (Ongoing)

Preliminary PK data as of 21 Mar 2019 showed that the ratio of trastuzumab deruxtecan and total anti-HER2 antibody was approximately 1 for Cmax and approximately 0.8 for areas under the plasma concentration-time curves (AUC) and trough concentrations. The serum concentrations of MAAA-1181a gradually increased and reached peak concentrations, with longer median Tmax (approximately 7 hours) than those for trastuzumab deruxtecan (approximately 4 hours). On a molar basis, the trastuzumab deruxtecan Cmax and trough concentrations were approximately 54-fold and 74-fold higher, respectively, than those for MAAA-1181a. These results demonstrate the in vivo stability of the ADC.

For further details related to the clinical PK of trastuzumab deruxtecan, please see the latest version of the IB.[21]

1.2. Study Rationale

Gastric cancer is diagnosed at an advanced stage in approximately 50% of patients, when it has a poor outcome (details in Section 1.1.1).[2] Overexpression or amplification of HER2 has been reported in approximately 15% of gastric or GEJ tumors. The tumor's HER2 status has important clinical implications in the management of patients with metastatic disease, and HER2

testing is recommended at the time of diagnosis for all patients with metastatic GC. In first-line therapy for advanced GC, preferred regimens based on NCCN guidelines include combination of a fluoropyrimidine and cisplatin or oxaliplatin. For patients with HER2-overexpressing metastatic adenocarcinoma and tumor score of 3+ by IHC, or IHC 2+ and evidence of HER2 amplification by the in-site hybridization (ISH) method, the addition of trastuzumab to first-line chemotherapy is now part of SoC after its efficacy was demonstrated in the ToGA trial.[2, 11]

There is no established targeted therapy for HER2-positive advanced GC in the second-line setting after progression on first-line treatment with a trastuzumab-containing regimen. Preferred second-line regimens for metastatic or locally advanced GC include Ram + PTX (as single agents or in combination) or other chemotherapeutic agents as detailed in Section 1.1.1. Further studies of potential chemotherapeutic regimens in patients with HER2-positive advanced GC in second-line therapy conducted to date failed to improve the clinical outcomes over existing second-line treatment options.[1, 18] Thus, patients with HER2-positive advanced GC who fail first-line chemotherapy have no molecular-based patient-enriched treatment options. As the survival outcome for these patients is generally poor, there is a high unmet medical need for this patient population.

Preliminary clinical data from Phase 1 study DS8201-A-J101 of trastuzumab deruxtecan in 45 heavily-pretreated subjects with HER2-positive gastric or GEJ adenocarcinoma who had received trastuzumab show encouraging efficacy, with an acceptable safety profile (details in Section 1.1.2.2). Similar preliminary results were seen in subjects who had also received prior CPT-11 treatment.[23]

Given the results from the interim analysis of study DS8201-A-J101, trastuzumab deruxtecan, administered earlier during treatment (in the second-line setting), may further improve the survival outcome of patients with HER2-positive GC and compare favorably with the SoC treatment, Ram + PTX.

For targeted therapy to be efficacious, it is important that tumor cells express the target receptor. In the GC patient population, HER2 protein down-regulation is reported in 30% to 60% of patients after trastuzumab-containing therapy.[25, 26, 27] This loss of HER2 expression after treatment with trastuzumab may be the potential mechanism for resistance to future HER2-targeted therapy in GC patients. Enrollment in the Phase 1 DS8201-A-J101 trial was based on the tumor locally confirmed HER2 status from archival tissue and most subjects had received additional chemotherapy after progression on or after a trastuzumab-containing regimen and prior to study enrollment. In contrast, the DS8201-A-U205 trial is enrolling subjects who have progressed on or after a trastuzumab-containing regimen and have not received any additional systemic therapy. Thus, it is important to ensure the tumor is still HER2 positive based on tissue biopsy after a trastuzumab-containing regimen in order for the study subjects to expect to receive benefit from trastuzumab deruxtecan treatment.

The sample size was 80 subjects in the original protocol to accommodate dropouts or loss to follow-ups. Seventy-two is the number of targeted subjects without considering any potential dropouts.

This is a Phase 2 trial to determine the efficacy and safety of trastuzumab deruxtecan in subjects with advanced or metastatic HER2-positive gastric or GEJ cancer who have previously progressed on or after a trastuzumab-containing regimen.

1.3. Risks and Benefits for Study Subjects

Trastuzumab deruxtecan is being developed for the treatment of HER2-expressing malignant tumors. Nonclinical studies have demonstrated a potent antitumor activity of trastuzumab deruxtecan in tumor-bearing mouse models. Based on the preliminary clinical observations in the Phase 1 study (DS8201-A-J101), trastuzumab deruxtecan demonstrates antitumor activity in HER2 expressing cancers including GC. As of 08 Jun 2018, the HER2-positive GC cohort had an ORR of 43.2% and a DCR of 79.5%.[21, 24]

As of 01 Feb 2019 from Study DS8201-A-J101, the overall efficacy results in subjects with HER2-positive breast cancer at 5.4 mg/kg or 6.4 mg/kg demonstrated a confirmed ORR by ICR of 52.5%. Among the subjects with HER2-low breast cancer, confirmed ORR by ICR was 37.0%. The overall efficacy results in subjects with HER2-positive gastric/GEJ cancer at 5.4 mg/kg or 6.4 mg/kg demonstrated a confirmed ORR by ICR of 29.5%. The overall efficacy results in subjects with other cancers demonstrated a confirmed ORR by ICR of 29.5%.

The most frequently reported TEAEs (at least 20% of subjects) in Study DS8201-A-J101 were gastrointestinal or hematological in nature. See Section 1.1.2.3.2. The majority of the TEAEs were Grade 1 or Grade 2 in severity based on the Common Terminology Criteria for Adverse Event (CTCAE) v5.0. Overall, the study-reported AEs are manageable and consistent with the expected safety profile of trastuzumab deruxtecan based on data available from nonclinical toxicology studies as well as from drugs of similar class.

Based on the cumulative review of the safety data, including available nonclinical, clinical, and epidemiologic information and scientific literature (published and unpublished) and taking into consideration biological plausibility, ILD, anemia, neutrophil count decrease including febrile neutropenia, and platelet count decrease are classified as important identified risks. LVEF decrease is classified as an important potential risk. Infusion-related reactions, which were previously classified as an important potential risk, are reclassified as an identified risk. QT prolongation is no longer considered an important potential risk and has been removed from the list of safety concerns for trastuzumab deruxtecan.

In the trastuzumab deruxtecan clinical program, the inclusion/exclusion criteria and monitoring/management guidelines are currently in place in all protocols to mitigate the important identified risks of ILD, anemia, neutrophil count decrease including febrile neutropenia, and platelet count decrease, and important potential risk of LVEF decrease.

ILD is a known serious risk of trastuzumab deruxtecan, and cases with fatal outcomes have been reported. Most events were Grade 1 or Grade 2 and were manageable by dose modification and following clinical treatment guidelines for drug-induced ILD, with specific recommendations including close monitoring of signs/symptoms of ILD (eg, cough, fever, and dyspnea) to identify potential ILD and proactively managing ILD with dose modification and treatment (eg, steroids).

ILD requires proper monitoring, dose modification, and supportive care instituted in a timely fashion.

Other identified risks of trastuzumab deruxtecan in order of descending frequencies are nausea, decreased appetite, alopecia, vomiting, fatigue, constipation, diarrhoea, WBC count decrease, stomatitis, aspartate aminotransferase increased, cough, headache, abdominal pain, alanine

aminotransferase increased, hypokalaemia, epistaxis, dyspnoea, dyspepsia, dizziness, dry eye, upper respiratory tract infection, asthenia, and infusion-related reactions.

These identified risks were generally manageable through dose modification and routine clinical practice.

Trastuzumab deruxtecan has demonstrated a generally acceptable safety profile in the treated populations.

In conclusion, given the data available on the efficacy and safety of trastuzumab deruxtecan, the overall benefit/risk remains positive for clinical development.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to investigate the efficacy of trastuzumab deruxtecan based on confirmed ORR, as assessed by an independent central imaging facility review using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, in subjects with HER2-positive unresectable or metastatic gastric or GEJ adenocarcinoma that has progressed on or after a trastuzumab-containing regimen.

2.1.2. Secondary Objectives

The key secondary objective is to evaluate the efficacy of trastuzumab deruxtecan on PFS, based on independent central review using RECIST v1.1.

Other secondary objectives are as follows:

- To further evaluate the efficacy of trastuzumab deruxtecan using the following endpoints:
  - OS
  - PFS, based on Investigator assessment using RECIST v1.1
  - ORR, based on Investigator assessment using RECIST v1.1
  - DoR, based on independent central review and Investigator assessment using RECIST v1.1
- To determine the PK of trastuzumab deruxtecan in serum
- To further evaluate the safety of trastuzumab deruxtecan based on TEAEs and anti-drug antibodies (ADAs)
- To evaluate Health Economics and Outcomes Research (HEOR) endpoints based on patient-reported outcomes (PROs)

2.1.3. Exploratory Objectives

The exploratory objectives are to evaluate the following:

- DCR, based on independent central review and Investigator assessment
- Time to response, based on both independent central review and Investigator assessment
- Best percentage change in the sum of diameters of measurable tumors
- Predictive, prognostic, and pharmacodynamics exploratory biomarkers in tissue samples and blood, and their association with disease status and/or response to treatment.

2.2. Study Hypothesis

Trastuzumab deruxtecan confers an ORR benefit in subjects with unresectable or metastatic HER2-positive gastric or GEJ cancer who have previously progressed on or after a trastuzumab-containing regimen in the first-line setting.

2.3. Study Endpoints

The efficacy endpoints will be based on central assessments unless otherwise stated.

2.3.1. Primary Endpoint

The primary endpoint (ie, primary outcome measure) is confirmed ORR, defined as the proportion of subjects who achieved a best overall response of confirmed CR or partial response (PR), as determined by independent central review using RECIST v1.1.

2.3.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is PFS, based on independent central review using RECIST v1.1.

2.3.3. Other Secondary Efficacy Endpoint(s)

The other secondary efficacy endpoints are as follows:

- PFS, defined as the time interval from the date of first dose of study drug to the date of disease progression or death due to any cause.
- ORR, based on Investigator assessment using RECIST v1.1
- OS, defined as OS is defined as the time interval from the date of first dose of study drug to the date of death due to any cause.
- DoR, defined as the time from the date of first documentation of objective response to the date of the first documentation of disease progression, based on independent central review and Investigator assessment, or to death due to any cause, using RECIST v1.1.

2.3.4. Exploratory Endpoints

- DCR, defined as CR rate plus PR rate plus stable disease (SD) rate, based on independent central review and Investigator assessment
- Time to response, based on both independent central review and Investigator assessment
- Best percentage change in the sum of diameters of measurable tumors
- Serum extracellular domain of HER2 (HER2ECD)
- Biomarker analysis using cell-free DNA (cfDNA) and cell-free RNA (cfRNA)

2.3.5. Pharmacokinetic (PK) Endpoints (Trastuzumab Deruxtecan and MAAA-1181a):

The PK endpoints are as follows:

- Serum concentration for trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a
- Cmax, Tmax, area under the plasma concentration-time curve, from time 0 to last point with quantifiable concentration (AUClast), AUC21d, and, if appropriate, AUCinf, t1/2, CL, and Vss for each of the components.

2.3.6. Safety Endpoint(s)

The safety endpoints are as follows:

- SAEs
- TEAEs
- Drug-related TEAEs
- Discontinuations due to AEs
- Adverse events of special interest (AESIs)
- Physical examination findings
- Eastern Cooperative Oncology Group performance status (ECOG PS)
- Vital sign measurements
- Standard clinical laboratory parameters
- Electrocardiogram (ECG) parameters
- Echocardiogram (ECHO)/multigated acquisition (MUGA) scan findings
- ADAs

2.3.7. Health Economic and Outcomes Research Endpoints

The HEOR endpoints based on PROs are as follows:

- European Organization for Research and Treatment of Cancer (EORTC) 5-dimension 5-levels quality-of-life questionnaire (EQ-5D-5L; see sample in Section 17.2.1)[28, 29, 30, 31]
- Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) questionnaire (see sample in Section 17.2.2)[32]

3. STUDY DESIGN

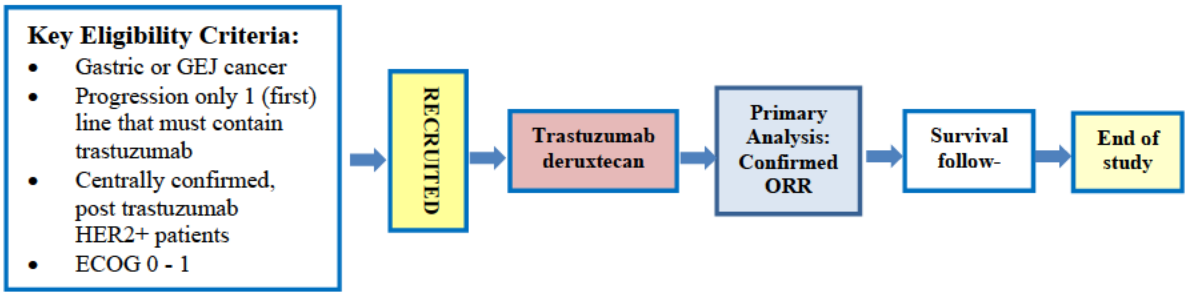
3.1. Overall Design

3.1.1. Overview

This is an open-label, multicenter Phase 2 study to evaluate the efficacy and safety of trastuzumab deruxtecan in subjects with unresectable or metastatic GC or GEJ previously treated with a trastuzumab-containing regimen. The sample size will be approximately 80 subjects, recruited at approximately 45 study sites including but not limited to North America and the EU.

Trastuzumab deruxtecan will be administered as a sterile IV solution at a dose of 6.4 mg/kg every 3 weeks.

Figure 3.1: Study Design Schema



GEJ = gastro-esophageal; HER2 = human epidermal growth factor receptor 2; ECOG = Eastern Cooperative Oncology Group
Note: Sample size is 80

3.1.2. Duration of the Study

Recruitment is expected to occur over approximately 18 to 24 months.

Treatment and follow-up are projected to be continued for at least 12 months after the last subject's first dose. Thus, the anticipated duration of the study is at least 30 to 36 months.

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

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

3.1.3. Duration of Subject Participation

Cycle 1 Day 1 (first dose) for the subject should occur within 28 days from signing the Main ICF and after all eligibility criteria are met. Once a subject meets the eligibility criteria, each cycle of treatment will be 21 days (±2 days). Upon commencing study treatment, subjects may continue receiving trastuzumab deruxtecan according to the dosing criteria until the occurrence of any of the events defined in Section 5.8.1 as reasons for discontinuation of study treatment.

Most subjects are expected to receive between 10 and 20 cycles of treatment. If the study treatment is delayed more than 28 days from the planned date of administration, the subject will be withdrawn from the study drug (see Section 5.8.2).

Long-term/Survival Follow-up Visits will occur every 3 months (± 14 days) from the date of the 40-day (+7 days) Follow-up Visit, until death, withdrawal of consent, or loss of follow-up, whichever comes first, and can be conducted via phone or in person at a site visit. In the event subjects withdraw consent to participate in the study, survival status will be obtained from public records (death certificate, obituary, etc.) unless prohibited by local laws.

3.1.4. Definition of the End of the Study

The end of the study will occur when all recruited subjects have either completed their last scheduled visit or died or withdrawn from study participation or moved into another study or when the Sponsor decides to discontinue the study. This is anticipated to occur approximately 12 months after the last subject is enrolled.

3.2. Discussion of Study Design

The sample size will be approximately 80 subjects, recruited at approximately 45 study sites including, but not limited to, North America and the EU.

Modeling results on efficacy and safety endpoints supported the selection of 5.4, 6.4, and 7.4 mg/kg, given the benefit:risk considerations. The selected dose of 6.4 mg/kg was based on clinical data from DS8201-A-J101 and subsequent exposure-response analysis of doses up to 8.0 mg/kg. Early efficacy results at the most recent DCO date (18 Apr 2018) from 45 heavily-pretreated subjects with gastric or GEJ adenocarcinoma enrolled in the ongoing Phase 1 study DS8201-A-J101 are encouraging.[22]

On the basis of the Part 1 results of the study, IV doses of 5.4 mg/kg and 6.4 mg/kg were selected for the dose-expansion phase of the study. The promising findings from dose-escalation were replicated at the interim analysis of the dose-expansion part of the study, which included a cohort of subjects with advanced HER2-positive GC previously treated with a trastuzumab-containing regimen. Patients with GC had received a median of 3.0 (range: 1 to 7) prior treatment regimens before entering the study. With a median duration of follow-up of 204.0 days (95% CI: 136.0, 267.0), the confirmed ORR was 43.2%, the median DoR was 7.0 months (95% CI not available), and the median PFS was 5.6 months (95% CI: 3.0, 8.3; range: 1.2 to 19.6+). Given the comparable efficacy and no additional safety risks for the 6.4 mg/kg dose, this dose was selected for Phase 2 and subsequent studies in HER2-positive GC subjects.

4. STUDY POPULATION

Each subject will sign a Tissue Screening Informed Consent Form (ICF) and a Main ICF provided by the site. A subject is considered a participant in the study upon the Investigator or designee obtaining the main informed consent from the subject (Section 15.3).

Investigators will maintain a confidential Screening Log of all potential study candidates that includes limited subject information (initials, age, gender) and outcome of the Screening process (ie, first dose of the study, reason for ineligibility, refused to participate, and/or others).

Investigators will be expected to maintain a log of all subjects receiving doses in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification (SID) code list. This confidential list of the names of all subjects, allocated study numbers on recruitment to the study, allows the Investigator to reveal the identity of any subject when and/or if necessary.

4.1. Inclusion Criteria

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

1. Must be able to comprehend, sign, and date a main ICF approved by the Institutional Review Board (IRB) or Ethics Committee (EC) before any study-specific procedures or tests are performed.
2. Men or women ≥18 years of age (please follow local regulatory requirements if the legal age of consent for study participation is >18 years of age)
3. Has pathologically documented gastric or GEJ cancer that is:
   - Unresectable or metastatic, and
   - Centrally confirmed HER2-positive disease (IHC3+ or IHC2+ and evidence of HER2 amplification by ISH) as determined according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines based on a new tumor biopsy obtained after progression on or after a first-line trastuzumab-containing regimen. If a tumor biopsy was already collected after discontinuation of first-line treatment with a trastuzumab-containing regimen, it is acceptable to consider that biopsy to be a new biopsy for the purpose of this study, provided that there is sufficient tissue for exploratory biomarker studies.
4. Experienced disease progression (based on RECIST version 1.1 criteria) during or after first-line therapy with a trastuzumab-containing regimen. Note: Prior first-line treatment with trastuzumab brand name (Herceptin) or approved biosimilar is acceptable.
   – Note: Prior adjuvant therapy with a trastuzumab-containing regimen can be counted as a line of therapy if the subject progressed on or within 6 months of completing adjuvant therapy.
5. Has at least 1 measurable lesion per RECIST v1.1 (details in Section 17.5) as confirmed by the investigator review
6. ECOG PS of 0 or 1

7. LVEF ≥50% within 28 days before first dose per ECHO/MUGA scan
8. Has adequate organ function within 14 days before randomization, defined as:

Parameter	Laboratory Value
Adequate Bone Marrow Function	
Platelet count	≥ 100 000/mm^3 (Platelet transfusion is not allowed within 1 week prior to screening assessment)
Hemoglobin	≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 week prior to screening assessment)
Absolute neutrophil count (ANC)	≥ 1500/mm3 (granulocyte colony-stimulating factor [G-CSF] administration is not allowed within 1 week prior to screening assessment)
Adequate renal function	
Creatinine	Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation*
Adequate hepatic function	
Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)	≤ 5 × the upper limit of normal (ULN)
Total bilirubin	≤ 1.5 × ULN if no liver metastases or < 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline.
Serum Albumin	≥ 2.5 g/dL
Adequate Blood Clotting Function	
International normalized ratio (INR) / Prothrombin time (PT) and activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN

*Cockcroft-Gault equation:

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

9. Has adequate treatment washout period before randomization, defined as:

Treatment	Washout Period
Major surgery	≥ 4 weeks
Radiation therapy including palliative stereotactic radiation to chest	≥ 4 weeks (palliative stereotactic radiation therapy to other areas ≥ 2 weeks)

Treatment	Washout Period
Chemotherapy (Immunotherapy [non-antibody-based therapy]), retinoid therapy	≥ 3 weeks (≥ 2 weeks or 5 half-lives , whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥ 6 weeks for nitrosureas or mitomycin C), ≥ 1 week for tyrosine kinase inhibitors (TKIs) approved for the treatment of NSCLC - baseline CT scan must be completed after discontinuation of TKI)
Antibody-based anticancer therapy	≥ 4 weeks
Chloroquine /Hydroxychloroquine	>14 days

10. Male and female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months for females and 4 months for males after the last dose of study drug.[34] Methods considered as highly effective methods of contraception include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 months for females and 4 months for males after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.
11. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and/or 72 hours before the first dose of study drug, during the Treatment Period, and for 7 months, following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) with surgery at least 1 month before the first dose or confirmed by follicle stimulating hormone (FSH) test.

12. 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.
13. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study treatment period, and for at least 7 months after the final study drug administration.

4.2. Exclusion Criteria

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

1. Use of anticancer therapy after first-line treatment with a trastuzumab-containing regimen.
2. Uncontrolled or significant cardiovascular disease, including any of the following:
   - History of myocardial infarction (MI) within 6 months of first dose
   - History of symptomatic congestive heart failure (New York Heart Association Class II to IV) (details in Section 17.6)[35]
   - Troponin levels consistent with MI as defined according to the manufacturer within 28 days prior to first dose
   - QTc prolongation to >470 ms (females) or >450 ms (male) based on Screening triplicate 12-lead ECG
3. History of non-infectious ILD/pneumonitis that required corticosteroid therapy or has current ILD/pneumonitis or is suspected to have such diseases by imaging at Screening.
4. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (i.e. pulmonary emboli within three months of the first dose, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc.), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (i.e. Rheumatoid arthritis, Sjogren's, sarcoidosis etc.), or prior pneumonectomy.
5. Pleural effusion, ascites, or pericardial 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.)
6. Spinal cord compression or clinically active CNS metastases, defined as untreated and symptomatic or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms. Baseline brain CT/MRI scan is mandatory.
   - Subjects with clinically inactive brain metastases may be included in the study.
   - Subjects with treated brain metastases that are no longer symptomatic and who require no treatment with corticosteroids or anticonvulsants may be included in the study if they have recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and signing of main ICF (1 week for stereotactic radiotherapy).

7. History of other malignancy(ies), except adequately treated non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated, with no evidence of disease for ≥3 years
8. History of severe hypersensitivity reactions to either the drug substance or inactive ingredients in the drug product
9. History of severe hypersensitivity reactions to other monoclonal antibodies
10. Current uncontrolled infection requiring IV antibiotics, antivirals, or antifungals
11. Substance abuse or any other medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that may, in the opinion of the Investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results
12. Social, familial, or geographical factors that would interfere with study participation or follow-up
13. Known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Subjects should be tested for HIV prior to enrollment if required by local regulations or IRB/EC. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
14. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the Investigator after consultation with the Sponsor Global Clinical Lead or designee (eg, Grade 2 chemotherapy-induced neuropathy)
15. Prior treatment with an ADC consisting of an exatecan derivative that is a topoisomerase I inhibitor.
16. Therapeutic radiation therapy (including palliative stereotactic radiation to chest) or major surgery within 4 weeks before study drug treatment or palliative stereotactic radiation therapy within 2 weeks before study drug treatment (please refer to exclusion criterion 6 for whole brain radiotherapy and stereotactic radiotherapy for CNS metastases).
17. Systemic treatment with anticancer chemotherapy therapy [Immunotherapy (non-antibody-based therapy)], retinoid therapy) within 3 weeks (≥ 2 weeks or 5 half-lives , whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥ 6 weeks for nitrosureas or mitomycin C).
18. Antibody-based anticancer therapy within 4 weeks of Cycle1, Day1
19. Participation in a therapeutic clinical study within 3 weeks before study treatment (for small-molecule targeted agents, this non-participation period is 2 weeks or 5 half-lives, whichever is longer); or current participation in other investigational procedures.
20. Pregnant or breastfeeding subjects or subjects planning to become pregnant.
21. Subject is an immediate family member of study site personnel or of Sponsor personnel.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)

This is an open-label study with a single trastuzumab deruxtecan treatment arm.

5.1.2. Method of Treatment Allocation

Prior to the subject's first dose, all eligibility criteria must be met.

5.1.3. Blinding

Not applicable

5.1.4. Emergency Unblinding Procedure

Not applicable

5.1.5. Re-screening Procedures

Re-screening (tissue and main screening) is permitted for any subject who failed to meet eligibility criteria upon initial screening. The limit of re-screening is once each for tissue screening and main screening after HER2 confirmation. If the subject fails eligibility using HER 2 prescreened tissue sample testing, then a different sample can be submitted for HER2 eligibility analysis.

The Re-screening Subject ID number must remain the same as the main Screening Subject ID number. The initial Screening information and the reason for initial Screening ineligibility will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for a subject who was re-screened.

5.2. Study Drug

5.2.1. Description

Trastuzumab deruxtecan drug product (trastuzumab deruxtecan for injection 100 mg) will be supplied as Lyo-DP. Lyo-DP is a sterile lyophilized powder provided in an amber glass vial for IV infusion. Each glass vial contains 100 mg of trastuzumab deruxtecan. Each vial is designed for single use and is not to be used to treat more than 1 subject.

Lyo-DP is reconstituted with 5 mL of water for injection to provide a solution with a concentration of 20 mg/mL of trastuzumab deruxtecan in a buffer containing L histidine, L 4 histidine hydrochloride monohydrate, sucrose, and polysorbate 80.

The starting dose of 6.4 mg/kg is based on body weight (BW) taken at the screening visit (baseline) and thereafter, within 3 days before infusion of Day 1 of all cycles.

5.2.2. Labeling and Packaging

Trastuzumab deruxtecan for injection will be supplied as Lyo-DP by the Sponsor. Trastuzumab deruxtecan for injection 100 mg, will be packaged and labeled in compliance with regulatory requirements. The packaging will clearly display the name of the study treatment, the lot number, storage condition, and other required information in accordance with local regulations.

5.2.3. Preparation

Prior to use, trastuzumab deruxtecan 100 mg for IV infusion will be prepared by the study site pharmacist by dilution of the required volume of study treatment calculated based on the subject's BW in a volume of 100 mL, according to the pharmacy instructions provided by the Sponsor. The starting dose of trastuzumab deruxtecan will be 6.4 mg/kg.

The subject's weight at screening (baseline) could be used to calculate the initial dose. If during the course of treatment, subject weight changes by ±10% from the baseline BW, the trastuzumab deruxtecan dose to be administered will be recalculated based on the updated BW. See Section 5.2.4.

Prepared study drug solutions should be used as directed in the pharmacy instructions. Refer to the Pharmacy Instructions for detailed information about preparation of trastuzumab deruxtecan.

Procedures for proper handling and disposal of anticancer drugs should be followed in compliance with the standard operating procedures (SOPs) of the study site.

5.2.4. Administration

Treatment cycles will be 21 days (±2 days) in length. Trastuzumab deruxtecan at a BW-based dose of 6.4 mg/kg will be administered as an IV infusion on Day 1 (±2 days) of every 21-day cycle (Q3W).

The first infusion of trastuzumab deruxtecan will occur over at least 90 minutes. If there is no infusion-related reaction (IRR), the subsequent infusions of trastuzumab deruxtecan will be over at least 30 minutes. In case of IRR of any severity grade at any time during the first administration of trastuzumab deruxtecan, all subsequent infusions will occur over approximately 90 minutes.

Refer to the Pharmacy Instructions for detailed information about administration of trastuzumab deruxtecan.

5.2.5. Storage

Trastuzumab deruxtecan Lyo-DP must be stored in a secure, limited-access storage area protected from light at temperatures between 2°C and 8°C.

If storage conditions are not maintained per specific requirements, the site should contact the Sponsor or contract research organization (CRO).

Instructions and precautions for storage and handling of infusion solutions are available in the Pharmacy Instructions.

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, check the drug expiration date, and acknowledge receipt in the Interactive Voice/Web Response System (IXRS). The original form will be retained at the site.

The Investigator or designee shall contact Sponsor as soon as possible if there is a problem with the drug shipment.

A Drug Accountability Record will be provided for the study drug or the site can use their own after getting approval from the Sponsor. The record must be kept current and should contain the following:

- Dates and quantities of drug received
- SID number and/or subject initials or supply number (as applicable)
- The date and quantity of investigational product dispensed and remaining
- The initials of the dispenser.

At the end of the study, or as directed, the Investigator will appropriately dispose of empty carton(s), empty vial(s), and vial(s) with remaining study drug, preparation materials, administration materials, etc. using clinical site disposal procedure to prevent infection or other illness/injury. The site may destroy the empty containers/vials and any unused drug after drug accountability has been verified by the site personnel as per their SOP. Alternatively, the investigational product may be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation 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 designee and provided to the Sponsor. Unused drug supplies may be destroyed by the Investigator when approved in writing by the Sponsor and the Sponsor has received copies of the study site's drug handling and disposition SOPs and it is assured that the Sponsor will receive copies of the certificate of destruction that is traceable to the study treatment.

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

5.3. Control Treatment

Not applicable

5.4. Dose Interruptions and Reductions

All dose modifications should be based on the worst preceding toxicity (CTCAE v5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of trastuzumab deruxtecan are listed in Table 5.1 which is applicable only to TEAEs that are assessed as related to use of trastuzumab deruxtecan by the investigator(s). For non-drug related TEAEs, follow standard clinical practice. All interruptions or modifications must be recorded on

the AE and drug administration electronic case report form (eCRF). Appropriate clinical experts should be consulted as deemed necessary.

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

5.4.1. Guidelines for Dose Modifications

Two dose reductions of trastuzumab deruxtecan will be permitted, from the original dose of 6.4 mg/kg to 5.4 mg/kg and subsequently to 4.4 mg/kg. Trastuzumab deruxtecan dose increases are not allowed in the study. There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified in Table 5.1.

Once the dose of trastuzumab deruxtecan 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 subjects will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.**

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

Treatment cycles for a subject for whom trastuzumab deruxtecan dosing is temporarily withheld for any reason may have future cycles scheduled based on the date the last trastuzumab deruxtecan dose is administered.

All confirmed or suspected COVID-19 events must be recorded in the eCRF. Please refer to Section 17.7 for additional information on dose modification.

Table 5.1: Management Guidelines for Trastuzumab Deruxtecan

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	**Management Guidelines for Trastuzumab Deruxtecan**
No Toxicity	Maintain dose and schedule
Infusion-related Reaction	
Grade 1 (mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion-related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	**Management Guidelines for Trastuzumab Deruxtecan**
Grade 2 (therapy or infusion interruption indicated but responds promptly to symptomatic treatment [eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids]; prophylactic medications indicated for ≤24 hours)	Administration of trastuzumab deruxtecan should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, IV fluids). If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (prolonged or life-threatening consequences, urgent intervention indicated)	Administration of trastuzumab deruxtecan should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation, etc., should be administered.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3	Delay dose until resolved to ≤ Grade 2, then maintain dose.
Grade 4	Delay dose until resolved to ≤ Grade 2, then reduce dose by 1 level.
Febrile Neutropenia (absolute neutrophil count <1 × 10^9/L, fever >38.3°C or a sustained temperature of ≥38°C for more than 1 hour)	Delay dose until resolved, then reduce dose by 1 level.
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	No dose modification
Grade 4 (<0.2 × 10^9/L)	Delay dose until resolved to ≤ Grade 2: • If resolved in ≤14 days from day of onset, maintain dose • If resolved in >14 days from day of onset, reduce dose by 1 level.
Anaemia	
Grade 3 (hemoglobin <8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose.
Grade 4 (life-threatening consequences, urgent intervention indicated)	Delay dose until resolved to ≤ Grade 2, then reduce dose by 1 level.

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	**Management Guidelines for Trastuzumab Deruxtecan**
Platelet Count Decreased	
Grade 3 (platelets <50 to 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 4 (platelets <25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose by 1 level.
Cardiac Toxicity	
Symptomatic congestive heart failure	Discontinue subject from study treatment.
Decrease in LVEF 10-20% (absolute value), but LVEF >45%	Continue treatment with trastuzumab deruxtecan.
LVEF 40% to ≤45% and decrease is <10% (absolute value) from baseline level	Continue treatment with trastuzumab deruxtecan. Repeat LVEF assessment within 3 weeks.
LVEF 40% to ≤45% and decrease is ≥10% (absolute value) from baseline level	Interrupt trastuzumab deruxtecan dosing. Repeat LVEF assessment within 3 weeks. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment.
LVEF <40% or >20% (absolute value) drop from baseline level	Interrupt trastuzumab deruxtecan dosing. Repeat LVEF assessment within 3 weeks. If LVEF <40% or >20% drop from baseline level is confirmed, discontinue subject from study treatment.
Electrocardiogram prolonged	
Grade 3 (Average QTc >500 ms or >60 ms change from baseline)	Delay dose until resolved to ≤Grade 1 (QTc ≤480 ms), determine if another medication the subject was taking may be responsible and can be adjusted or if there is any changes in serum electrolytes that can be corrected if attributed to trastuzumab deruxtecan, reduce dose by 1 level.
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study treatment.
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

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	Management Guidelines for Trastuzumab Deruxtecan
	"Other Non-Laboratory Adverse Events" dose modification section as follows. 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 (complete blood count). Other blood tests could be considered as needed. • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered • Pulmonary function tests and pulse oximetry (peripheral oxygen saturation [SpO2]) • Arterial blood gases if clinically indicated • 1 Blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined for Grades 1 through 4. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.
Grade 1	The administration of trastuzumab deruxtecan 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 to 2 weeks (or as clinically indicated). • Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines.* For Grade 1 events, trastuzumab deruxtecan can be restarted only if the event is fully resolved to Grade 0, then: • If resolved in ≤28 days from day of onset, maintain dose • If resolved in >28 days from day of onset, reduce dose 1 level.

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	**Management Guidelines for Trastuzumab Deruxtecan**
	However, if the event Grade 1 ILD/pneumonitis occurs beyond cycle Day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued. * If patient is asymptomatic, then patient should still be considered as Grade 1 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 1mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • 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 (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone). – Re-consider additional work-up for alternative etiologies as described previously. – Escalate care as clinically indicated.
Grade 3 and 4	Permanently discontinue subject from study treatment. • Hospitalization is required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500 to1000 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 alternative etiologies as described above. Consider other immuno-suppressants and/or treat per local practice.

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	**Management Guidelines for Trastuzumab Deruxtecan**
Ocular	
Grade 3	Delay dose until resolved to ≤Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment.
Blood Creatinine Increased	
Grade 3 (>3 to 6 × ULN)	Delay dose until resolved to ≤Grade 2 or baseline, then reduce dose by 1 level.
Grade 4 >6 × ULN)	Discontinue subject from study treatment.
Hepatic Toxicity	
Aspartate amino transaminase (AST) or Alanine amino transaminase (ALT) with Simultaneous Blood Bilirubin Increased	
AST/ALT ≥3.0 × ULN with simultaneous blood bilirubin >2.0 × ULN	Delay study medication until drug-induced liver injury can be ruled out. If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study drug may occur after discussion between the Investigator and Sponsor. If drug-induced liver injury cannot be ruled out from diagnostic work-up, permanently discontinue study treatment. Monitor AST/ALT and blood bilirubin twice weekly until resolution or return to baseline.
AST or ALT Increased	
Grade 2 (>3.0 - 5.0 × ULN if baseline was normal; >3.0 - 5.0 × baseline if baseline was abnormal)	No action for Grade 2 AST/ALT **but** if hepatic event meets combination abnormalities (ALT or AST ≥3 × ULN with concurrent [± 21 days] blood bilirubin ≥2 × ULN), • Repeat testing within 7 days (see Section 9.4.2 for SAE reporting), and • Delay dose until resolved to ≤ baseline. If confirmed Hy's Law case, discontinue subject from study drug.

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	**Management Guidelines for Trastuzumab Deruxtecan**
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 × baseline if baseline level was abnormal) In subjects without liver metastases and subjects with liver metastases and baseline level ≤3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1, if baseline level ≤3 × ULN, otherwise ≤ 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 by 1 level.
Grade 3 (>8.0 - 20.0 × ULN if baseline level was normal; >8.0 – 20.0 × baseline level if baseline level was abnormal) In subjects with liver metastases, if the baseline level was >3 × ULN	Repeat testing within 3 days. Delay dose until resolved to ≤ baseline level, then: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 4 (>20 × ULN if baseline level was normal; >20.0 × baseline level if baseline level was abnormal)	Discontinue subject from study treatment.
Total Bilirubin Increased	
Grade 2 (>1.5 - 3.0 × ULN if baseline level was normal; >1.5 - 3.0 × baseline if baseline level was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline, delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose by 1 level. If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment.

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	**Management Guidelines for Trastuzumab Deruxtecan**
Grade 3 (>3.0 - 10.0 × ULN if baseline level was normal; >3.0 - 10.0 × baseline if baseline level was abnormal) In subjects with liver metastases, if the baseline level was >3 × ULN	If no documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 1: • If resolved in ≤7 days from day of onset, reduce dose by 1 level • If resolved in >7 days from day of onset, discontinue trastuzumab deruxtecan. If documented Gilbert's syndrome or liver metastases at baseline, repeat testing within 3 days. Delay dose until resolved to ≤ Grade 2: • If resolved in ≤7 days from day of onset, reduce dose by 1 level • If resolved in >7 days from day of onset, discontinue trastuzumab deruxtecan.
Grade 4 (>10.0 × ULN if baseline level was normal; >10.0 × baseline level if baseline level was abnormal)	Discontinue subject from study treatment.
Blood Alkaline Phosphatase Increased	
Grade 3 (>5.0 - 20.0 × ULN if baseline level was normal; >5.0 - 20.0 × baseline if baseline level was abnormal) or Grade 4 (>20.0 × ULN if baseline level was normal; >20.0 × baseline level if baseline level was abnormal)	No modification unless determined by the Investigator to be clinically significant or life-threatening.
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤Grade 1 • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose by 1 level.
Diarrhea/Colitis	

Worst CTCAE v5.0 Toxicity Grade (unless otherwise specified)	Management Guidelines for Trastuzumab Deruxtecan
Grade 3	Delay dose until resolved to ≤Grade 1 • If resolved in ≤3 days from day of onset, maintain dose • If resolved in >3 days from day of onset, reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment
Other Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤Grade 1 or baseline level: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment.
Other Non-laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤Grade 1 or baseline: • If resolved in ≤7 days from day of onset, maintain dose • If resolved in >7 days from day of onset, reduce dose by 1 level.
Grade 4	Discontinue subject from study treatment.

CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; ms = milliseconds; NSAID = nonsteroidal anti-inflammatory drug; PK = pharmacokinetic; QTc = QT interval corrected for heart rate; ULN = upper limit of normal
All dose modifications should be based on the worst preceding toxicity.

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

5.5. Method of Assessing Treatment Compliance

Intravenous trastuzumab deruxtecan will be administered only to subjects participating in the study and under the supervision of clinical study personnel at the site. Start and stop times of IV infusion and amount of drug administered are to be recorded by clinical study personnel.

5.6. Concomitant Medications, Treatments, and Procedures

Medications used from the time the subject signs the ICF to 40 days (+7 days) after the last administration of trastuzumab deruxtecan will be recorded. All concomitant medications and therapies, including all prescription, over-the-counter (OTC), and herbal remedies will be recorded on the eCRF.

Permitted Therapies/Products:

- Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the Investigator after the subject starts receiving study drug (see

Section 4.1).Prophylactic or supportive treatment of study drug-induced AEs will be otherwise as per Investigator's discretion and institutional guidelines.

- Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged but not prohibited.
- On the basis of the currently available clinical safety data, it is recommended that subjects who receive prophylactic anti-emetic agents prior to infusion of trastuzumab deruxtecan and on subsequent days. Antiemetics such as 5-hydroxytryptamine receptor (5-HT3) antagonists or Neurokinin-1 (NK1) receptor antagonists and/or steroids (e.g. dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines

5.7. Prohibited medications and treatments

With the exception of medications that are under investigation in the study the following medications, treatments, and procedures will be prohibited during the treatment period (refer to Exclusion Criteria no. 17, 18 and 19 in Section 4.2 for required washout periods). The Sponsor must be notified if a patient receives any of these during the study:

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anticancer hormonal treatment [concurrent use of hormones for noncancer-related conditions (e.g. insulin for diabetes and hormone replacement therapy) is acceptable].
- Chloroquine or hydroxychloroquine;
  - if treatment with chloroquine or hydroxychloroquine is required for COVID-19, trastuzumab deruxtecan must be interrupted and a washout period of >14 days is required before restarting trastuzumab deruxtecan.
- Other investigational therapeutic agents.
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in dose modification section).
- Radiotherapy to the thorax and to other tumor sites (except for palliative radiation to known metastatic sites, as long as it does not affect the assessment of response or interrupt treatment for more than the maximum time specified in the dose modification section [Section 5.4]).
- Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications. (Inhaled or topical steroids or intra articular steroid injections are permitted in this study.)
  - Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.

5.7.1.1. Restricted products

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

5.8. Removal of Subjects from Treatment and/or Study

5.8.1. Reasons for Discontinuation of Study Treatment

Any subject who is withdrawn from the study treatment for any reason will have the reason for withdrawal recorded. Subjects may be withdrawn from study treatment after signing the ICF for the following reasons:

- Progressive disease per criteria set forth in RECIST v1.1 (refer to Section 17.5 for details)
- Clinical progression (definitive clinical signs of PD) but a recent radiographic assessment did not meet the criteria for PD according to RECIST v1.1 (refer to Section 17.5 for details)
- AE
- Withdrawal by subject
- Physician decision
- Death
- Pregnancy
- Protocol deviation
- Study termination by the Sponsor
- Loss to follow-up
- Sponsor decision.

If there is evidence that the subject is receiving benefit from treatment even though the subject has met a criterion for discontinuation as listed above, the subject may remain on study treatment after discussion with and approval from the Sponsor's Medical Monitor.

All subjects who are withdrawn from study treatment should complete protocol-specified withdrawal procedures (details in Section 5.8.3) and follow-up procedures (details in Section 6.5).

Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) as allowed by local laws.

5.8.2. Reasons for Withdrawal from the Study

Subject participation in the study will continue until 1 of the following occurs:

- Subject withdraws.
- Subject dies.

- Study is terminated.
- Subject is lost to follow-up.
- Sponsor decides to terminate the study.

All subjects will be followed for survival status even after consent for study procedures is withdrawn. Subjects discontinued from the study because of withdrawal of consent will be followed for survival by collecting public records (eg, death certificates) unless prohibited by local laws. Recruited subjects will not be replaced.

5.8.3. Withdrawal Procedures

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

If the subject is withdrawn from the study as a result of an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be obtained after the last administration of study drug during the EOT Visit (±7 days) (see Section 6.4) and the 40-day (+7 days) Follow-up Visit (see Section 6.5.1).

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 17.1.

6.1. Tissue Screening

To determine eligibility, subjects must have gastric or GEJ cancer that has confirmed HER2-positive disease (tumor score of IHC 3+ or IHC 2+ and evidence of HER2 amplification by FISH), as determined according to ASCO-CAP HER2 test guideline recommendations evaluated at a central laboratory based on a new tissue biopsy obtained after progression on or after a trastuzumab-containing treatment regimen.[36]

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

The following procedures will be conducted at the time of Tissue Screening:

- Obtain a signed and dated written Tissue Screening ICF from the subject prior to collecting tissue.
- Obtain an adequate recent tumor tissue sample for HER2 testing.
  - A tissue sample is considered a recent sample if it is collected from a biopsy performed after a subject's discontinuation of the last treatment regimen and most recent disease progression and prior to the patient's consent for tissue screening. The sample must be a formalin-fixed paraffin embedded (FFPE) block and not stored slides cut previously from such an FFPE block. This recent sample must have sufficient tissue remaining after HER2 pre-screening for exploratory biomarker analyses. At least 2 cores are requested but if the risk of biopsy complications from a second biopsy is unacceptable (at the discretion of the Investigator), then a single mandatory biopsy core will suffice. Refer to the study Laboratory Manual for preparation, number of slides required, storage, and shipment procedures.
  - Bone biopsies are not acceptable (Section 4.1)
  - Fine needle aspirate is not an acceptable technique;
- When perform new biopsy and send wet tissue to the central laboratory, an additional biopsy for exploratory biomarker analyses is not needed.
- If a recent tissue sample is not available or is inadequate, a new tumor biopsy is mandatory for HER2 screening.
- Prepare and send the tissue samples to the central laboratory as per instructions provided in the central Laboratory Manual.
- The central laboratory will assess the HER2 status and provide results to investigators and Daiichi Sankyo Inc. (DSI)
- If a new tumor biopsy is performed after the subject signs the tissue screening ICF but before the main ICF, report any SAEs directly related to tissue pre-screening procedure (ie, tumor biopsy) via paper SAVER forms. Unless documentation of

other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

- Assign Subject ID (SID) number.

6.2. Screening (Day -28 to Day -1)

The duration of the Screening Period is up to 28 days Informed consent will be obtained from the subject before any study-specific procedures are initiated. After the subject has a positive HER2 pre-screening result the subject is eligible to enter the screening period.

The following activities and/or assessments will be performed **within 14 days before** the first dose, during the Screening Period, except as specified otherwise:

- Obtain a signed and dated Main ICF before any study-related procedures or assessments are conducted.
- Obtain:
  - Demographics (eg, birth date, sex, race, ethnicity)
  - Medical and surgical history, including all previous, now resolved, significant medical conditions, date of diagnosis, extent of disease, disease staging, and previous cancer therapies (including prior radiation therapy).
- From the time the subject signs the Main ICF:
  - Record concomitant medications (details in Section 5.6).
  - Record AEs. For details on AE collection and reporting, refer to Section 9.2.
- Perform a complete physical examination, including weight and height (details in Section 9.11).
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; details in Section 9.9).
- Obtain SpO2; details in Section 9.12.
- Assess functional status using the ECOG PS scale (details in Section 17.3).
- Confirm subject eligibility (inclusion and exclusion criteria in Section 4).
- Obtain a new tumor biopsy and submit the tissue sample to the central laboratory for exploratory biomarker testing. Tumor biopsy is not required at Screening,
  - If a new tumor biopsy was already performed and wet tissue sample (not slide) was submitted for HER2 testing during pre-screening as per Section 6.1 above.
  - If there is sufficient remaining pre-screening tissue sample after HER2 confirmation, this specimen can be used and there is no need for an additional biopsy. Refer to Laboratory Manual for further guidance.
- Details regarding shipping instructions to the central laboratory will be provided in the Laboratory Manual.

- Collect and send blood samples to the laboratory for the following tests (details in Section 9.8)
  - Hematology
  - Blood chemistry
  - Coagulation (should also be performed as clinically indicated throughout the study)
  - Troponin (preferably high-sensitivity troponin-T); the test used to test troponin should remain the same throughout the course of a subject's time on study.
- Perform an HIV antibody test as required by local regulations or IRB/ECs (may be done within 28 days of enrollment).
- Perform hepatitis B surface antigen and hepatitis C antibody test (may be done within 28 days of first dose). Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Obtain urine sample for urinalysis (protein, glucose, blood, microscopy assessment [if indicated], and specific gravity; details in Section 9.8).
- Perform an ECHO or MUGA scan for measurement of the LVEF. (Note: The same test [ECHO or MUGA scan] must be used for the subject throughout the study; details in Section 9.12.1.)
- Perform a 12-lead ECG in triplicate within 3 days before first dose (details in Section 9.10). Electrocardiograms should be performed before blood draws.
- Perform a tumor assessment by computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and any other sites of disease within 28 days before first dose. CT/MRI scan obtained within 2 weeks of signing the main ICF could be used as baseline assessment. Note: To assess the objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use it as comparator for subsequent measurements. Therefore, all lesions (target and non-target) have to be assessed at Screening according to RECIST v1.1 (details in Section 17.5). Copies of CT or MRI images should be provided to central review within 2 weeks after confirmation of eligibility.
- A CT or MRI of the brain must be performed for all subjects (details in Section 9.12.4) within 28 days before recruitment. CT/MRI scan obtained within 2 weeks of signing the main ICF could be used as baseline assessment. Copies of CT or MRI images should be provided to central review vendor within 2 weeks after Cycle1 Day.
- Perform ophthalmologic assessment, including visual acuity testing, slit lamp examination, and fundoscopy (details in Section 9.12.3).
- For women of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test within 72 hours prior to the beginning of dosing and document the results. A positive urine pregnancy test result must be confirmed immediately

using a serum test, with a confirmed negative test result within 72 hours prior to drug administration. For subjects of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.

6.3. Treatment Period

6.3.1. Cycle 1 to Cycle 4 and Subsequent Cycles

6.3.1.1. Between 3 Days Before Through Immediately Before Infusion (All Cycles Unless Otherwise Noted)

The following activities and/or assessments will be performed between 3 days before through immediately before the infusion for all cycles unless otherwise noted. (Note: All assessments performed at Cycle 1 are not to be used for screening purposes).

- Assess the HEOR outcomes: The subject must complete the HEOR outcomes questionnaires (FACT-Ga and EQ-5D-5L) before any other assessments or procedures are done. The EQ-5D-5L should be completed before the FACT-Ga questionnaire (details in Section 10.1; sample questionnaires in Section 17.2). Both questionnaires will be self-administered before infusion (BI) and before the completion of any other study-related procedures at Cycle 1 Day 1, at every other cycle (Cycles 3, 5, 7, etc.), and at the EOT Visit.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) (details in Section 9.9) and SpO2 (details in Section 9.12). More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Perform a physical examination, including weight (details in Section 9.11). More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Assess functional status using the ECOG PS scale (details in Section 17.4).
- Perform 12-lead ECG at every infusion before blood draws. Triplicate ECG to be performed if an abnormality is noted. Electrocardiograms should be performed before blood draws (details in Section 9.10).
- Collect and send blood samples to the laboratory for the following clinical laboratory tests (details in Section 9.8). These need not be repeated if performed within 3 days before the first dose of study drug.
  - Hematology
  - Blood chemistry
  - Coagulation, if clinically indicated.
- For women of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test within 72 hours prior to the beginning of dosing and document the results. A positive urine pregnancy test result must be confirmed immediately using a serum test, with a confirmed negative test result within 72 hours prior to drug

administration. For subjects of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.

- Obtain blood samples for:
  - Pharmacogenomics assessment (optional) on Cycle 1 Day 1 only, if the subject provides consent by signing the consent form allowing pharmacogenomics sample banking. This sample is not required for study participation (details in Section 8.4).
  - Collect blood samples for HER2ECD and for cfDNA and cfRNA biomarkers (details in Section 8.3) within 3 days BI on Cycle 1 Day 1 and on Day 1 of every 3 cycles (Cycles 4, 7, etc.).
  - Pharmacokinetic assessment within 8 hours BI at Cycles 1, 2, 3, 4, 6, and 8 (details in Section 8.1).
  - Collect a blood sample for ADA measurement within 8 hours BI on Day 1 of Cycles 1, 2, and 4, and then every 4 cycles (Cycles 8, 12, 16, etc.). If the ADA test is positive at any follow-up visit, collect samples for ADA measurements every 3 months ±14 days up to 1 year after the last dose of study treatment, or until the ADA level returns to baseline or is undetectable, or the subject starts a new anticancer treatment or withdraws consent to participate in the study (details in Section 8.3.2).
- If subject provides consent, samples should be collected prior to study drug infusion on Day 1 of Cycle 1 then starting at Cycle 5, Day 1 and every 4 cycles thereafter. For subjects with suspected or confirmed COVID-19, follow the dose modifications in Section 17.1.
- Record concomitant medications and AEs.
- Perform a tumor assessment every 6 weeks (±7 days) starting at Cycle 1 Day 1 in the first year and every 12 weeks (±7 days) thereafter until objective disease progression or until start of new anticancer treatment, if patient discontinues study treatment for any reason other than disease progression. Refer to RECIST v1.1 guidelines in Section 17.5.
- Perform a CT or MRI of the brain every 6 weeks (±7days) from Cycle 1 Day 1. The brain CT/MRI scan is mandatory for all subjects with stable brain metastases at baseline. For all other subjects, the brain CT/MRI is to be performed as clinically indicated (details in Section 9.12.4).
- Perform an ECHO or MUGA scan for measurement of the LVEF (Note: The same test [ECHO or MUGA scan] must be used for the subject throughout the study; details in Section 9.12.1) on Cycle 5 (±7days) Day 1 BI and every 4 cycles ±7 days thereafter (at Day 1 of Cycles 9, 13, etc.).
- Collect a tumor sample at the end of Cycle 3/prior to Cycle 4 Day 1 (up to 7 days prior to start of Cycle 4) infusion for biomarker analysis, including HER2 status. At least 2 core biopsies are requested at Cycle 3 but if the risk of biopsy complications

from a second core biopsy is unacceptable (at the discretion of the Investigator), then a single core biopsy will suffice.

- Administer trastuzumab deruxtecan as an IV infusion over at least 90 minutes for the first dose (details in Section 5.2.4). If no IRR of any severity is recorded during the first administration, administer subsequent infusions over a minimum of 30 minutes. If IRR is recorded during the first administration, all subsequent infusions will occur over approximately 90 minutes. Record the start and stop times of infusion and amount of drug administered.

6.3.1.2. End of Infusion (All Cycles Unless Otherwise Noted)

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; details in Section 9.9) and SpO2 (details in Section 9.12) for Cycles 1, 2, and 3. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Collect PK blood (serum) samples at the following time points (details in Section 8.1):
  - Within 15 minutes after the end of infusion at Cycles 1, 2, 3, 4, 6, and 8
  - At 5 hours ± 2 hours from the infusion start time at Cycle 1 Day 1 only.
- Continue recording of concomitant medications and AEs.

6.3.1.3. Cycle 1 Day 8 and Cycle 1 Day 15 (± 1 Day)

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; details in Section 9.9) and SpO2 (details in Section 9.12). More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.
- Collect and send blood samples to the laboratory for the following clinical laboratory tests (details in Section 9.8).
  - Hematology
  - Blood chemistry
  - Coagulation, if clinically indicated.
- Collect PK blood (serum) sample (details in Section 8.1).
- Continue recording of concomitant medications, and AEs.

6.4. End of treatment Visit

The EOT is defined as the date the Investigator decides to discontinue study treatment (+7 days). An EOT Visit should be scheduled 30 days (±7 days) after a subject's last dose of study drug. After treatment discontinuation, all subjects will be followed for survival. The following procedures should be performed (details in Table 17.1):

- Assess HEOR outcomes: The subject must complete the HEOR outcomes questionnaires (FACT-Ga and EQ-5D-5L) before any other assessments or procedures are done. The EQ-5D-5L should be completed before the FACT-Ga questionnaire (details in Section 10.1; sample questionnaires in Section 17.2).
- For women of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test and document the results. For subjects of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.
- Obtain vital signs: systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (Section 9.9).
- Obtain SpO2 (details in Section 9.12).
- Perform a physical examination, including weight (details in Section 9.11).
- Assess functional status using the ECOG PS scale (details in Section 17.4).
- Collect and send blood samples to the laboratory for the following clinical laboratory tests (details in Section 9.8).
  - Hematology
  - Blood chemistry
  - Coagulation (if clinically indicated).
- Collect a blood sample for troponin (preferably high-sensitivity troponin-T)
- Collect blood samples for biomarker analysis (HER2ECD, cfDNA and cfRNA) (details in Section 8.3).
- Collect a blood sample for ADA measurement (details in Section 8.3.2).
- Perform ophthalmologic assessment, including visual acuity testing, slit lamp examination, and fundoscopy.
- Perform an ECHO or MUGA scan for measurement of the LVEF (Note: The same test [ECHO or MUGA scan] must be used for the subject throughout the study [details in Section 9.12.1]).
- Perform 12-lead ECG. (details in Section 9.10).
- Mandatory tumor sample for HER2 status and biomarker analysis.
- Continue recording of concomitant medications, AEs, and hospitalization-related records.
- Tumor assessments to evaluate efficacy will be performed until progression of disease or the start of a new anticancer treatment in cases of study treatment discontinuation due to reasons other than disease progression. Tumor assessments should include all sites of disease identified at Screening and any other locations if PD is suspected (eg, MRI of the brain if brain metastases are suspected) should also be imaged, per RECIST v1.1 (Section 17.5). If the previous scan was within the last 6 weeks, this assessment does not need to be performed at the EOT Visit. Copies of

CT or MRI images should be provided to the central review vendor within 2 weeks from images being taken.

6.5. Follow-up

6.5.1. 40-day (+ 7 Days) Follow-up Visit

Forty days (+7 days) after last study drug administration or before starting new anticancer treatment, whichever comes first, the following procedures will be performed as specified in the Schedule of Events (Table 17.1). If EOT is >47 days after last treatment, the EOT assessments can also function as the Follow-up Visit.

- Obtain vital signs: systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature (Section 9.9).
- Obtain SpO2 (details in Section 9.12).
- Perform a physical examination, including weight (details in Section 9.11).
- Assess functional status using the ECOG PS scale (details in Section 17.4).
- Collect and send blood samples to the laboratory for the following clinical laboratory tests (details in Section 9.8).
  - Hematology
  - Blood chemistry
  - Coagulation if clinically indicated.
- Collect a blood sample for ADA measurement. If the ADA test is positive, collect a sample for ADA measurement every 3 months ±14 days, up to 1 year after the last dose of study treatment, or until the ADA level returns to baseline or is undetectable, or until the subject starts a new anticancer treatment or withdraws consent to participate in the study (details in Section 8.3.2).
- Continue recording of concomitant medications, AEs, and hospitalization-related records.
- Record of any additional anticancer therapy for gastric/GEJ cancer, including names of drugs, dosage, dates of administration, response to therapy, if available, and reason for discontinuation, if applicable.
- Perform tumor assessment if not performed at EOT Visit if study treatment was discontinued for any reason other than disease progression. If study treatment was discontinued for reason other than PD, perform at the 40-day Follow-up Visit if not performed at the EOT Visit, and perform every 3 months after the first year, until PD or the start of a new anticancer treatment.

6.5.2. Long-term/Survival Follow-up (Every 3 Months ±14 Days)

After completion of the 40-day (+7 days) Follow-up Visit, the Long-term/Survival Follow-up Visits will be performed every 3 months (±14 days) from the date of 40-day (+7 days) Follow-up

Visit until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

The following activities will take place during Long-term/Survival Follow-up Visits at the study site or by telephone contact:

- Collect a blood sample for ADA measurement. If the ADA test is positive collect a sample for ADA measurement every 3 months ±14 days, up to 1 year after the last dose of study treatment, or until the ADA level returns to baseline or is undetectable, or until the subject starts a new anticancer treatment or withdraws consent to participate in the study (details in Section 8.3).
- Perform tumor assessment every 6 weeks (±7 days) from Cycle 1 Day 1 in the first year and every 12 weeks (±7 days) thereafter until objective disease progression (based on radiologic assessment) or until start of new anticancer treatment, if patient discontinues study treatment for any reason other than disease progression. If study treatment was discontinued for reason other than PD, perform at the 40-day Follow-up Visit if not performed at the EOT Visit, and perform every 3 months after the first year, until PD or the start of a new anticancer treatment.
- Record of any new subsequent line of therapy for gastric/GEJ cancer, including names of drugs, dosage, dates of administration, response to therapy, if available, and reason for discontinuation of each, if applicable.
- Once subjects progress or start other anticancer treatment, they will be followed for survival until death, withdrawal of consent, loss to follow-up, or study closure. If direct contacts are not possible due to withdrawal of consent or the subject becomes lost to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws. Further details on how subjects will be followed for survival status if they withdraw consent are available in Section 5.8.3.

6.6. Additional PK assessments due to Coronavirus disease 2019 (COVID-19)

In case of chloroquine or hydroxychloroquine administration for COVID-19, additional PK serum samples should be collected at the following time points (See Table 8.2)

7. EFFICACY ASSESSMENTS

Baseline tumor assessments will be performed prior to first dose (Cycle 1 Day 1) recruitment, and every 6 weeks (±7 days) from Cycle 1 Day 1 during the treatment period during the first year, and every 12 weeks (±7 days) thereafter until progression of disease or the start of a new anticancer treatment in cases of study treatment discontinuation due to reasons other than disease progression (see Schedule of Events in Table 17.1). All tumor scans during the study period should be submitted for independent central review in a timely manner. Copies of CT or MRI images should be provided to central review within 2 weeks after the images are taken (baseline image is within 2 weeks after Cycle1 Day1).

7.1. Primary Efficacy Endpoint

The primary efficacy endpoint (ie, primary outcome measure) is confirmed ORR, defined as the proportion of subjects who achieved a best overall response of confirmed CR or confirmed PR, as determined by independent central review using RECIST v1.1 (details in Section 17.5).

7.2. Secondary Efficacy Endpoint(s)

7.2.1. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoints is PFS, based on independent central review, defined as the time from the date of start of study treatment to the earliest date of the objective disease progression per RECIST v1.1 or death due to any cause. (details in Section 17.5) or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the DCO date for PFS analysis will be censored at the date of their last evaluable tumor assessment.

7.2.2. Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints include the following:

- PFS, based on Investigator assessment
- OS
- ORR, based Investigator assessment
- DoR, based on both independent central review and Investigator assessment

7.2.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include the following:

- DCR, based on both independent central review and Investigator assessment, defined as the sum of CR, PR, and SD rates, assessed according to RECIST v1.1 (details in Section 17.5)
- Time to response, based on both independent central review and Investigator assessment
- Best percentage change in the sum of diameters of measurable tumors

7.3. Appropriateness of Selected Efficacy Assessments

All selected efficacy endpoints provide evidence of drug activity. ORR is defined as the proportion of subjects with CR and PR as defined by RECIST v 1.1 in this trial. ORR is a direct measure of drug antitumor activity, which can be evaluated in a single-arm study. Because ORR is directly attributable to study drug effect, it is an appropriate measure of efficacy in single-arm trials.

Patients with GC face an illness associated with significant symptoms. Moreover, they are also aware that despite the availability of various treatments, it is ultimately incurable. The success of modern therapies in achieving better disease control and prolonged survival means that more GC patients can receive several lines of treatment and, in the process, the key goals are to prolong survival and to improve health-related QoL. That is why it is particularly valuable to involve subjects in clinical studies by asking them to provide assessment of their health and QoL. The HEOR assessments considered most appropriate for this population are the FACT-Ga and the EQ-5D-5L.

The index scores will be used in further analyses and economic models to generate evidence for access and reimbursement purposes.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic (PK) Assessment(s)

Blood samples for trastuzumab deruxtecan PK analyses will be obtained at the time points specified in Table 8.1 and in the Schedule of Events (Table 17.1).

Table 8.1: Schedule of PK Sample Collection

Cycle	Sampling Time Point (Acceptable Ranges)
1	Day 1: Before infusion: Within 8 hours before the beginning of infusion End of infusion: Within 15 minutes after the end of infusion 5 ± 2 hours from the infusion start time Day 8 ± 1 days Day 15 ± 1 days
2, 3, 4, 6, and 8	Day 1: Before infusion: Within 8 hours before the beginning of infusion End of infusion: Within 15 minutes after the end of infusion

In case of chloroquine or hydroxychloroquine administration for COVID-19, additional PK serum samples should be collected at the following time points (Table 8.2):

Table 8.2: Schedule of PK Sample Collections in Case of Chloroquine and Hydroxychloroquine Treatment

Day of chloroquine or hydroxychloroquine administration	Sampling Time point
Day 1	Prior to chloroquine or hydroxychloroquine dose
Day 3 or 4	Prior to chloroquine or hydroxychloroquine dose (within 4 hours)
EOT with chloroquine or hydroxychloroquine	Prior to chloroquine or hydroxychloroquine dose (within 4 hours)
Prior to re-initiation of trastuzumab deruxtecan	BI (within 8 hours)

BI = before infusion; EOT = End of Treatment

At each time point, blood will be collected for trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a PK analysis. The actual time of study drug administration and the exact time of blood sampling for trastuzumab deruxtecan PK analysis must be recorded on the electronic CRF (eCRF), including those samples collected in case of chloroquine or hydroxychloroquine administration for COVID-19.

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

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

The PK parameters listed in Section 2.3.5 for each subject will be estimated using standard non-compartmental methods.

8.2. Pharmacodynamic Assessment(s)

Not applicable

8.3. Biomarker Assessment(s)

8.3.1. Biomarker assessments

Biomarker analyses will be used to investigate the effect of trastuzumab deruxtecan at the molecular and cellular levels, as well as to determine how changes in the biomarkers may relate to exposure and clinical outcomes.

Plasma samples for assessment of biomarkers such as cfDNA, cfRNA or serum samples for assessment of biomarkers such as HER2ECD will be collected for all subjects within 3 d before the beginning of the infusion on Cycle 1 Day 1; on Day 1 of every 3 cycles thereafter (Cycles 4, 7, etc.); and at the EOT Visit. The sample collection information as required should be recorded on the eCRF page(s) and central laboratory requisition form(s).

Tumor specimens will be used to assess HER2 expression using IHC and/or ISH, and possibly, but not limited to, mRNA expression and mutation profiling, using next-generation sequencing technology or other methods.

For HER2 testing by central laboratory during pre-screening, a new tumor biopsy is required if recent tumor tissue is inadequate or not available for HER2 testing by the central laboratory. A tissue sample is considered a "recent sample" if it is collected from a biopsy performed after the subject's discontinuation of the last treatment regimen and most recent disease progression and prior to patient's consent for tissue screening.

A new tumor biopsy is mandatory at the end of Cycle 3 / prior to Cycle 4 Day 1 infusion (up to 7 days prior to start of Cycle 4), and at the EOT Visit (see Table 17.1). Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the study Laboratory Manual.

8.3.2. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, exploratory biomarker research may be conducted on any collected samples. These studies would extend the search for other potential biomarkers relevant to the effects of trastuzumab deruxtecan, cancer and/or the resistance to the treatment. This may include the development of ways to detect, monitor or treat cancer. These additional investigations would be dependent upon clinical outcome, reagent and sample availability.

The remaining samples (tumor tissues, blood and plasma) may be stored for up to 15 years at the longest, according to the regulation in each country or region respectively, and further analyzed to address scientific questions related to trastuzumab deruxtecan and/or cancer.

8.3.3. Immunogenicity (Anti-drug Antibodies)

Blood samples for ADA analyses will be collected at the time points specified in the Schedule of Events (Table 17.1). If the ADA test is positive at any follow-up visit, collect samples for ADA measurements every 3 months ±14 days up to 1 year after the last dose of study treatment, or until the ADA level returns to baseline or is undetectable, or the subject starts a new anticancer treatment or subject withdraws consent to participate in the study.

Serum concentrations of trastuzumab deruxtecan and/or total anti-HER2 antibody may be measured using the same ADA samples for purpose of ADA assessment.

Details for ADA serum sampling, processing, storage, and shipment for ADA samples will be provided in the study Laboratory Manual.

The ADA testing will be performed by using a validated ADA assay following tiered-assay steps including screening, confirmatory, and titer determination testing. The neutralizing ADA assay will be performed by using the sample confirmed positive. Sample storage time will not exceed 15 years.

8.4. Pharmacogenomic Analysis

8.4.1. Genomic or Genetic Banking and Analysis

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

The DNA samples will be extracted from the blood sample for pharmacogenomics analysis. The pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of trastuzumab deruxtecan. Additionally, samples may be analyzed for genes involved in trastuzumab deruxtecan related signaling pathways, or to examine diseases or physiologic processes related to trastuzumab deruxtecan. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study treatment, as well as helping in the development of new drugs or improvement of existing drugs.

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

8.4.2. Disclosure of the Results of Genomic or Genetic Analysis

Please refer to the ICF for details on disclosure of results.

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

Samples will be retained for up to 15 years at the longest, according to the regulations in each country or region respectively, or until the sample has been exhausted or until the Sponsor instructs the laboratory for sample storage and/or analysis to destroy the sample (in accordance with laboratory procedures).

During the period of storage, the samples will not be immortalized or sold to anyone.

Subjects will have the right to withdraw consent and have their sample destroyed at any time. However, the data will not be discarded if the genetic analysis has been completed before the subject withdraws consent.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoints

Safety parameters will include SAEs, TEAEs, drug-related TEAEs, AESIs, discontinuations due to AEs, ECHO/MUGA scan findings; ophthalmologic findings, physical examination findings, ECOG PS, vital sign measurements, standard clinical laboratory parameters (central laboratory) (blood chemistry, coagulation, and hematology), ADA, and ECG parameters. AEs will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA). AEs and abnormal laboratory test results, if applicable, will be graded using National Cancer Institute (NCI) CTCAE v5.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

9.2. Adverse Event Collection and Reporting

A Treatment-emergent adverse event (TEAE) is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after the initiating the study drug until 47 days after last dose of the study drug. SAEs with an onset or worsening 48 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs.

All clinical AEs and SAEs (see Section 9.4.1 and Section 9.4.2 for definitions), whether observed by the Investigator or reported by the subject, that occur after the subject signs the ICF (including those reported at each follow-up visit) will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to signing the ICF after the subject signs the pre-screening ICF until the first study drug administration, should be recorded as part of medical history.

All AEs, SAEs, and AESIs are to be reported according to the procedures in Section 9.5.

If a tumor biopsy is needed after the subject signs the pre-screening ICF and before the main ICF, report any SAEs directly related to tissue screening procedures (ie, tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy before the subject signs the main ICF, will be recorded during tissue screening.

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

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

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

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

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression/worsening of GC will not be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression, such as nausea, vomiting, and diarrhea, may be recorded as AEs.

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

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

9.3. Adverse Events of Special Interest

Based on available preclinical data, review of the cumulative literature, reported toxicities for the same class of agents, and biological plausibility, the following events are considered to be AESIs: ILD/pneumonitis, and LVEF decrease.

9.3.1. Interstitial Lung Disease/Pneumonitis

9.3.1.1. Clinical Summary

Interstitial lung disease/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the clinical development program, as well as the results of potential ILD/pneumonitis cases reviewed by the independent ILD AC, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.[21]

9.3.1.2. Management Guidance

Interstitial lung disease/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 "Other Non-Laboratory Adverse Events" dose modification section of the protocol (Section 5.4).

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

Evaluations should include:

- High resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Pulmonary function tests and pulse oximetry (SpO_2)
- Blood culture and CBC (other blood tests could be considered as needed)
- Bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered
- Arterial blood gases if clinically indicated
- 1 Blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

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

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

Interstitial Lung Disease Adjudication Committee

An independent ILD AC for the trastuzumab deruxtecan program is responsible for reviewing all cases of potential ILD/pneumonitis. To ensure adequate and relevant independent evaluation, systematic additional data collection will be conducted for all cases that will be brought for adjudication. This additional data collection will cover a more in-depth relevant medical history (eg, smoking, radiation, chronic obstructive pulmonary disease and other chronic lung conditions), diagnostic evaluation, treatment and outcome of the event. This data collection will be triggered for AEs reported by using selected 42 PTs [all from the ILD Standard MedDRA Query (SMQ)] plus 2 PTs of acute respiratory failure and respiratory failure.

9.3.2. LVEF Decrease

9.3.2.1. Clinical Summary

LVEF decrease is considered to be an important potential risk based on the available preclinical data, clinical data, literature and available safety information for drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.[21]

9.3.2.2. LVEF decrease Management Guidance

Left ventricular ejection 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 at EOT locally. Patients may also have local troponin testing as clinically indicated during the treatment phase based on subject-reported cardiac signs or symptoms suggesting congestive heart failure, MI, or other causes of cardiac

myocyte necrosis. An additional sample will be submitted for central laboratory troponin-T testing, and ECG will be performed in triplicate. If the ECG is abnormal, follow institutional guidelines.

ECG will be taken in triplicate at screening. Subsequent ECGs will be performed in triplicate if an abnormality is noted. 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 the ECG was performed, the date performed, the results, and the findings for each parameter will be recorded in the eCRF.

9.4. Adverse Events

9.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Conference on Harmonisation [ICH] E2A Guideline).[37]

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

9.4.2. Serious Adverse Event

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

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

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline).[37]

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

Note:

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

9.4.3. Severity Assessment

The severity of AEs will be graded using the NCI CTCAE v5.0. For each episode, the highest severity grade attained should be reported.

The NCI CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can be only Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can be only Grade 1 or 2. The NCI CTCAE guidelines should be followed closely.

- Grade 1: Mild = asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate = minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe = Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE.

<u>Severity versus Seriousness:</u>

Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness of an event is based upon a universal and global Regulatory definition for reporting SAEs to regulatory agencies. For example, 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 grade may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the Investigator as Grade 1 or 2, but if the subject presents to the emergency facility for evaluation and is hospitalized overnight for observation that immediately makes the event serious based upon hospitalization without regard to the Investigator assessment of severity.

9.4.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be

made on the basis of the available information and can be updated as new information becomes available.

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

    or

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

9.4.5. Action Taken Regarding Study Drug(s)

The final action taken in response to an AE will be recorded as follows:

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.
- Drug Interrupted: The study drug was temporarily stopped.
- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

9.4.6. Other Action Taken for Event

Other actions taken for an AE will be recorded as follows:

- None: No treatment was required
- Medication required: Prescription and/or OTC medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required: Hospitalization was required or prolonged due to the AE, regardless of whether medication was required.
- Other.

9.4.7. Adverse Event Outcome

Outcome of an AE will be recorded as follows:

- Recovered/Resolved: The subject fully recovered from the AE with no residual effect observed.

- Recovered/Resolved with Sequelae: The residual effects of the AE are still present and observable (include sequelae/residual effects).
- Recovering/Resolving: The AE improved but has not fully resolved.
- Not Recovered/Not Resolved: The AE itself is still present and observable.
- Fatal: Death is a direct outcome of the AE.
- Unknown: Should be used if subject is lost to follow-up before an outcome can be determined.

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

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

Additional relevant information regarding the AESIs ILD/pneumonitis, QT prolongation and LVEF decrease for the trastuzumab deruxtecan clinical program regardless of seriousness is to be collected through the targeted questionnaires within the clinical study database. Additional relevant information regarding the AESI IRR is to be collected through the narrative form within the clinical study database.

Serious events that are also efficacy endpoints (eg, PD) and/or safety endpoints will be exempted from SAE processing and expedited reporting. Disease progression should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, "disease progression" should be reported as an SAE and captured on the designated eCRF page. 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 eCRF electronic data capture (EDC) AE page(s) in the clinical database within 24 hours of becoming aware of the event:

- SAEs (see Section 9.4.2 for definition).
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD is defined by the Event Adjudication Site Manual List of PTs).
- Hepatic events (both serious and non-serious) that meet the potential Hy's Law criteria defined as an elevated (ALT or AST) ≥3 × ULN and an elevated blood bilirubin >2 × ULN that may occur either at different time points or simultaneously 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 medically important. An "excessive and medically important" overdose includes any overdose in which an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, ie, poses an actual or potential risk to the subject.

- Overdose is always serious. By definition an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including trastuzumab deruxtecan dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the CRF within eDC.

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

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

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

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

Daiichi Sankyo and/or CRO will inform Investigators IRBs/ECs, and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in other study centers or other studies of the investigational drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

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

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

9.7. Exposure in Utero During Clinical Studies

Daiichi Sankyo must be notified of any subject or the female partner of any subject who becomes pregnant while receiving or within 7 months for females and 4 months for males of discontinuing the study drug.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female subject using the Exposure in Utero (EIU) Reporting Form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum 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 as described in the Schedule of Events (Table 17.1):

1. Hematology tests
    - Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, and differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
2. Blood chemistry tests
    - Total protein, albumin, alkaline phosphatase, ALT, AST, blood bilirubin, blood urea nitrogen, blood urea, calcium, chloride, serum creatinine, lactate dehydrogenase, potassium, sodium, and magnesium
    - A coagulation test (international normalized ratio) will be performed at Screening and thereafter as clinically indicated
    - Creatinine clearance (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation (Section 17.3)
3. Blood samples for troponin (preferably high-sensitivity troponin-T) should be obtained at Screening, at the EOT Visit locally, and as clinically indicated.
4. Urinalysis
    - Protein, glucose, blood, microscopy assessment (if indicated), and specific gravity.
5. Pregnancy test (serum or urine) for all female subjects of childbearing potential. A positive urine pregnancy test result must be confirmed immediately using a serum test.

Information will be entered in the CRF on whether the parameter was measured and the date of measurement. For clinical laboratory parameters, the reference range of the institution that performs the measurements will be used. Local laboratory test results will be transferred to a central laboratory for data entry.

All laboratory values must be appraised by the Investigator as to clinical significance and used to take appropriate clinical management measures. All abnormal laboratory values considered

clinically significant by the Investigator should be recorded on the AE page of the eCRF. If the abnormal laboratory value constitutes an SAE, relevant procedures must be followed (Section 9.5). Abnormal laboratory values (NCI CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

Information will be entered in the eCRF on whether the parameter is measured, the date of the measurement, and measurement results for the following items: systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Blood pressure and pulse rate will be measured after the subject has rested in a recumbent position for 5 minutes or more.

Vital signs will be collected as described in the Schedule of Events (Table 17.1).

9.10. Electrocardiograms

Standard supine/semi-recumbent 12-lead ECGs) will be performed as described in the Schedule of Events (Table 17.1). The ECG will be measured after the subject has rested in a recumbent position for 5 minutes or more. Electrocardiograms should be performed before blood draws.

Standard ECG parameters will be measured, including heart rate, PR interval, RR interval, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities.

QTc intervals will be calculated at each time point according to Fridericia's formula.

9.11. Physical Examinations and Functional Status

Physical examination will be performed as described in the Schedule of Events (Table 17.1).

The following body systems/organs will be evaluated: general appearance; dermatological; head; ears, nose, mouth, and throat; pulmonary; cardiovascular; abdominal; genitourinary (optional); lymphatic; musculoskeletal/ extremities; and neurological.

Weight (kg) and height (cm; collected at Screening only) will be recorded.

Functional status will be assessed using the ECOG PS scale (refer to Section 17.4).

9.12. Other Examinations

9.12.1. Cardiac Assessments

Either an ECHO or MUGA scan will be performed as shown in the Schedule of Events (Table 17.1).

The same method (ECHO or MUGA scan) should be used for the same subject during the entire study.

9.12.2 Pulmonary Assessments

Pulmonary assessments, including CT and additional assessments as outlined in the SOE and ILD management algorithm and SpO2, will be performed as described in the Schedule of Events (Table 17.1).

An ILD AC will review all cases of (potential) ILD on an ongoing basis (details in Section 9.3.1.2).

9.12.3 Ophthalmologic Assessment

An ophthalmologic assessment (including visual acuity testing, slit lamp examination, and fundoscopy) will be performed according to the Schedule of Events (Table 17.1).

9.12.4 Brain Imaging

Baseline brain CT/MRI scan is mandatory. A CT or MRI scan of the brain will be performed as shown in the Schedule of Events (Table 17.1).

For all subjects with asymptomatic brain metastases at Screening, subsequent CT/MRI brain imaging should be performed every 6 weeks (±7 days) from Cycle 1 Day 1. For subjects without brain metastases at Screening, CT/MRI brain imaging will be performed as per Investigator's discretion based on symptoms suspicious of new brain metastases. Baseline CT/MRI scan obtained within 2 weeks of signing main ICF could be used as baseline assessment. Copies of CT or MRI images should be provided to central review within 2 weeks the images taken the image taken (baseline image should be provided after confirmation of subject eligibility).

The same technique (CT or MRI) should be used for the same subject throughout the study.

10. OTHER ASSESSMENTS

10.1. Health Economics and Outcomes Research

Health Economics and Outcomes Research based on PRO will be used to evaluate study treatment. The impact of GC on symptoms and QoL will be assessed based upon the EORTC EQ-5D-5L (Section 17.2.1) and FACT-Ga (Section 17.2.2) questionnaires. The EQ-5D-5L should be completed before the FACT-Ga questionnaire.

Both questionnaires will be self-administered at BI, and before the completion of any other study-related procedures (including blood collection) on Cycle 1 Day 1, on Day 1 of every other cycle beginning with Cycle 3 Day 1 (ie, Cycle 3, 5, 7, etc.), and at the EOT Visit (Table 17.1).

10.1.1. EORTC Five-dimension Five-level Patient-reported Outcome Questionnaire

The EORTC EQ-5D-5L is a self-administered generic measure of standardized health status that consists of 2 parts: the EQ-5D-5L descriptive system and the EuroQual quality-of-life visual analogue scale (EQ-VAS) (see sample in Section 17.2.1).

- The descriptive system consists of 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 cardinal score.
- 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. Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) Questionnaire

The FACT-Ga questionnaire is a self-administered questionnaire that measures QoL in GC.[28,29]

The questionnaire is divided into 5 domains (Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, Functional Well-Being, and Additional Concerns) (see sample in Section 17.2.2). For each statement reflecting his/her QoL with GC, the respondent is asked to choose 1 of 5 responses (Not at all [0], A little bit [1], Somewhat [2], Quite a bit [3], or Very much [4]) applying to the past 7 days.

10.2. Pharmacoeconomic Assessment: Hospitalization-related Endpoint

Time to hospitalization will be assessed. Each hospitalization event will prompt the completion by the site of a detailed hospitalization eCRF containing the following components:

- Date of admission to hospital

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

11. STATISTICAL METHODS

Full details will be specified in the Statistical Analysis Plan (SAP).

11.1. General Statistical Considerations

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized using frequency counts and percentages.

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

The primary efficacy analysis will be performed on the basis of the Full Analysis Set (FAS) population and repeated on the Response Evaluable Set (RES) as a supportive analysis. The other efficacy analyses will be performed on the 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 on the basis of the FAS and availability of assessment.

11.2. Analysis Sets

11.2.1. Full Analysis Set

The FAS will include all subjects who were recruited and have received at least 1 dose of the study drug. (This is the same as the Safety Analysis Set.)

11.2.2. Response Evaluable Set

The RES will include recruited subjects who took at least 1 dose of trastuzumab deruxtecan, had measurable disease at baseline, and had at least 1 postbaseline tumor assessment.

11.2.3. Safety Analysis Set

The Safety Analysis Set will include all recruited subjects who received at least 1 dose of study drug. (This is the same as the FAS.)

11.2.4. Pharmacokinetic Analysis Set

The PK Analysis Set will include all recruited subjects who received at least 1 dose of study drug and had measurable serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and/or MAAA-1181a.

11.3. Study Population Data

Subject disposition will be summarized for the FAS population. The total number of subjects for each defined analysis set will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the FAS population, Safety Analysis Set, RES, and PK

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

11.4. Efficacy Analysis

Definitions of the efficacy endpoints are provided in Section 7.

The convention to be followed when assessing response or progression will be to assign a single date to evaluations performed within that time point. The date of response (CR, PR, SD, or not evaluable [NE]) will be recorded as the date of the last radiographic evaluation included in the series for that assessment. The date of PD will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

11.4.1. Primary Efficacy Analysis

The primary efficacy endpoint is ORR by independent central review. Only confirmed ORR will be considered in the primary analysis. Analysis of ORR will be performed for all enrolled subjects at the 18-week tumor assessment. The estimate of ORR and its 2-sided 95% exact CI will be provided using Clopper-Pearson method. The primary efficacy analysis will be performed on the basis of the ITT population and repeated on the RES as a supportive analysis.

11.4.2. Secondary Efficacy Analyses

The key secondary endpoint PFS as assessed based on independent central review. Subjects who are alive with no objective documentation of (radiographic) disease progression as assessed by independent central review by the DCO date for PFS analysis will be censored at the date of their last evaluable tumor assessment. Kaplan-Meier estimate and survival curve will be presented. The median event time and the corresponding 95% CI will be provided using the Brookmeyer and Crowley method.

Additional secondary efficacy endpoints are as follows:

- PFS by Investigator assessment will be analyzed in the same way as that used for PFS, based on independent central review.
- OS: If a subject is alive at the time of data analysis, OS will be censored at the last contact date at which the subject is known to be alive. Kaplan-Meier estimate and survival curve will be presented. The median event time and the corresponding 95% CIs will be provided using Brookmeyer and Crowley method.
- ORR based on Investigator assessment, measured for responding subjects (PR or CR) only, will be analyzed in the similar approach as used for the primary endpoint.
- DoR will be measured for responding subjects (PR or CR) only. Subjects who are alive and progression-free at the time of the analyses will be censored at the date of the last evaluable tumor assessment. DoR based on independent central review and Investigator assessment will be summarized separately with median event times and its 95% CIs using the Brookmeyer and Crowley method. DoR will be analyzed based on tumor assessment by independent central review and by Investigator.

11.4.3. Exploratory Efficacy Analyses

- DCR will be measured for subjects with CR, PR, or SD. DCR will be analyzed on the basis of tumor assessment by independent central review and by Investigator.
- Time to response is defined as the time from the date of first dose to the date of the first documentation of confirmed objective response. Time to response will be measured for responding subjects (PR or CR) only. Time to response based on independent central review and Investigator assessment will be summarized separately with median event times and their 95% CIs for the median by using Brookmeyer and Crowley methods by part/dose group and overall.
- Best percentage change in tumor size will be graphed by using waterfall plot.

11.5. Health Economics and Outcome Research Analyses

Health Economic and Outcomes Research endpoints based on the hospitalization-related data collection form and the 2 PRO questionnaires (EQ-5D-5L and FACT-Ga) will be summarized. A detailed analysis plan of QoL endpoints will be provided in the SAP. Some descriptive analysis will be performed.

11.5.1. EORTC Five-dimension Five-level Quality-of-life Questionnaire

Based on results of the EQ-5D-5L assessment, the EQ-5D-5L summary index score across disease states will be assessed. Descriptive statistics for the actual value and change from baseline will be computed for the EQ-5D-5L health profile utilities and EQ-5D VAS by scheduled time of evaluation (including EOT Visit) for all subjects. Results of the EQ-VAS will be presented as a measure of overall self-rated health status.

11.5.2. FACT-Gastric Questionnaire

Descriptive statistics for the actual value and change from baseline will be computed for by scheduled time of evaluation (including the EOT Visit) and treatment group.

11.6. Pharmacokinetic/Biomarker/Pharmacogenomic Analyses

Pharmacokinetic analyses will be performed on the PK Analysis Set (definition in Section 11.2.4).

11.6.1. Pharmacokinetic Analyses

Serum concentrations for trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a will be listed, plotted, and summarized by using descriptive statistics at each time point. PK parameters for trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a will be listed and summarized using descriptive statistics.

11.6.2. Population-PK Analyses

The population-PK analysis to evaluate the effect of intrinsic and extrinsic factors of trastuzumab deruxtecan, and if appropriate, total anti-HER2 antibody and MAAA-1181a will be characterized including available PK data from the other trastuzumab deruxtecan clinical trials.

After establishment of the population-PK model, a population-PK/pharmacodynamic model may be developed to evaluate the relationship between exposure and efficacy and toxicity. The results of the nonlinear mixed effects population-PK and population-PK/pharmacodynamic models may be reported separately from the clinical study report.

11.6.3. Biomarker Analyses

A new tissue sample after progression on first-line treatment with a trastuzumab-containing regimen will be requested for analysis of HER2 status by IHC and/or ISH for eligibility assessment. Remaining tissue samples, if available, will be used to perform exploratory biomarker analysis. If there is no sample left over then a new biopsy would be needed at the screening visit prior to C1D1. Mandatory biopsies on treatment will be collected between the end of Cycle 3 and the beginning of Cycle 4 (Day 1) and at EOT to assess exploratory biomarkers. In addition, biomarkers in plasma and serum may be analyzed. Biomarkers will be summarized by using descriptive statistics.

11.6.4. Pharmacogenomic Analyses (Optional)

See details on the optional pharmacogenomics in Section 8.4. Pharmacogenomic analyses will be described in a separate SAP, as applicable.

11.7. Safety Analyses

Safety analysis will be performed using the Safety Analysis Set.

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

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

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

11.7.1. Adverse Event Analyses

A TEAE is defined as an AE that occurs, having been absent before the first dose of study drug, or has worsened in severity or seriousness after the initiating the study drug until 47 days after last dose of the study drug. SAEs with an onset or worsening 48 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs.

Non-SAEs or non-related SAEs that occur 48 days or more after the last dose will not be included in the analysis of TEAE but will be summarized separately and briefly stated in the text. TEAEs will be coded by using the latest version of MedDRA and assigned grades based on NCI CTCAE v5.0. The number and percentage of subjects reporting TEAEs will be tabulated by SOC, PT, relationship to the study treatment, and the worst CTCAE grade.

Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated, as well as TEAEs leading to discontinuation of study treatments.

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

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

11.7.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline at each scheduled time of evaluation, including the EOT Visit. The change from baseline will be summarized for the maximum and minimum post-treatment values.

Abnormal clinical laboratory results will be graded according to NCI CTCAE v5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table will present a 2-way frequency tabulation for baseline and the worst post-treatment value according to NCI CTCAE grade.

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

11.7.3. Vital Sign Analyses

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

11.7.4. Electrocardiogram Analyses

Descriptive statistics will be provided for ECG parameters and changes from baseline by scheduled time of evaluation, including the EOT Visit and maximum post-treatment values. In addition, the number and percentage of subjects with categorical ECG interval values meeting the CTCAE v5.0 criteria will be tabulated. The QT intervals will be corrected for heart rate by Fridericia's formula ($QTcF = QT/[RR]^{1/3}$). The ECG data will also be listed.

11.7.5. Physical Examination Analyses

Physical examination findings will be listed.

11.7.6. Concomitant Medication Analyses

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

11.7.7. Immunogenicity (Anti-drug Antibody) Analyses

Immunogenicity will be assessed through characterization of incidence and titer of ADA. The number and percentage of subjects will be calculated for the presence or absence of development

of ADA after the start of administration, defining subjects who are negative for ADA at all time points as negative and subjects who are positive for ADA at ≥1 time point after drug treatment as positive. The raw values and change from baseline for ADA titers will be summarized by time point using descriptive statistics.

All other safety variables per Section 9.12 will be listed.

11.7.8. Other Safety Analyses

All other safety endpoints (eg, ECOG PS and LVEF) will be listed and an analysis of change from baseline will be performed.

11.8. Sample Size Determination

On the basis of historical data of current SoC, western patients with second-line gastric or GEJ cancer have reported best ORR of ~27%. Seventy-two subjects provides a 90% power to achieve a lower limit of 95% CI for the ORR that exceeds 27% (threshold) under the expected ORR of 45%. Taking into consideration potential dropouts, a sample size of approximately 80 subjects will be recruited. The sample size computation was performed by using EAST v6.4.

11.9. Statistical Analysis Process

The clinical study data will be analyzed by the Sponsor or its designated agent/CRO.

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

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

All statistical analyses will be performed by using SAS® v9.3 or higher (SAS Institute Inc., Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

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

12.1. Monitoring and Inspections

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

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

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

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

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

12.2. Data Collection

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

The eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study.

An eCRF must be completed for each subject who signs a main ICF and undergoes any Screening procedures. For subjects who are screened but not recruited, minimal data will be recorded on the eCRF, including demography, subject status, and AEs (or SAEs, as appropriate). All study-related data for these subjects will be maintained in the medical records at the site.

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

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

12.3. Data Management

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

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

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

Serious AEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA.

All concomitant medications and prior cancer therapies will be coded using the WHO Drug Dictionary.

12.4. Study Documentation and Storage

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

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

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These

records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

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

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

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

All study-related essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

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

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor will comply with US, EU, and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. The Sponsor will follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3),"[38] and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Committee of Medical Journal Editors (ICMJE).[39]

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

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

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

- US FDA GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate;

and/or

- Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal product for human use;

and/or

- Other applicable local regulations.

15.2. Subject Confidentiality

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

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

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

15.3. Informed Consent

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study, and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries and should have adequate time to decide whether to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that

have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB/EC prior to being provided to potential subjects.

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

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the IB, written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the IRB/EC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

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

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

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

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

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

15.5. Protocol Deviations

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

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

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

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

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

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

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

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

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

15.7. Protocol Amendments

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

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

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

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

15.8. Study Termination

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

15.9. Data and Safety Monitoring Board

A Data Monitoring Committee is not applicable for this trial given that it is an open-label trial. However, measures are put in place for monitoring the safety of the subjects participating in the study. Individual subject data will be reviewed on an ongoing basis and aggregate safety data will be monitored monthly by the study team across the duration of the trial following the Sponsor's established safety monitoring SOPs. The data review and analysis will be based on the available Investigator reported data in the clinical database.

15.10. Address List

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

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17. APPENDICES

17.1. Appendix1: Schedule of Events

Table 17.1 Schedule of Events

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment[b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
			Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
		Day -28 to Day -1	BI	EOI			BI	EOI	BI	EOI	BI	EOI				
Informed consent	●	●														
Assign subject ID	●															
Tumor sample for HER2 status and biomarkers	●										●		●			New tissue post-trastuzumab therapy is required for eligibility. Collect a mandatory tumor sample at the end of Cycle 3/prior to Cycle 4 Day 1 infusion for biomarker analysis, including HER2 status. At least 2 core biopsies are requested at Cycle 3 but if the risk of biopsy complications from a second core biopsy is unacceptable (at the discretion of the Investigator), then a single mandatory core biopsy will suffice.
Medical/surgical history		●														Collect within 14 days before recruitment
Demographics		●														Collect within 14 days before recruitment

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment [b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
			Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
		Day -28 to Day -1	BI	EOI			BI	EOI	BI	EOI	BI	EOI				
HEOR outcomes			●						●		●		●			The subject must complete the HEOR outcomes questionnaires (FACT-Ga and EQ-5D-5L) before any other assessments or procedures are done. The EQ-5D-5L should be completed before the FACT-Ga questionnaire (details in Section 10.1 ; sample questionnaires in Section 17.2). Both questionnaires will be self-administered BI and before the completion of any other study-related procedures at Cycle 1 Day 1, at every other cycle (Cycle 3, 5, 7, etc.), and at the EOT Visit.
Pregnancy test		●	●				●		●		●		●			For women of childbearing potential (as defined in Section 4.1), perform a serum or urine pregnancy test within 72 hours prior to the beginning of dosing and document the results. A positive urine pregnancy test result must be confirmed immediately using a serum test, with a confirmed negative test result within 72 hours prior to drug administration. For subjects of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.
Vital signs		●	●	●	●	●	●	●	●	●	●		●	●		Within 14 days before first dose and within 3 days BI, measured in a supine/semi-recumbent position.

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment[b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
			Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
		Day -28 to Day -1	BI	EOI			BI	EOI	BI	EOI	BI	EOI				
SpO2		●	●	●	●	●	●	●	●	●	●		●	●		Within 14 days before first dose and within 3 days BI
Physical examination		●	●				●		●		●		●	●		Within 14 days before first dose and within 3 days BI
Height		●														
Weight		●	●				●		●		●		●	●		Within 3 days BI
Inclusion/ exclusion		●														Within 14 days before first dose
ECOG PS		●	●				●		●		●		●	●		Within 14 days before first dose and within 3 days BI
12-lead ECG		●	●								●		●			ECG will be taken in triplicate at screening. Subsequent ECGs will be performed in triplicate if an abnormality is noted. ECGs will be taken in close succession, while in a supine/semi-recumbent position. ECGs will be taken at every 4th cycle.
Hematology, blood chemistry, coagulation tests		●	●		●	●	●		●		●		●	●		Within 14 days before first dose and within 3 days BI Coagulation test (international normalized ratio) will be performed at Screening and thereafter as clinically indicated.

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment[b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
			Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
		Day -28 to Day -1	BI	EOI			BI	EOI	BI	EOI	BI	EOI				
Troponin		●											●			Collect blood samples for troponin (preferably high-sensitivity troponin-T) at Screening (for eligibility), EOT, and if at any time a subject reports signs or symptoms suggesting congestive heart failure, MI, or other causes of myocyte necrosis. See Section 6.2 Section 6.4
HIV antibody test		●														See Section 4.2
Hepatitis B/C Serology		●														See Section 4.2
COVID-19 Sample			●								●					If subject provides consent, samples should be collected prior to study drug infusion then starting at C5 D1 and every 4 cycles thereafter. Section 6.3.1 For subjects with suspected or confirmed COVID-19 infections, follow the dose modifications in Section 17.7
Urinalysis		●														Within 14 days before first dose.
Ophthalmologic assessment		●											●			Within 14 days before first dose and EOT. Includes visual acuity testing, slit lamp examination, and fundoscopy

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment [b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
			Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
		Day -28 to Day -1	BI	EOI			BI	EOI	BI	EOI	BI	EOI				
Echocardiogram or MUGA scan (LVEF)		●									●		●			At Screening (within14 days before recruitment) and BI on Cycle 5 Day 1, and then every 4 cycles ± 7 days (Cycles 9, 13, etc.) and at the EOT Visit. Use same test throughout the study.
Tumor assessment		●										●	●		●	Within 28 days before recruitment and every 6 weeks (± 7days) from Cycle 1 Day 1 in the first year and every 12 weeks (± 7days) thereafter until objective disease progression or until start of new anticancer treatment, if patient discontinues study treatment for any reason other than disease progression. To be done at EOT if not done within the previous 6 weeks. If study treatment was discontinued for reason other than PD, perform at 40-day Follow-up Visit if not performed at EOT, and perform Q3M after the first year, until PD or the start of a new anticancer treatment.
CT/MRI of the brain (Baseline brain CT/MRI scan is mandatory)		●										●	●			A CT or MRI of the brain must be performed for all subjects (details in Section 9.12.4) within 28 days before recruitment. CT/MRI scan obtained within 2 weeks of signing main ICF could be used as baseline assessment. Copies of CT or MRI images should be provided to central review vendor within 2 weeks after Cycle1 Day1.

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment[b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
			Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
		Day -28 to Day -1	BI	EOI			BI	EOI	BI	EOI	BI	EOI				
Administer trastuzumab deruxtecan			●			●		●		●						Administer Q3W ± 2 days unless discontinuation criteria are met. The first infusion of trastuzumab deruxtecan will occur over at least 90 minutes. If there is no IRR, the subsequent infusions of trastuzumab deruxtecan will be over at least 30 minutes. In case of IRR of any severity grade at any time during the first administration of trastuzumab deruxtecan, all subsequent infusions will occur over 90 minutes.
Blood samples for biomarker analysis			●								●		●			Cycle 1 Day 1 sample can be collected within 3 days before beginning infusion; thereafter, samples will be collected every 3 cycles (Cycles 4, 7, etc.) until EOT. See Section 8.3
Blood sample for pharmaco-genomics			●													Participation in this part of the study is optional for all subjects.
Blood (serum) sample for PK			●	●	●	●	●	●	●	●	●	●				Cycle 1 Day 1: Within -8 hours BI, within 15 minutes of EOI, at 5 ± 2 hours from infusion start time; Cycle 1 Day 8 ±1 day; Cycle 1 Day 15 ±1 day; Cycles 2, 3, 4, 6, and 8: Day 1 within -8 hours BI and within 15 minutes of EOI.

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment[b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
		Day -28 to Day -1	Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
			BI	EOI			BI	EOI	BI	EOI	BI	EOI				
PK Sampling for CQ/HCQ Administration[e]			If CQ or HCQ is administered for COVID-19, additional PK blood samples should be collected at the following visits: • Prior to the first CQ or HCQ dose (Day 1) • Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) • Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) • The day of trastuzumab deruxtecan resumption, after the CQ/HCQ washout period[g], (within 8h BI of trastuzumab deruxtecan)													[g]A washout period of > 14 d is required before restarting trastuzumab deruxtecan. See Table 8.2
Blood sample for ADA			•				•				•		•	•	•	Within 8 hours BI on Day 1 in Cycles 1, 2, and 4, and then every 4 cycles (Cycles 8, 12, 16, etc.). If positive ADA at any Follow-up Visit, collect samples every 3 months ± 14 days up to 1 year after the last dose, or until the ADA returns to baseline or is undetectable, or start of new anticancer therapy, or subject withdraws consent from the study.
Record of anticancer therapy for gastric/GEJ cancer														•	•	Include names of drugs, dosage, dates of administration, response to therapy, if available, and reason for discontinuation, if applicable.
Concomitant medications		•													•	Collect from the time the subject signs the main ICF
		•													•	Collect from the time the subject signs the main ICF

	Tissue screening	Screening	Cycle 1				Cycle 2		Cycle 3		Cycles 4-x		End of treatment [b]	40-day follow-up[c]	Follow-up every 3 months ±14 d[d]	Comments
		Day -28 to Day -1	Day 1[a]		Day 8 ±1 d	Day 15 ±1 d	Day 1 (±2 days)		Day 1 (±2 days)		Day 1 (±2 days)					
			BI	EOI			BI	EOI	BI	EOI	BI	EOI				
AEs	●	●													●	Collect from the time the subject signs the main ICF At Tissue Screening, SAEs are recorded only if directly related to tissue screening procedure, unless documentation of other AEs is required by local law.
Survival follow-up															●	

ADA= anti-drug antibody; AEs = adverse events; BI = before infusion; CQ = Chloroquine; COVID-19 = coronavirus disease 2019; CT = computed tomography; d = day; ECG = electrocardiogram; ECOG PS= Eastern Cooperative Oncology Group PS = performance status; EOI = end of infusion; EOT = end of treatment; EQ-5D-5L = European Organization for Research and Treatment of Cancer 5-dimension 5-level patient-reported outcome questionnaire; FACT-Ga = Functional Assessment of Cancer Therapy-Gastric; HCQ = hydroxychloroquine; HEOR = Health Economics and Outcome Research; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; ID = identification number; ILD = interstitial lung disease; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PD = progressive disease; PK = pharmacokinetics; Q3M = every 3 months; SpO2 = peripheral oxygen saturation

[a] Cycle 1 Day 1 (first dose) for the subject should occur within 28 days from signing the Main ICF.

[b] The date the Investigator decides to discontinue study treatment (+7 days). Refer to Section 6.4 to determine whether new tests need to be conducted.

[c] 40 days (+7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first. If EOT is >47 days after last treatment, then the EOT assessments can also function as the 40-day Follow-up Visit. Refer to Section 6.5.1 to determine whether new tests need to be conducted.

[d] Long-term/Survival follow-up will occur every 3 months (± 14 days) from the date of the 40-day (+7 days) Follow-up Visit, until death, withdrawal of consent, or loss of follow-up, whichever comes first, and can be conducted via phone or in person at a site visit.

[e] If subject provides consent, samples should be collected

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);
- Pulmonary function tests and pulse oximetry (SpO2);
- Blood culture and CBC. Other blood tests could be considered as needed;
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible;
- Arterial blood gases if clinically indicated ;
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible.

Other tests could be considered, as needed.

17.2. Appendix 2: Quality-of-life Questionnaires

17.2.1. EORTC 5-dimension 5-level (EQ-5D-5L) Questionnaire

Note: The EQ-5D-5L questionnaire should be completed before the FACT-Ga questionnaire.

Source: Available at: https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf.

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

MOBILITY

- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE

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

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

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

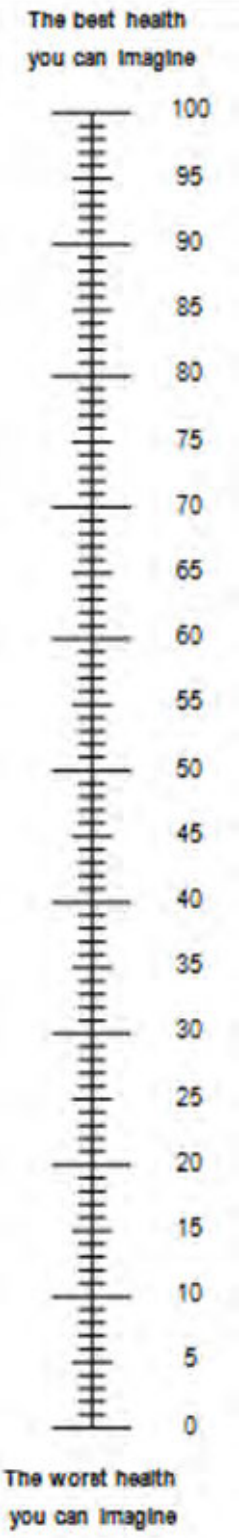
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- 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 = ☐



3

17.2.2. Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) Questionnaire

Source: http://www.facit.org/facitorg/questionnaires

Eremenco SL, Cashy J, Webster K, et al. FACT-Gastric: a new international measure of QOL in gastric cancer. J Clin Oncol. 2004;22(*Suppl 14*):abstract 8123.

Garland SN, Pelletier G, Lawe A, et al. Prospective evaluation of the reliability, validity, and minimally important difference of the functional assessment of cancer therapy-gastric (FACT-Ga) quality-of-life instrument. Cancer. 2011;117(6):1302-12.

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4

GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	<u>FUNCTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4

GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
Ga2	I am bothered by reflux or heartburn	0	1	2	3	4
HN1	I am able to eat the foods that I like	0	1	2	3	4
Ga6	I have discomfort or pain when I eat	0	1	2	3	4
Ga5	I have a feeling of fullness or heaviness in my stomach area	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
Ga 12	I have trouble swallowing food	0	1	2	3	4
Ga4	I am bothered by a change in my eating habits	0	1	2	3	4
E6	I am able to enjoy meals with family or friends	0	1	2	3	4
Ga 10	My digestive problems interfere with my usual activities	0	1	2	3	4

Ga9	I avoid going out to eat because of my illness	0	1	2	3	4
Ga7	I have stomach problems that worry me	0	1	2	3	4
Hep8	I have discomfort or pain in my stomach area	0	1	2	3	4
Ga 14	I am bothered by gas (flatulence)	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
Leu4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

17.3. Appendix 3:Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the modified Cockcroft-Gault equation based on actual weight in kilograms[33] (1 kilogram = 2.2 pounds):

Conventional – serum creatinine in mg/dL:

Male:

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

Female:

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

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

Male:

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

Female:

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

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

17.4. Appendix 4: Eastern Cooperative Oncology Group Performance Status (ECOG PS)

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.[42]

17.5. Appendix 5: Response Evaluation Criteria in Solid Tumors Version 1.1

This appendix is provided for convenience. The complete RECIST v1.1 guidelines are found as follows:

Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;4(2)5:228-47.

17.5.1. Measurability of Tumor at Baseline

17.5.1.1. Definitions

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

17.5.1.1.1. Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

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

17.5.1.1.2. Non-measurable

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

17.5.1.1.3. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, 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.

Cystic lesions:

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

Lesions with prior local treatment:

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

17.5.1.2. Specifications By Methods of Measurements

17.5.1.2.1. Measurement of Lesions

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

17.5.1.2.2. Method of Assessment

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

Clinical lesions:

Clinical lesions will only be considered measurable when they are superficial and ≥10mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging,

imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray:

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

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).

Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator-dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy:

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor markers:

Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the ULN, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease-specific, instructions for their measurement should be incorporated into protocols on a disease-specific basis.

Cytology, histology:

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ-cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

17.5.2. Tumor Response Evaluation

17.5.2.1. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least 1 measurable lesion (as detailed above in Section 17.5.1). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

17.5.2.2. Baseline Documentation of Target and Non-target Lesions

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

Target lesions should be selected on the basis of their size (lesions with the longest diameter [LD]), 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 in Section 17.5.1.1.1, pathological nodes which are defined as measurable and may be identified as TL must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions (NTL). 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 TLs will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as NTLs and should also be recorded at baseline. Measurements are not required and these lesions

should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple NTLs involving the same organ as a single item on the CRF (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

17.5.2.3. Response Criteria

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

17.5.2.3.1. Evaluation of Target Lesions

- CR: Disappearance of all TLs. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- PR: At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum diameters.
- PD: At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions [NLs] is also considered progression).
- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

17.5.2.3.2. Special Notes on the Assessment of Target Lesions

Lymph nodes:

Lymph nodes identified as TLs should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as TLs, 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. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of TLs.

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 TLs at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum;

however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment:

When non-nodal lesions "fragment," the LDs of the fragmented portions should be added together to calculate the TL 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 LD in this instance should be the maximal LD for the "coalesced lesion."

17.5.2.3.3. Evaluation of Non-target Lesions

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

- CR: Disappearance of all NTLs 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 NTL(s) and/or maintenance of tumor marker level above the normal limits.
- PD: Unequivocal progression of existing NTLs. (Note: the appearance of 1 or more NLs is also considered progression).

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

The concept of progression of NTLs requires additional explanation as follows:

When the patient also has measurable disease:

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

When the patient has only non-measurable disease:

This circumstance arises in some Phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied

when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

17.5.2.3.5. New Lesions

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

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

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

While fluorodeoxyglucose-positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). Please refer to the complete guidelines for further details.[40]

17.5.2.4. Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. On occasion, a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and non-target disease, and will also take into consideration the appearance of NLs. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

17.5.2.4.1. 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 patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 17.3 is to be used.

Table 17.2 Time Point Response: Patients with Target (±Non-target) Disease

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

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable

Table 17.3: Time Point Response: Patients with Non-target Disease Only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not All Evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; NE = not evaluable

17.5.2.4.2. Missing Assessments and Non-Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is 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 patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

17.5.2.4.3. Best Overall Response: All Time Points

The BOR is determined once all the data for the patient are known.

Best response determination in trials where confirmation of CR or PR is NOT required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient 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 patient lost to follow-up after the first SD assessment would be considered non-evaluable.

Best response determination in trials where confirmation of complete or partial response IS required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the BOR can be interpreted as in Table 17.4.

Table 17.4: Best Overall Response When Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

17.5.2.4.4. Special Notes on Response Assessment

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

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 17.2 to Table 17.4.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR.

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

17.6. Appendix 6: New York Heart Association Functional Classification

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

Source: New York Heart Association Criteria Committee. Functional capacity and objective assessment. In: Dolgin, M, editor. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Boston: Little, Brown & Co; 1994 p. 253-256.

17.7. Appendix 7: Instructions Related to Coronavirus disease 2019 (COVID-19)

Due to the potential impact of COVID-19, on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected COVID-19 while being treated with trastuzumab deruxtecan. Dose modifications will be based on the worst CTCAE grade. **Use CTCAE version 5.0 general grading criteria to evaluate COVID-19.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs

Dose modification criteria for suspected or <u>confirmed COVID-19</u>

If COVID-19 is suspected, interrupt trastuzumab deruxtecan and rule out COVID-19 per local guidance.

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Section 5.4.1
- If COVID-19 is confirmed or is still suspected after evaluation follow dose modification as outlined in Table 17.5 below and manage COVID-19 per local guidance until recovery. COVID-19 recovery is defined as no signs/symptoms of COVID-19, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

Table 17.5: COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity NCI CTCAE Version 5.0 Grade (unless otherwise specified)	Schedule Modification for trastuzumab deruxtecan
Grade 1	Resume study drug at the same dose[a]
Grade 2	Resume study drug at the same dose if chest CT findings are completely resolved[a] Reduce by 1 dose level if chest CT findings are nearly resolved
Grade 3	Reduce by 1 dose level if chest CT findings are completely resolved Discontinue drug if chest CT findings are <u>not</u> completely resolved
Grade 4	Discontinue study drug

COVID-19 = Coronavirus disease 2019; CT = computed tomography

[a] Closely monitor signs/symptoms after resuming trastuzumab deruxtecan, 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 17.5, Investigators may consider dose modifications of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee.

If an event is suspected to be drug-related ILD/pneumonitis, manage per protocol ILD/pneumonitis management guideline (Table 5.1).

Prior and Concomitant Medications

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 4.2).
  - If treatment is absolutely required for COVID-19, trastuzumab deruxtecan must be interrupted.
  - If administered, then a washout period of more than 14 days is required before restarting trastuzumab deruxtecan.

PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected from each subject who provides consent, if chloroquine or hydroxychloroquine is administered for COVID-19, at the time points specified in the Schedule of Events Section 17.1.

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

Coronavirus disease 2019 (COVID-19) Assessments

All confirmed or suspected COVID-19 events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of COVID-19, but the real-time RT-PCR test is not available at the site, the participant must not have any signs or symptoms of COVID 19 infection for at least 2 weeks and nearly or completely resolved chest CT findings/a sample kit will be provided for sample collection to be tested at a central laboratory. The results will be provided to the site from the central laboratory.

Serum samples will be used for COVID-19 testing from each subject who provides consent. Samples will be collected prior to the study drug infusion, will be shipped to a central laboratory and stored there until the tests become available.

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

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

Statistical Analysis - Assessment of the Impact of Coronavirus Disease 2019 (COVID-19)

If deemed appropriate, analyses will be performed to explore the impact of COVID-19 on the safety, efficacy, and any other endpoints, as appropriate, reported for the study.

As a result of the impact of COVID-19 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the SAP.