CLINICAL STUDY PROTOCOL

A PHASE 2, MULTICENTER, OPEN-LABEL, 2-COHORT STUDY OF TRASTUZUMAB DERUXTECAN (DS-8201a), AN ANTI-HER2 ANTIBODY DRUG CONJUGATE (ADC), FOR HER2-OVER-EXPRESSING OR -MUTATED, UNRESECTABLE AND/OR METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

[DESTINY-Lung01]

DS8201-A-U204
IND NUMBER 137009
EUDRACT NUMBER 2017-004781-94

VERSION 7.0, 14 JULY 2020

DAIICHI SANKYO, INC.
211 MT. AIRY ROAD
BASKING RIDGE, NJ 07920-2311
UNITED STATES

INVESTIGATOR AGREEMENT

A Phase 2, Multicenter, Open-Label, 2-Cohort Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2 Antibody Drug Conjugate (ADC), for HER2-Over-Expressing or -Mutated, Unresectable and/or Metastatic Non-Small Cell Lung Cancer (NSCLC)

[DESTINY-Lung01]

Sponsor Approval:

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

PPD	PPD
Print Name	Signa
Medical Monitor	14/07/2020
Title	Date (DD/MM/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 ethical principles that have their origin in the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 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
6.0	21 Feb 2020
5.0	12 Aug 2019
4.0	02 May 2019
3.0	19 Mar 2018
2.0	09 Feb 2018
1.0	13 Nov 2017

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 7.0 (dated 14 July 2020) vs. protocol Version 6.0 (dated 21 Feb 2020) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS8201-A-U204 clinical study protocol (Version 7.0) by section.

Amendment Rationale:

This amendment is primarily driven by the need for alignment with the latest safety information on-trastuzumab deruxtecan; additional information on Coronavirus disease 2019 (COVID-19) and update to interstitial lung disease (ILD) management.

This and other changes are briefly described in the table below.

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 following table.

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis	Destiny number was added. The description of the statistical analyses was updated	To provide clarification To align with the planned interim analyses
1.1.3.3. DS8201-A-U204: Treatment Emergent Events Table 1.3: Serious Treatment-Emergent Adverse Events in Study DS8201-A-U204 through 08 Jun 2019 1.1.3.4. DS8201-A-U204: Deaths, Serious Treatment-Emergent Adverse Events, and Dose Modifications Due to Treatment-Emergent Adverse Events	These subsections were deleted.	The safety data provided is now outdated

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis 4.1. Inclusion Criteria	Presentation of the Cockcroft-Gault equation in criterion 10 was updated. Use of chloroquine/hydroxychloroquine was added to criterion 11. Criteria 2 and 11 were also updated	To align with the latest safety information
Protocol Synopsis 4.1. Exclusion Criteria	Exclusion criterion 5 was deleted and criteria 11 and 14 updated	To align with the latest safety information
Table 5.1 Sample Dose Reduction Levels of Trastuzumab Deruxtecan	Dose Level -2 was changed from 3.4 mg/kg to 3.2 mg/kg	To align with the dose reduction used in other studies
5.4.1. Dose Reduction and Interruption Guidelines	The following sentence was added: All confirmed or suspected Coronavirus disease 2019 (COVID-19), adverse events must be recorded on the electronic case report form (eCRF). Please refer to Section 16.7 for additional information on dose modification	To include management guidelines for COVID-19
5.4.1.1. Dose Modifications	Tables 5.2, 5.3, 5.4 and 5.5 were updated.	To align with the latest safety information
5.6. Prior and Concomitant Medications	This section was updated.	To align with the latest safety information
6.4.1.1 Day 1 Before Infusion (All Cycles, Unless Otherwise Noted)	Collection of serum samples for COVID-19 testing was added	To align with the latest safety information
6.7 Additional PK assessments due to COVID-19 Table 8.2 Schedule of PK Sample Collections in case of Chloroquine and Hydroxychloroquine Treatment	The section and table were added.	To monitor potential drug-drug interactions between investigational/study drug treatment and COVID-19 specific treatment

Section # and Title	Description of Change	Brief Rationale
9.3.2.1 Interstitial Lung Disease Adjudication Committee	This section was updated	To align with the latest safety information
10.1. General Statistical Considerations	This section was updated	To align with the planned interim analyses
10.4 Efficacy Analyses 10.4 .2 Key Secondary Efficacy Analyses	These sections were updated	To align with the planned interim analyses
10.4.6. Immunogenicity (Anti-Drug Antibody [ADA]) Analyses	This section was updated	To provide further clarification
10.5.2. Adverse Event Analyses	This section was updated	To provide clarification
15. References	Reference 32 was deleted	To align with the latest safety information
Table 16.1 Schedule of Events	The table and footnotes were updated	To provide clarification To align with the latest safety information
16.7 Instructions Related to Coronavirus diesease 2019 (COVID-19)	This section was added.	To provide management guidelines for COVID-19
Throughout the protocol	The phrase, “interstitial lung disease (ILD)” was replaced by “interstitial lung disease (ILD)/pneumonitis”	To align with the latest safety information

PROTOCOL SYNOPSIS

IND Number:	137009
Protocol Number:	DS8201-A-U204
Investigational Product:	Trastuzumab deruxtecan
Active Ingredient(s)/ International Non-proprietary Name:	trastuzumab deruxtecan
Study Title:	A Phase 2, multicenter, open-label, 2-cohort study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody drug conjugate (ADC), for HER2-over-expressing or -mutated, unresectable and/or metastatic non-small cell lung cancer (NSCLC) [DESTINY-Lung01]
Study Phase:	Phase 2
Indication Under Investigation:	Human epidermal growth factor receptor 2 (HER2) over-expressing or -mutated, unresectable and/or metastatic non-squamous non-small cell lung cancer (NSCLC)
Study Objectives:	**Primary Objective:** The primary objective is to evaluate the overall response rate (ORR) of trastuzumab deruxtecan in HER2-over-expressing and/or –HER2 mutated advanced NSCLC subjects. **Secondary Objectives:** The secondary objectives are: • To evaluate duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) • To further evaluate the safety of trastuzumab deruxtecan • To determine the pharmacokinetics (PK) of trastuzumab deruxtecan

	Exploratory Objective: The exploratory objectives are: • To evaluate time to response (TTR) and best percent change in the sum of the diameters for all target lesions • To evaluate potential biomarkers for HER2 • To evaluate exposure-response relationships for efficacy and safety endpoints
Study Design:	This is a multicenter, open-label, 2-cohort, Phase 2 study to investigate the safety and efficacy of trastuzumab deruxtecan in HER2-over-expressing or -mutated non-small-cell lung cancer (NSCLC) subjects. Cohort 1 will enroll approximately 40 subjects with HER2-over-expressing (immunohistochemistry IHC 3+ or IHC 2+), unresectable and/or metastatic NSCLC with 6.4 mg/kg of trastuzumab deruxtecan dosing. Another approximately 40 subjects will receive 5.4 mg/kg of trastuzumab deruxtecan in Cohort 1a. Cohort 2 will enroll approximately 90 subjects with HER2-mutated, unresectable and/or metastatic NSCLC with 6.4 mg/kg of trastuzumab deruxtecan dosing. There will be follow-up visits after permanent discontinuation of study drug to obtain information about subsequent treatment(s) and survival status.
Study Duration:	Enrollment is planned to occur over approximately 31 mo. The total anticipated duration of the overall study is approximately 43 mo. There will be a 40-Day Follow-up visit (+7 d), followed by Long-Term Follow-up visits every 3 mo (±14 d) from the date of 40-Day Follow-up Visit, until death, withdrawal of consent, loss to follow-up, or study closure; whichever occurs first.
Study Centers and Location:	Approximately 170 subjects enrolled (40 in each Cohorts 1 and 1a and 90 in Cohort 2) in up to 30 sites in North America, Japan, and Europe

Eligibility Criteria:

Inclusion Criteria:

1. Must have provided informed consent for study participation (see Section 14.3) before performance of any study-specific procedure or test.
2. Age ≥20 y old in Japan, ≥18 y old in other countries.
3. Pathologically documented unresectable and/or metastatic non-squamous NSCLC.
4. Has relapsed from or is refractory to standard treatment or for which no standard treatment is available.
5. For Cohort 1 and Cohort 1a only: HER2-overexpression (IHC 2+ or 3+) status must be assessed and confirmed by Clinical Laboratory Improvement Amendments-certified laboratory or equivalent, from an archival tumor tissue sample.

   For Cohort 2 only: subject has any known documented activating HER2 mutation from an archival tumor tissue sample analyzed by CLIA laboratory or equivalent, specifically exon 20 insYVMA (Y772_A775dup), insGSP (G778_P780dup), insTGT (G776delinsVC), single base pair substitutions L755S, V777L, or S310F or another HER2 mutation listed in the appendix (see Table 16.5). Note: HER2 mutation documented only from a liquid biopsy sample cannot be used for enrollment.
6. Presence of at least 1 measurable lesion assessed by the investigator and based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
7. Is willing and able to provide an adequate archival tumor tissue sample. Fine needle aspirates are not acceptable
8. Is willing to undergo a tissue biopsy, after the completion of the most recent treatment regimen.
9. Has Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 1.
10. Has adequate organ function within 14 d before enrollment, defined as:

Parameter	Laboratory value
Adequate bone marrow function	
Platelet count	≥ 100 000/mm^3 (Platelet transfusion is not allowed within 1 wk prior to screening assessment)
Hemoglobin	≥ 9.0 g/dL

	(Red blood cell transfusion is not allowed within 1 wk prior to screening assessment)
Absolute neutrophil count (ANC)	≥ 1500/mm^3 (G-CSF administration is not allowed within 1 wk prior to screening assessment)
Adequate renal function	
Creatinine Clearance	Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation: CLcr (mL/min) = (140 - age [years]) × weight (kg) {× 0.85 for females} (72 × serum creatinine [mg/dL])
Adequate hepatic function	
ALT/AST	< 2.5 × ULN per institutional standards or < 5 × ULN if liver metastases are present
Total bilirubin (TBL)	≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline
Adequate blood clotting function	
International normalized ratio (INR)/Prothrombin time (PT) and either partial thromboplastin (PTT) or activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN

11. Has adequate treatment washout period before enrollment, defined as:

Treatment	Washout Period
Major surgery	≥ 4 wk
Radiation therapy including palliative stereotactic radiation to chest	≥ 4 wk (palliative stereotactic radiation therapy to other areas, ≥ 2 weeks)
Anti-cancer chemotherapy [Immunotherapy (non antibody based therapy)], retinoid therapy	≥ 3 wk (≥ 2 wk or 5 half-lives, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥ 6 wk for nitrosureas or mitomycin C, ≥ 1 wk for TKIs approved for the treatment of NSCLC - baseline CT scan must be completed after discontinuation of TKI)
Antibody-based anti-cancer therapy	≥ 4 wk
Chloroquine/Hydroxychloroquine	>14 d

12. 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 4.5 mo for male subjects, for at

least 7 mo for female subjects, after the last dose of study drug.

Methods considered as highly effective methods of contraception include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 4.5 mo for male subjects, for at least 7 mo for female subjects after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

Non-child-bearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 mo of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone [FSH] > 40 mIU/mL and estradiol < 40 pg/mL [< 147 pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for women of child-bearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT

to allow confirmation of postmenopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 wk will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their postmenopausal status, they can resume use of HRT during the study without use of a contraceptive method.

13. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4.5 mo after the final study drug administration. Preservation of sperm should be considered prior to enrollment in this trial.
14. 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 mo after the final study drug administration.
15. Subjects should be willing and able to comply with protocol visits and procedures.

Exclusion Criteria:

1. Previously treated with HER2-targeted therapies, except for pan-HER class tyrosine kinase inhibitors.
2. For Cohort 1 and Cohort 1a only: Has known HER2 mutation.
3. Uncontrolled or significant cardiovascular disease, including any of the following:
    a. Medical history of myocardial infarction within 6 mo prior to enrollment
    b. Symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV) 28 d prior to enrollment
    c. Troponin levels consistent with myocardial infarction (as defined by the manufacturer) 28 d prior to enrollment
    d. History of unstable angina, or serious cardiac arrhythmia requiring treatment
    e. Left ventricular ejection fraction (LVEF) < 50% within 28 d prior to enrollment
    f. Has a QT interval corrected by Fridericia's Formula (QTcF) prolongation to > 470 ms (females) or >450 ms (males) based on average of the screening triplicate12-lead electrocardiogram (ECG).

4. Has a history of (non-infectious) interstitial lung disease (ILD) /pneumonitis that required steroids or, current ILD /pneumonitis, or suspected ILD /pneumonitis that cannot be ruled out by imaging at screening.
5. Has 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 wk must have elapsed between the end of whole brain radiotherapy and study enrollment.
6. Has multiple primary malignancies within 3 y, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.
7. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
8. Has history of severe hypersensitivity reactions to other monoclonal antibodies.
9. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
10. Has substance abuse or any other medical conditions such as clinically significant cardiac 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.
11. Has known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects should be tested for HIV prior to enrollment if required by local regulations or institutional review board (IRB)/ethics committee (EC).
12. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not

	yet resolved to Grade ≤ 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator after consultation with the Sponsor Medical Monitor or designee (eg, Grade 2 chemotherapy-induced neuropathy). 13. Is a female subject who is pregnant or breastfeeding or planning to become pregnant. 14. 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 study enrollment, 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. 15. Has undergone prior treatment with an ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor. 16. Has social, familial, or geographical factors that would interfere with study participation or follow-up. 17. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the investigator. 18. Is a family member of the study site personnel or of the Sponsor personnel. 19. Is otherwise considered inappropriate for the study by the investigator.
Dosage Form, Dose and Route of Administration:	Trastuzumab deruxtecan for injection 100 mg, lyophilized powder (Lyo-DP): A trastuzumab deruxtecan sterile lyophilized powder containing 100 mg of trastuzumab deruxtecan in a glass vial. The drug for IV infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight in a volume of 100 mL, by the study site pharmacist. The study drug will be administered as an IV infusion every 3 wk ±2 d, initially for approximately 90 min, then, if there is no infusion-related reaction, for approximately 30 min thereafter.

Study Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint (primary outcome measure) is ORR assessed by independent central review (ICR) based on RECIST Version 1.1 for each cohort.

Secondary Efficacy Endpoints:

- DoR based on investigator assessment and ICR
- DCR based on investigator assessment and ICR
- PFS based on investigator assessment and ICR
- OS
- ORR based on investigator assessment

Secondary outcome measures include: ORR, DoR, PFS, and OS.

Safety Endpoints:

The safety endpoints will include:

- Serious adverse events (SAEs)
- Treatment-emergent adverse events (TEAEs)
- Physical examination findings (including ECOG PS)
- Vital sign measurements
- Standard clinical laboratory parameters (troponin)
- ECG parameters
- Echocardiogram (ECHO) or multigated acquisition (MUGA) scan findings
- Ophthalmologic findings
- Anti-drug antibody (ADA)

Pharmacokinetic (PK) Endpoints:

The PK endpoints (trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a) will include:

- PK parameters: maximum serum concentration (Cmax), time to Cmax (Tmax), area under the concentration time-curve to the (AUClast) and from time 0 to 21 d (AUC0-21d)
- Serum concentrations

	Exploratory and Biomarker Endpoints: The exploratory efficacy endpoints are: • TTR • Best percent change from baseline in the sum of the diameters for all target lesions • Analysis of biopsied materials for mechanisms of resistance to trastuzumab deruxtecan • To evaluate exposure-response relationships for efficacy and safety endpoints Biomarker endpoints are: • Analysis of tissue and/or blood for mechanisms of response/resistance to trastuzumab deruxtecan – To evaluate potential biomarkers of response – Biomarker analysis using cell-free DNA (cfDNA)
Planned Sample Size:	Approximately 40 subjects will be enrolled in each of Cohorts 1 and 1a and approximately 90 subjects will be enrolled in Cohort 2. In total, approximately 170 subjects will be enrolled in the study.
Statistical Analyses:	Efficacy analyses will be performed on the Full Analysis Set (FAS). In addition, select efficacy analyses will also be performed on the Response Evaluable Set (RES. 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 RES. A sample size of 40 response evaluable subjects each in Cohorts 1 and 1a is required so that the average distance from the limits of the respective 95% confidence intervals (CIs) to the observed ORR is approximately 0.14, assuming the expected ORR is 0.3. A sample size of 90 subjects in Cohort 2 ensures that the average distance from the limits of a 95% CI to the observed ORR is approximately 0.09, assuming the expected ORR is 0.3. The probability of the lower bound of the 95% CI exceeding 0.3 is more than 49% when the true ORR is 0.4 and the probability increases to more than 96% when the true ORR is 0.5. The upper 95% confidence limit of the ORR for the current standard of care (SOC) Docetaxel was observed to be under 0.2 or 20%

	(CheckMate057 study). The threshold of 0.3 or 30% was decided by benchmarking against this estimate of the upper limit of 20% and allowing a further increment of 10% to account for the sparseness of the available data. ORR and DCR will be summarized by cohort for FAS and RES, and their 95% exact CIs will be provided. For time to event endpoints (DoR, PFS, OS), Kaplan-Meier method will be used to estimate the survival distribution and present the results graphically. Additionally, estimates of medians and their corresponding 95% CIs using Brookmeyer and Crowley method will be reported.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AC	Adjudication Committee
ADA	Anti-drug Antibody(ies)
ADC	Antibody Drug Conjugate
ADCC	Antibody-dependent Cell-mediated Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANC	Absolute Neutrophil Count
Akt	Protein Kinase b
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMI	Acute Myocardial Infarction
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ARDS	Acute Respiratory Distress Syndrome
AUC_{0-a}	Area Under the Concentration-Time Curve
AUC_{0-21d}	Area Under the Concentration-Time Curve from the Time 0 to 21 d
AUCinf	Area Under the Concentration-Time Curve from 0 Extrapolated to Infinity
AUClast	Area Under the Concentration-Time Curve from time zero to time of last measurable concentration
BI	Before Infusion
BRAF	Proto-Oncogene B-raf
BUN	Blood Urea Nitrogen
cfDNA	Cell-free Deoxyribonucleic Acid
CHF	Congestive Heart Failure
CI	Confidence Interval
CHO	Chinese Hamster Ovary
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum Serum Concentration
COVID-19	Coronavirus disease 2019

ABBREVIATION	DEFINITION
CR	Complete Response
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CT	Computed Tomography
Ctrough	Trough serum concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
d	Day(s)
DAR	Drug-to-Antibody Ratio
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
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
eGFR	Estimated Glomerular Filtration Rate
EGFR	Epidermal Growth Factor Receptor
EIU	Exposure In Utero
EOT	End of Treatment
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HER2	Human Epidermal Growth Factor Receptor 2
hERG	Human Ether a-go-go Related Gene
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
IC50	50% inhibition
ICF	Informed Consent Form

ABBREVIATION	DEFINITION
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
IXRS	Interactive Web/Voice Response System
LDH	Lactate Dehydrogenase
LVEF	Left ventricular Ejection Fraction
MAPK	Mitogen-activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition (scan)
NCI	National Cancer Institute
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
PT	Preferred Term
Q3W	Once Every 3 Wk
QTc	Corrected QT Interval
QTcF	QT Interval Corrected for Heart Rate by Fridericia's Formula
RECIST	Response Evaluation Criteria in Solid Tumors
RES	Response Evaluable Set

ABBREVIATION	DEFINITION
ROS1	ROS Proto-Oncogene 1
SAVER	Serious Adverse Event Report
SID	Subject Identification
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Peripheral Oxygen Saturation
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
Tmax	Time to maximum serum concentration
TMF	Trial Master File
TTR	Time to Response
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal Elimination Half-life
TKI	Tyrosine Kinase Inhibitors
ULN	Upper Limit of Normal
Vss	Volume of Distribution at Steady-State

1. INTRODUCTION

1.1. Background

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related mortality worldwide; accounting for approximately 18% of all cancer deaths.[1] For years, platinum-based chemotherapy has been the cornerstone of treatment for NSCLC in the first-line. However, the 5-year survival with conventional chemotherapy regimens is around only 5%.[2]

In recent years, several targeted therapies have been approved and recommended for use in patients with advanced/metastatic NSCLC including those with non-squamous disease. In particular, the advent of targeted therapies for specific driver mutations such as epidermal growth factor receptor (EGFR) and well immune checkpoint inhibitors have significantly changed the outlook for this disease. Despite these recent advances, however, a significant number of patients are either not eligible for the new therapies or eventually progress on these treatments. Hence, a significant unmet need exists for patients with advanced/metastatic NSCLC.

Human epidermal growth factor receptor 2 (HER2) overexpression has been reported in approximately 10% to15% of NSCLC, with a reported incidence as high as 30% in adenocarcinoma.[3, 4] This overexpression is also associated with poor disease prognosis and shortened overall survival (OS).[4, 5, 6] HER2 activating mutation is also reported in approximately 2% to 3% of all NSCLC adenocarcinoma, particularly in patients who are Asian, women, and nonsmokers.[7, 8, 9, 10, 11, 12] HER2 mutations and other driver oncogene abnormalities are reported to be mutually exclusive.[7]

Results from clinical studies suggest a potential role of HER2-targeting antibody drug conjugate (ADC) in NSCLC. A recent study of trastuzumab emtansine (T-DM1) in NSCLC based on HER2 immunohistochemistry (IHC) expression showed an objective response rate (ORR) of 0% for IHC 2+ tumors, but did demonstrate efficacy with ORR 20% in IHC 3+ tumors.[13] A separate T-DM1 study reported an ORR of 44% in patients with HER2-mutant NSCLC.[14] While there is no direct HER2-targeted therapies approved for NSCLC, further investigation of HER2-targeting strategies are warranted in this patient population.

1.1.1. Investigational Product

1.1.1.1. Name

Trastuzumab deruxtecan

1.1.1.2. Description

Trastuzumab deruxtecan is an ADC targeting HER2. Trastuzumab deruxtecan consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component, MAAA-1181a. MAAL-9001 is an in-house humanized immunoglobulin G1 monoclonal antibody with the same amino acid sequence as trastuzumab. MAAA-1181a, an exatecan derivative, is a topoisomerase I inhibitor that is cell-membrane permeable, and more potent than SN-38 (active metabolite of irinotecan).[15,16,17] This ADC achieves a high drug-to-antibody ratio (DAR) (7 - 8:1) with homogeneous conjugation with MAAA-1181a.[18]

Trastuzumab deruxtecan is cleaved by lysosomal enzymes and releases MAAA-1181a in the cytoplasm after it binds to the HER2 receptor, which gets internalized in tumor cells.

Three forms of trastuzumab deruxtecan drug product being investigated in clinical trials include: FL-DP1, FL-DP2, and lyophilized powder (Lyo-DP). Only the Lyo-DP form will be administered in this trial.

The trastuzumab deruxtecan Phase 1 clinical study, DS8201-A-J101, was initiated with the antibody component, MAAL-9001, produced using the Chinese hamster ovary (CHO) CCI cell line (FL-DP1). To support this study, as well as commercial development, transition has been made to MAAL-9001 production by using a Chinese hamster ovary CCI cell line (FL-DP2/Lyo-DP). Analytic comparison of the 2 cell line products has shown comparability across a wide range of variables. Minor differences have been observed in glycan profile, charge variants, size variants, FcgRIIIA binding, FcRn binding, and antibody-dependent cellular cytotoxic (ADCC) activity. Following single intravenous (IV) administration of trastuzumab deruxtecan to cynomolgus monkeys, mean maximum plasma concentration (Cmax) of trastuzumab deruxtecan was similar, while area under the concentration-time curve (AUC) was approximately 15% lower, for FL-DP2 material as compared to FL-DP1 material. However, in a xenograft model, no difference was seen in cytotoxicity between the 2 products.

1.1.1.3. Intended Use Under Investigation

This study will investigate the safety and efficacy of trastuzumab deruxtecan in HER2-over-expressing or -mutated NSCLC subjects.

1.1.1.4. Nonclinical Studies of Trastuzumab Deruxtecan

In nonclinical studies for MAAA-1181a (free form), MAAA-1181c (additive form [3/10 MeCN 2/5 MeOH 3/10 H_2O]) or MAAA-1181d (monohydrate) were used. The doses and concentrations of MAAA-1181c and MAAA-1181d are expressed as those of MAAA-1181a, the free form.

1.1.2. Nonclinical Studies

1.1.2.1. Pharmacology

In studies on the mechanism of action of trastuzumab deruxtecan, trastuzumab deruxtecan was confirmed to have an HER2-mediated protein kinase b (Akt) phosphorylation inhibition and an ADCC activity, and has also been confirmed to cause DNA damage and induce apoptosis, effects that are assumed to be the result of MAAA-1181c, which has topoisomerase I inhibitory activity.

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

1.1.2.2. Safety Pharmacology

In a safety pharmacology study in monkeys treated with single IV doses of trastuzumab deruxtecan, no effects on the cardiovascular system, the respiratory system, or the central

nervous system were observed under the study condition. In addition, in human ether- a-go-go-related gene (hERG) studies of MAAA-1181a, MAAA-1181a did not inhibit the hERG channel current.

1.1.2.3. Pharmacokinetics and Drug Metabolism

In cynomolgus monkeys, the clearance of trastuzumab deruxtecan was much lower than the hepatic flow, and it decreased with increasing dose, suggesting a non-linear process. The volume of distribution at steady state (Vss) was close to the plasma volume. Both trastuzumab deruxtecan and the total antibody, bound and unbound antibody combined, exhibited similar pharmacokinetics (PK) profiles, indicating that the majority of the administered trastuzumab deruxtecan circulates in plasma unchanged. The plasma concentrations of MAAA-1181a, the drug that is released from trastuzumab deruxtecan, were quite low. No anti-trastuzumab deruxtecan antibody was detected in any animals.

After a single IV administration of 3H-labeled trastuzumab deruxtecan (^{3}H-trastuzumab deruxtecan, antibody portion [MAAL-9001] was ^{3}H-labeled) or ^{14}C-labeled trastuzumab deruxtecan (^{14}C-trastuzumab deruxtecan, drug portion [MAAA-1181a] was ^{14}C-labeled) to cynomolgus monkeys, the highest radioactivity was observed in the blood during the study period. The concentrations of radioactivity in all tissues declined in proportion to the decline in the blood concentration, suggesting no accumulation and retention in specific tissues. The plasma protein binding ratios of MAAA-1181a (10 ng/mL to 100 ng/mL) were 90.3% to 92.5% in mice, 94.2% to 96.7% in rats, 86.5% to 89.1% in monkeys, and 96.8% to 98.0% in humans, respectively.

In vitro release rates of MAAA-1181a from trastuzumab deruxtecan in mouse, rat, monkey, and human plasma up to 3 wk were 3.9% or less. Cytochrome P450 (CYP) 3A4 was the primary CYP enzyme involved in the metabolism of MAAA-1181a. No human specific metabolites were detected in vitro. The major peaks inferred to be metabolites were MAAA-1181a, a methylglycinamide form of MAAA-1181a, a cysteine conjugate of the drug and linker moieties of trastuzumab deruxtecan and its isomer, a succinimide form of the linker and the drug conjugate of trastuzumab deruxtecan, and a thiomethylate of the linker and the drug conjugate of trastuzumab deruxtecan.

In monkeys, excretion of radioactivity from administered ^{14}C-trastuzumab deruxtecan into feces was predominant. In rats, excretion of radioactivity from administered 14C-labeled MAAA-1181a (^{14}C-MAAA-1181a) into feces via bile was predominant.

MAAA-1181d did not show any inhibition potential to CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A (concentration producing 50% inhibition [IC_{50}] >50 μmol/L). MAAA-1181d did not show any induction potential to CYP3A4, CYP1A2, and CYP2B6 up to 30 μmol/L. MAAA-1181d did not inhibit organic anion transporter (OAT) 3, organic cation transporter (OCT) 1, OCT2, organic anion- transporting polypeptide (OATB) 1B3, multidrug and toxin extrusion protein (MATE) 1, MATE2-K, P-glycoprotein, breast cancer resistance protein, and bile salt export pump (IC50 >30 μmol/L). MAAA-1181d inhibited OAT1 and OATP1B1 with the IC50 values of 12.7 μmol/L and 14.4 μmol/L, respectively; however, the values were much higher than the Cmax of MAAA-1181a in humans (9.25 ng/mL

[0.019 μmol/L] at 8.0 mg/kg of trastuzumab deruxtecan). In addition, OATPs were considered to contribute to the human hepatic uptake of MAAA-1181a.

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

1.1.2.4. Toxicology

In a study of intermittent IV dosing of trastuzumab deruxtecan in rats (Q3W × 2), no deaths or moribund animals were found at dose levels up to 197 mg/kg, the maximum dose. The major observed findings included testicular and intestinal toxicity at dose levels of 20 mg/kg and greater, and lymphatic/hematopoietic, skin, incisor tooth, and renal toxicity at dose levels of 60 mg/kg and greater. Except for the testicular and incisor tooth changes, these changes were all found to recover.

In an intermittent IV dosing study of trastuzumab deruxtecan in cynomolgus monkeys (Q3W × 2), 1 female was sacrificed moribund at 78.8 mg/kg, the highest dose level. The major toxicity findings in this moribund animal were observed in the intestine, hematopoietic system, skin, and kidney. The cause of the moribundity appeared to be the deteriorated condition of the animal from decreased body weight and food consumption, as well as bone marrow toxicity and intestinal toxicity. The major findings of toxicity in the surviving animals were observed in the intestine at dose levels of 10 mg/kg and greater, and in the lung, testes, and skin at dose levels of 30 mg/kg and greater. In addition, hematopoietic system toxicity, renal toxicity, and electrocardiogram (ECG) abnormalities (shortened PR interval and corrected QT interval [QTc] prolongation) were found at 78.8 mg/kg. Except for the pulmonary and skin toxicity (pigmentation), these findings tended to recover.

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

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

intestinal and lymphatic/hematopoietic system toxicities. For trastuzumab deruxtecan treatment, pulmonary, testicular, skin, and renal toxicities were observed while heart, liver, and corneal toxicities were found only when MAAA-1181a was administered.

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

In an in vitro 3T3 NRU phototoxicity study, MAAA-1181a was found to be phototoxic to Balb/c 3T3 mouse fibroblasts. However, in an in vivo single dose phototoxicity study of MAAA-1181d in pigmented rats, no phototoxic reaction was noted at 3 mg/kg, the highest dose tested. For additional nonclinical data supporting trastuzumab deruxtecan use in nonclinical studies, please refer to the current Investigator's Brochure (IB).

1.1.3. Clinical Experience

As of 08 Jun 2019, trastuzumab deruxtecan has been evaluated in 12 company-sponsored clinical studies (11 monotherapy studies and 1 combination therapy study) in multiple oncology indications, with an estimated 1036 subjects exposed to at least 1 dose of trastuzumab deruxtecan.

The trastuzumab deruxtecan first-in-human study (Protocol DS8201-A-J101) is an open-label, dose finding study to assess the safety and tolerability of trastuzumab deruxtecan in subjects with advanced solid tumors. Part 1 (dose escalation) enrolled subjects with either advanced breast cancer or gastric/gastroesophageal junction adenocarcinoma that is refractory or intolerant to standard treatment, or for which no standard treatment is available. Part 2 is the expansion phase and focuses on HER2-expressing breast (previously treated ado- T-DM1 HER2-positive breast cancer) and gastric/gastroesophageal junction adenocarcinoma, HER2-low-expressing breast cancer, as well as other HER2-expressing solid cancers.

As of the data cutoff date of 01 Feb 2019, in the Study DS8201-A-J101[34] 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).

1.1.3.1. Efficacy: DS8201-A-J101 (Ongoing)

Preliminary efficacy results[34] as of 01 Feb 2019 showed confirmed ORR by independent central review (ICR) of 52.5% (95% confidence interval [CI]: 43.1, 61.8) among the 118 subjects with HER2-positive breast cancer, with confirmed ORR of 51.0% (95% CI: 36.6 to 65.2) for the 51 subjects in the 5.4-mg/kg dose group and confirmed ORR of 53.7% (95% CI: 41.1 to 66.0) for the 67 subjects in the 6.4 mg/kg dose group. The median confirmed duration of response (DoR) by ICR was 13.3 months, 12.7 months, and 13.6 months for the pooled, 5.4 mg/kg, and

6.4-mg/kg dose groups, respectively. The median progression-free survival (PFS) by ICR was 13.7 months, 13.7 months, and 14.1 months for the pooled, 5.4 mg/kg, and 6.4-mg/kg dose groups, respectively. Median OS was not reached as of the data cutoff.

Among the 54 subjects with HER2-low breast cancer, confirmed ORR by ICR was 37.0% (95% CI: 24.3 to 51.3) by ICR. Median confirmed DoR by ICR was 10.4 months (95% CI: 8.8 to not estimable). Median PFS by ICR was 11.1 months (95% CI: 7.6 to not estimable). Median OS was 29.4 months (95% CI: 12.9 to 29.4).

Among the 61 subjects with other cancers, confirmed ORR by ICR was 29.5% (95% CI: 18.5 to 42.6) and median confirmed DoR by ICR was 11.5 months (95% CI: 7.0 to not estimable). Median PFS by ICR was 7.2 months (95% CI: 4.8 to 11.1) and median OS was 23.4 months (95% CI: 15.6 to not estimable).

As of the data cutoff date of 01 Feb 2019, efficacy results for all subjects with NSCLC in the Study DS8201-A-J101 are summarized in Table 1.1.

In the Enrolled Analysis Set, a confirmed ORR by ICR was observed in 55.6% (95% CI: 30.8 to 78.5) of subjects with NSCLC, 5.0% (95% CI: 0.1 to 24.9) of subjects with colorectal cancer, and 30.4% (95% CI: 13.2 to 52.9) of subjects with cancer of other tumor type. In subjects with other cancers, 18 subjects had best overall responses of CR (2 [3.3%] subjects) or partial response [PR) (16 [26.2%]subjects).

The median confirmed DoR based on complete response (CR) (calculated using the Kaplan-Meier [KM] method) was 10.7 months in subjects with NSCLC and 13.4 months in subjects with colorectal cancer and was not reached in subjects with cancer of other tumor type. Of the 18 subjects with confirmed response by ICR assessment, 7 (38.9%) 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 88.5% at 6 months, 46.8% at 12 months, and 31.2% at 18 months.

At the time of the data cutoff, 38 of 61 (62.3%) subjects had PD based on ICR assessment and/or death. The median PFS by ICR was 11.3 months (95% CI: 7.2 to 14.3) in subjects with NSCLC, 4.0 months (95% CI 2.7 to 5.6) in subjects with colorectal cancer, and 11.0 months (95% CI: 2.8 to not estimable) in subjects with cancer of other tumor type.

At the time of the data cutoff, 21 of 61 (34.4%) subjects in the Enrolled Analysis Set had died. The median OS was 23.4 months in all subjects with other cancers. Based on the KM analysis, the estimated proportion of subjects alive was 77.8% at 6 months, 69.9% at 12 months, 61.2% at 18 months, and 46.7% at 24 months.

Overall, 52 of 61 (85.2%) subjects with other cancers had baseline and postbaseline tumor assessments by ICR. The mean tumor shrinkage of target lesions was -30.65% (30.793). Most subjects had tumor shrinkage by ICR (80.8% [42/52]), which occurred at the first postbaseline tumor assessment in 92.9% (39/42) of subjects.

Table 1.1: Efficacy Results in NSCLC Cancers in Study DS8201-A-J101 (Enrolled Analysis Set)

Efficacy Variable	**NSCLC (N = 18)**
Confirmed ORR, n (%) (95% CI[a])	
ORR by ICR	10 (55.6) (30.8, 78.5)
ORR by investigator	10 (55.6) (30.8, 78.5)
ORR by ICR in response evaluable set, n/N	10/17 (58.8) (32.9, 81.6)
- CR	0
- PR	10 (55.6)
- Stable disease	5 (27.8)
- PD	2 (11.1)
- NE	1 (5.6)
Confirmed best overall response by investigator, n (%)	
CR	0
PR	10 (55.6)
Stable disease	4 (22.2)
PD	3 (16.7)
NE	1 (5.6)
Confirmed DoR, median[b] (95% CI) (months)	
DoR by ICR	10.7 (6.9, 11.5)
DoR by investigator	9.9 (6.9, 11.5)
Confirmed DCR,[c] n (%) (95% CI[a])	
DCR by ICR	15 (83.3) (58.6, 96.4)
DCR by investigator	14 (77.8) (52.4, 93.6)
Time to confirmed response by ICR, median[b] (95% CI) (months)	1.4 (1.2, 2.8)
Duration of confirmed stable disease by ICR, median[b] (95% CI) (months)	- (2.1, -)
PFS	
PFS by ICR	
Events, n (%)	9 (50.0)

Efficacy Variable	**NSCLC (N = 18)**
Confirmed ORR, n (%) (95% CI[a])	
Median[b] (95% CI) (months)	11.3 (7.2, 14.3)
PFS by investigator	
Events, n (%)	11 (61.1)
Median[b] (95% CI) (months)	11.3 (5.5, 14.1)
Events, n (%)	4 (22.2)
Median[b] (95% CI) (months)	Not reached (17.3, -)
Survival at 6 months, % (95% CI[d])	88.9 (62.4, 97.1)
Survival at 12 months, % (95% CI[d])	83.3 (56.8, 94.3)
Survival at 18 months, % (95% CI[d])	66.7 (26.2, 88.4)
Survival at 24 months, % (95% CI[d])	- (-, -)

CI = confidence interval; CR = complete response; DCR = disease control rate; DoR = duration of response; HER2 = human epidermal growth factor receptor 2; ICR = independent central review; NE = nonevaluable; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response

[a] 95% exact binomial CI.

[b] Median was from Kaplan-Meier estimate. CI for median as 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 calculated as days × 12/365.25.

Part 2 subjects are included.

Data cutoff date: 01 Feb 2019.

Source: Preliminary data as of 01 Feb 2019[34].

1.1.3.2. Safety: DS8201-A-J101 (Ongoing)

As of 01 Feb 2019, a total of 288 (99.7%) subjects experienced at least 1 TEAE, with most of the common TEAEs being gastrointestinal or hematological in nature.

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

- 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.

- 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.

Treatment-emergent adverse events reported in ≥20% of total subjects (N = 289) by PT and grouped term, tumor type, and dose are provided in Table 1.2.

The TEAEs of Grade ≥3 were reported in 168 (58.1%) subjects. The most frequently (≥5% of subjects) reported TEAEs of Grade ≥3 in any tumor type and dose by PT were anaemia (60 [20.8%] subjects), neutrophil count decreased (53 [18.3%] subjects), white blood cell (WBC) count decreased (37 [12.8%] subjects), platelet count decreased (33 [11.4%] subjects), and hypokalaemia (18 [6.2%] subjects).

Across all tumor types, a numerically higher proportion of subjects in the 6.4-mg/kg dose group than in the 5.4-mg/kg group experienced AEs of Grade ≥3 (overall and causally related), SAEs (including causally related), AEs leading to drug withdrawal (overall and causally related), and AEs leading to dose reduction (overall and causally related).

Table 1.2: Summary of Treatment-Emergent Adverse Events (≥20% of Subjects) in Study DS8201-A-J101

MedDRA Preferred Term	Number (%) of Subjects[a]									
	HER2-Positive Breast Cancer		HER2-Low Breast Cancer		HER2-Positive Gastric/GEJ Cancer		Other Cancers[b]	Total (N = 274)		Total (N = 289)
	5.4 mg/kg (N = 50)	6.4 mg/kg (N = 66)	5.4 mg/kg (N = 21)	6.4 mg/kg (N = 33)	5.4mg/kg (N = 19)	6.4 mg/kg (N = 25)	6.4 mg/kg (N = 59)	5.4 mg/kg (N = 91)	6.4 mg/kg (N = 183)	All Doses
Subjects with any TEAEs	50 (100.0)	66 (100.0)	20 (95.2)	33 (100.0)	19 (100.0)	25 (100.0)	59 (100.0)	90 (98.9)	183 (100.0)	288 (99.7)
Nausea	43 (86.0)	52 (78.8)	15 (71.4)	26 (78.8)	12 (63.2)	19 (76.0)	44 (74.6)	71 (78.0)	141 (77.0)	222 (76.8)
Decreased appetite	23 (46.0)	47 (71.2)	7 (33.3)	20 (60.6)	8 (42.1)	22 (88.0)	35 (59.3)	38 (41.8)	124 (67.8)	168 (58.1)
Vomiting	28 (56.0)	35 (53.0)	10 (47.6)	14 (42.4)	3 (15.8)	8 (32.0)	31 (52.5)	41 (45.1)	88 (48.1)	133 (46.0)
Alopecia	19 (38.0)	45 (68.2)	6 (28.6)	18 (54.5)	4 (21.1)	4 (16.0)	20 (33.9)	29 (31.9)	87 (47.5)	120 (41.5)
Anaemia[c]	24 (48.0)	30 (45.5)	7 (33.3)	14 (42.4)	4 (21.1)	14 (56.0)	23 (39.0)	35 (38.5)	81 (44.3)	118 (40.8)
Fatigue	24 (48.0)	32 (48.5)	11 (52.4)	9 (27.3)	4 (21.1)	3 (12.0)	21 (35.6)	39 (42.9)	65 (35.5)	111 (38.4)
Diarrhoea	18 (36.0)	28 (42.4)	9 (42.9)	16 (48.5)	3 (15.8)	5 (20.0)	19 (32.2)	30 (33.0)	68 (37.2)	102 (35.3)
Constipation	18 (36.0)	30 (45.5)	7 (33.3)	14 (42.4)	5 (26.3)	7 (28.0)	16 (27.1)	31 (34.1)	67 (36.6)	100 (34.6)
Platelet count decrease[d]	15 (30.0)	24 (36.4)	3 (14.3)	14 (42.4)	5 (26.3)	12 (48.0)	22 (37.3)	24 (26.4)	72 (39.3)	100 (34.6)
Neutrophil count decrease[e]	12 (24.0)	25 (37.9)	3 (14.3)	13 (39.4)	2 (10.5)	12 (48.0)	21 (35.6)	18 (19.8)	71 (38.8)	91 (31.5)
White blood cell count decrease[f]	9 (18.0)	22 (33.3)	4 (19.0)	13 (39.4)	3 (15.8)	11 (44.0)	17 (28.8)	17 (18.7)	63 (34.4)	82 (28.4)
Aspartate aminotransferase increased	9 (18.0)	23 (34.8)	3 (14.3)	10 (30.3)	1 (5.3)	3 (12.0)	12 (20.3)	13 (14.3)	48 (26.2)	63 (21.8)
Malaise	6 (12.0)	19 (28.8)	2 (9.5)	13 (39.4)	3 (15.8)	5 (20.0)	13 (22.0)	11 (12.1)	50 (27.3)	62 (21.5)
Pyrexia	10 (20.0)	7 (14.0)	18 (27.3)	9 (27.3)	3 (15.8)	8 (32.0)	9 (15.3)	14 (15.4)	44 (24.0)	60 (20.8)
Stomatitis[g]			4 (19.0)	13 (39.4)	1 (5.3)	4 (16.0)	10 (16.9)	12 (13.2)	45 (24.6)	58 (20.1)

GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event

[a] Part 1 and Part 2 subjects are included. Percentage was calculated using the number of subjects in the column heading as the denominator.

[b] Does not include 1 subject with HER2-low gastric cancer who received trastuzumab deruxtecan at 5.4 mg/kg.

[c] Grouped term that includes PTs anaemia, hemoglobin count decreased, and red blood cell count decreased.

[d] Grouped term that includes PTs platelet count decreased and thrombocytopenia.

[e] Grouped term that includes PTs neutrophil count decreased and neutropenia.

[f] Grouped term that includes PTs white blood count decreased and leukopenia.

[g] Grouped term that includes PTs stomatitis, aphthous stomatitis, mouth ulceration, oral mucosa erosion, and oral mucosal blistering.

Adverse events were coded using MedDRA Version 20.1.

Table is presented by decreasing order of preferred terms within the Total (N = 289) All Doses column.

Data cutoff date: 01 Feb 2019.

Source: DS8201-A-J101 CSR, Table 10.6.

1.1.4. Summary of Clinical Pharmacokinetics

Following a single IV administration of trastuzumab deruxtecan, the systemic exposure of trastuzumab deruxtecan increased approximately proportional to dose across the dose range of 0.8 to 8.0 mg/kg evaluated in the dose escalation part of Study DS8201-A-J101. The trastuzumab deruxtecan PK parameters at 5.4, 6.4, and 8.0 mg/kg in Cycle 1 are shown in Table 1.3.

The Cmax of trastuzumab deruxtecan was achieved with a median time to Cmax (Tmax) approximately 2 h. The Cmax and AUClast from time 0 to 21 days (AUC0-21d), at 5.4 mg/kg were 127 µg/mL and 544 µg•d/mL, respectively, and at 6.4 mg/kg were 181 µg/mL and 901µg•d/mL, respectively.

The systemic exposures at 5.4 and 6.4 mg/kg doses in subjects in Cycle 1 were observed to exceed the systemic efficacious exposure observed during the nonclinical pharmacology evaluation[34]. The mean terminal elimination half-life ($t_{1/2}$) of trastuzumab deruxtecan was approximately 6.0 to 7.0 days

The PK parameters of total antibody were close to that of trastuzumab deruxtecan.

The Cmax and AUC of MAAA-1181a for the dosing interval were quite low compared with the corresponding values for trastuzumab deruxtecan.

The $t_{1/2}$ of MAAA-1181a was similar to that of trastuzumab deruxtecan.

Table 1.3: Mean Pharmacokinetic Parameters of Trastuzumab Deruxtecan Following Cycle 1 (± Standard Deviation)

Trastuzumab deruxtecan Dose (mg/kg)	Cmax (µg/mL)	Tmax (h) Median (range)	AUC_{0-21d} (µg•d/mL)	AUCinf (µg•d/mL)	$t_{1/2}$ (d)	CL (mL/d/kg)	Vss (mL/kg)
5.4 (N=6)	127±17.2	2.02 (1.87, 2.07)	544±165	590±186	6.03±0.603	10.1±3.90	75.2±24.2
6.4 (N=6)	181±33.1	2.06 (1.50, 3.97)	901±155	1030±209	7.33±1.64	6.41±1.12	58.6±11.0
8.0 (N=5)	224±41.0	1.97 (1.70, 6.80)	996±229	1100±259	6.44±0.793	7.60±1.73	62.1±14.0

AUC = area under the concentration-time curve; AUC_{0-21d} = AUC from the time 0 to 21 d; AUCinf = AUC from time 0 extrapolated to infinity; CL = clearance; Cmax = maximum serum concentration; d = day, N = number of evaluable subjects; $t_{1/2}$ = terminal elimination half-life; Tmax = time to Cmax; Vss = volume of distribution at steady-state.

Table 1.4: Mean Pharmacokinetic Parameters of Total Antibody Following Cycle 1 (± Standard Deviation)

Trastuzumab deruxtecan Dose (mg/kg)	Cmax (µg/mL) mean±SD	Tmax (h) (min, max) Median (range)	AUC_{0-21d} (µg·d/mL)	AUCinf (µg·d/mL)	$t_{1/2}$ (day)
5.4 (N=6)	116±13.9	2.03 (1.87, 6.88)	609±151	682±172	6.78±2.39
6.4 (N=6)	146±18.9	3.94 (2.05, 6.87)	878±97.1	1050±149	8.25±2.16
8.0 (N=5)	188±23.3	2.07 (1.97, 6.83)	1120±213	1270±261	6.79±0.821

AUC = area under the concentration-time curve; AUC_{0-21d} = AUC from the time 0 to 21 d; AUCinf = AUC from 0 extrapolated to infinity; Cmax = maximum serum concentration; d = day; N = number of evaluable subjects; $t_{1/2}$ = terminal elimination half-life; Tmax = time to Cmax.

Table 1.5: Mean Pharmacokinetic Parameters of MAAA-1181a Following Cycle 1 (± Standard Deviation)

Trastuzumab deruxtecan Dose (mg/kg)	Cmax (µg/mL)	Tmax (h) (min, max) Median (range)	AUC_{0-21d} (µg·d/mL)	AUCinf (µg·d/mL)	$t_{1/2}$ (d)
5.4 (N=6)	10.8±7.56	5.38 (3.83, 23.75)	40.6±19.8	43.6±21.2	6.11±0.811
6.4 (N=6)	6.80±1.72	6.83 (4.05, 7.15)	31.0±5.11	34.2±5.63	6.28±1.17
8.0 (N=5)	9.65±2.56	6.80 (2.07, 7.00)	40.3±5.66	44.5±7.03	6.456±1.56

AUC = area under the concentration-time curve; AUC_{0-21d} = AUC from the time 0 to 21 d; AUCinf = AUC from 0 extrapolated to infinity; Cmax = maximum serum concentration; d = day; N = number of evaluable subjects; $t_{1/2}$ = terminal elimination half-life; Tmax = time to Cmax.

1.2. Study Rationale

HER2 is a member of the HER superfamily that initiates signal transduction via the phosphatidylinositol-3 kinase Akt and Ras/mitogen-activated protein kinase pathways.[19] In human advanced solid tumors, expression of HER2 protein has been reported in various tumor tissues and in a variety of cultured tumor cell lines including breast cancer,[20] gastric cancer,[21, 22] lung cancer,[23] pancreatic cancer,[24] colorectal cancer,[25] and ovarian cancer.[26]

HER2 overexpression is an established target of treatments for patients with breast or gastric cancer; however, no direct HER2-targeted therapy is approved for NSCLC. In a CALGB 39810 study to assess the antitumor activity of trastuzumab in patients with HER2 overexpressing NSCLC, ORR was 5%, and median PFS was 2.6 mo (95% CI, 2.2-4.2).[27]

Targeted therapies (eg, EGFR, anaplastic lymphoma kinase, ROS proto-oncogene 1 tyrosine kinase inhibitor [TKI]) are recommended during the course of treatment as systemic treatments

for a subset of patients with NSCLC who have those driver mutations/rearrangements. However, the current unmet medical needs in NSCLC remains in patients who have no known mutation or mutations without approved targeted therapy. HER2 mutation is also considered a distinct molecular target since few overlap with other driver oncogene abnormalities were reported. Several pan-class HER family TKIs were investigated in HER2-mutated NSCLC; however, clinical activity of those treatments were very limited, with ORR range of 0% to 19%.[28, 29, 30, 31] Additionally, once subjects have developed acquired resistance to the various TKIs, there are limited treatment options. Platinum- or Taxane-based chemotherapy or immune checkpoint inhibitor remain the treatment options for no known mutation or after disease progression against molecular targeted therapy.

Results from clinical studies suggest a potential role of HER2-targeting ADC in NSCLC. A recent study of T-DM1 in NSCLC based on HER2 IHC expression showed an ORR of 0% for IHC 2+ tumors, but did demonstrate efficacy with ORR 20% in IHC 3+ tumors.[13] A separate T-DM1 study reported an ORR of 44% in patients with HER2-mutant NSCLC.[14] While there is no direct HER2-targeted therapies approved for NSCLC, further investigation of HER2 targeting strategies are warranted in this patient population.

Trastuzumab deruxtecan is a HER2-targeting ADC with a high drug to antibody ratio (7 to 8), and a novel topoisomerase I inhibitor. Trastuzumab deruxtecan is expected to inhibit tumor growth on the basis of the following reasons: it exhibits ADCC activities and Akt phosphorylation inhibition similar to those of trastuzumab when it binds to HER2; and the MAAA-1181a that is released from trastuzumab deruxtecan after the internalization induces apoptosis by inhibiting topoisomerase I. Nonclinical evidence demonstrates that the HER2 targeting of trastuzumab deruxtecan is highly specific. In a study conducted in tumor-bearing mouse models, trastuzumab deruxtecan has antitumor activity against HER2 overexpressing NSCLC.

In the Phase 1 study, DS8201-A-J101, the preliminary results as of 08 Jun 2017, indicates that trastuzumab deruxtecan has acceptable safety and PK profiles, and antitumor activity. There have been no reported dose-limiting toxicities, the maximum tolerated dose was not reached in the 0.8 to 8.0 mg/kg Q3W dose range, and 5.4 mg/kg or 6.4 mg/kg are being considered as the recommended Phase 2 dose. In Part 1 of the Phase 1 study, several doses of trastuzumab deruxtecan were administered in a total of 24 subjects and the ORR was 34.8% and the disease control rate (DCR) was 91%. One out of 5 evaluable subjects with NSCLC achieved confirmed PR and 2 subjects had stable disease (SD).

Based on the non-clinical and the clinical observations in the Phase 1 study (DS8201-A-J101), trastuzumab deruxtecan was well tolerated and efficacy is suggested by the data in HER2 overexpressing NSCLC subjects. Therefore a Phase 2, multicenter, open-label study will be conducted to determine the efficacy and safety profile of trastuzumab deruxtecan for HER2 overexpressing or mutated NSCLC.

1.2.1. Rationale for Expansion

Given the high level of activity[32]observed in Phase 1 study DS8201-A-J101, further understanding of safety and efficacy of trastuzumab deruxtecan in subjects in Cohort 1 is of interest. The increased sample size will facilitate the computation of more precise safety and

efficacy estimates. Cohort 2 expansion has been initiated to include 50 additional subjects. The addition of Cohort 1a of subjects treated at 5.4 mg/kg is required for a preliminary assessment of the safety and efficacy of this dose vis-à-vis the slightly higher dose of 6.4 mg/kg that had been administered in the other cohorts.

1.3. Risks and Benefits for Study Subjects

Trastuzumab deruxtecan is under development for the treatment of HER2-expressing cancers and HER2-mutant tumors. Based on the preliminary clinical observations in the Phase 1 study (Study DS8201-A-J101), trastuzumab deruxtecan demonstrates antitumor activity in HER2 expressing cancers, including breast cancer and gastric cancer.

As of 01 Feb 2019 from the ongoing 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/gastroesophageal junction 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%. In the Enrolled Analysis Set, a confirmed ORR by ICR was observed in 55.6% (95% CI: 30.8 to 78.5) of subjects with NSCLC, 5.0% (95% CI: 0.1 to 24.9) of subjects with colorectal cancer, and 30.4% (95% CI: 13.2 to 52.9) of subjects with cancer of other tumor type.

As of 08 Jun 2019, 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 /pneumonitis, 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 /pneumonitis, anemia, neutrophil count decrease including febrile neutropenia, and platelet count decrease, and important potential risk of LVEF decrease.

ILD /pneumonitis 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 /pneumonitis, with specific recommendations including close monitoring of signs/symptoms of ILD (eg, cough, fever, and dyspnea) to identify potential ILD /pneumonitis and proactively managing ILD /pneumonitis with dose modification and treatment (eg, steroids). ILD /pneumonitis 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.

For current details on safety and tolerability profile of trastuzumab deruxtecan and assessments of risks and benefits to subjects, please refer to the current IB for trastuzumab deruxtecan.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objective is to evaluate the ORR of trastuzumab deruxtecan in HER2-overexpressing and/or –HER2 mutated advanced NSCLC subjects.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate DoR, DCR, PFS, and OS.
- To further evaluate the safety of trastuzumab deruxtecan
- To determine the PK of trastuzumab deruxtecan

2.1.3. Exploratory Objectives

The exploratory objectives are:

- To evaluate time to response (TTR) and best percent change in the sum of the diameters for all target lesions
- To evaluate potential biomarkers
- To evaluate exposure-response relationships for efficacy and safety endpoints

2.2. Study Hypothesis

Trastuzumab deruxtecan confers an ORR benefit in HER2-overexpressing and/or –mutated NSCLC subjects.

2.3. Study Endpoints

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

2.3.1. Primary Endpoint(s)

The primary efficacy endpoint is ORR.

2.3.2. Key Secondary Endpoint(s)

The secondary efficacy endpoints are:

- DoR
- DCR
- PFS
- OS
- ORR per investigator’s assessments

The safety endpoints will include:

- SAEs
- TEAEs
- Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS])
- Vital sign measurements
- Standard clinical laboratory parameters
- ECG parameters
- Echocardiogram (ECHO)/multigated acquisition (MUGA) findings
- Ophthalmologic findings
- • Antidrug antibody (ADA)

The PK Endpoints (trastuzumab deruxtecan, total anti-HER2 antibody and MAAA-1181a) will include:

  - PK parameters: Cmax, Tmax, AUC from time 0 to the last measurable concentration (AUClast), and AUC0-21d
  - Serum concentrations

2.3.3. Exploratory and Biomarker Endpoint(s)

The exploratory efficacy endpoints are:

- TTR
- Best percentage change from baseline in the sum of the diameters for all target lesions
- Analysis of biopsied materials for mechanisms of resistance to trastuzumab deruxtecan
- Exposure-response relationships for efficacy and safety endpoints

Biomarker endpoints are:

- Analysis of tissue and/or blood for mechanisms of response/resistance to trastuzumab deruxtecan
  - To evaluate potential biomarkers of response
  - Biomarker analysis by cell-free deoxyribonucleic acid (cfDNA)

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

This is a multicenter, open-label, 2-cohort, Phase 2 study to investigate the safety and efficacy of trastuzumab deruxtecan in HER2-overexpressing or -mutated NSCLC subjects.

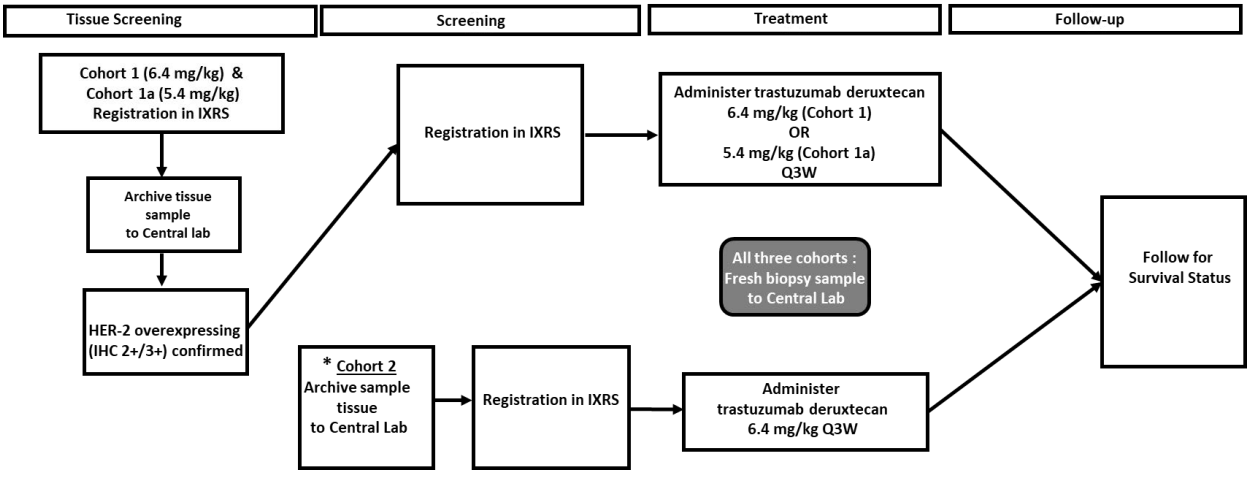
Cohort 1 will enroll approximately 40 subjects with HER2-overexpressing (IHC 3+ or IHC 2+), unresectable and/or metastatic non-squamous NSCLC with 6.4 mg/kg of trastuzumab deruxtecan dosing. Another approximately 40 subjects will receive 5.4 mg/kg of trastuzumab deruxtecan in Cohort 1a.

Cohort 2 will enroll approximately 90 subjects with HER2-mutated, unresectable and/or metastatic non-squamous NSCLC after the planned expansion adding 50 subjects to the original 40 subject cohort.

Trastuzumab deruxtecan will be administered as a sterile IV solution at a dosage of 6.4 mg/kg Q3W or 5.4 mg/kg Q3W.

The study treatment will be continued according to the dosing criteria to derive clinical benefit in the absence of withdrawal of subject consent, progressive disease (PD), or unacceptable toxicity. If the study treatment is delayed more than 28 d from the planned date of administration, the subject will be withdrawn from the study treatment (see Section 5.4).

Figure 3.1: Study Design Schema for DS8201-A-U204



HER = human epidermal growth factor receptor; IHC = immunohistochemistry; IXRS = Interactive Web/Voice Response System; Q3W = every 3 weeks
*Central lab testing of archival/fresh tissue sample is not utilized for enrollment in Cohort 2.

3.1.2. Duration of the Study

Enrollment is planned to occur over approximately 31 mo. The anticipated duration of the study is approximately 43 mo.

There will be a 40-Day (+7d) Follow-up visit, followed by Long-Term Follow-up visits every 3 mo (±14 d) from the date of 40-Day Follow-up visit, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.

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

3.1.3.1. Screening Phase

The screening period is up to 28 d after the Main Informed Consent Form (ICF) is signed.

3.1.3.2. Treatment Phase

Each cycle of treatment of trastuzumab deruxtecan will be every 21 d. The number of treatment cycles with trastuzumab deruxtecan is not fixed. Upon commencing study drug, subjects may continue receiving the study drug until the occurrence of any of the events defined in Section 5.8.

3.1.4. Follow-up Phase

Regardless of reason for discontinuation from study drug, all subjects should be contacted for follow-up every 3 mo (±14 d) from the date of 40-Day (+7 d) Follow-Up Visit until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurs first, OR until follow-up data collection is no longer of scientific value or otherwise needed (at the Sponsor's discretion), to obtain information about subsequent treatment(s) and survival status.

The end of the study is defined as approximately 6 mo after the last subject is registered.

3.2. Discussion of Study Design

This study will be conducted in up to 30 study sites in North America, Japan, and Europe.

The target sample size will be approximately 170 subjects: 40 in Cohort 1, 40 in Cohort 1a, and 90 in Cohort 2.

3.3. Selection of Dose and Usage

The dose selection was based on the efficacy, safety, tolerability and pharmacokinetic data of trastuzumab deruxtecan from prior clinical studies in subjects with breast cancer (BC), NSCLC and other solid tumors.

In the dose escalation part (Part 1) of the first-in-human study DS8201-A-J101, no dose-limiting toxicities were observed, and the maximum tolerated dose was not reached in the evaluated dose range of 0.8 to 8.0 mg/kg. Based on the efficacy and safety data in Part 1 of Study DS8201-A-J101, the 5.4 and 6.4 mg/kg doses exhibited clinical activity with a qualitatively similar safety profile, and therefore were selected for the dose expansion portion (Part 2) of Study DS8201-A-J101 in subjects with metastatic breast cancer (mBC), gastric/GEJ cancer,

NSCLC, colorectal cancer and other solid tumors; subjects with NSCLC received only a 6.4 mg/kg dose of trastuzumab deruxtecan in Study DS8201-A-J101 (Part 2d).

A dose of 6.4 mg/kg was selected for Study DS8201-A-U204, based on available efficacy data from subjects with NSCLC in Part 2d of Study DS8201-A-J101 and a preliminary logistic-regression analysis for efficacy from Part 1 of Study DS8201-A-J101, which indicated a numeric trend of achieving higher ORR (approximately 7% higher) with trastuzumab deruxtecan dose of 6.4 mg/kg compared to a dose of 5.4 mg/kg. Prior to the initiation of Study DS8201-A-U204, 1 out of 5 evaluable subjects with NSCLC achieved a confirmed partial response (PR) and 2 patients were in SD at the 6.4 mg/kg dose in Part 2d of Study DS8201-A-J101. As of the most recent data-cut (01 Feb 2019) in subjects with NSCLC in Part 2d of Study DS8201-A-J101, 18 evaluable subjects, in the Enrolled Analysis Set had confirmed ORR of 55.6% (10/18; 95% CI for ORR: 30.8% - 78.5%) with median DoR of 10.7 months (95% CI: 6.9 – 11.5 months) and median PFS of 11.3 months (95% CI: 7.2 – 14.3 months; based on 9 events) has been achieved at trastuzumab deruxtecan dose of 6.4 mg/kg. Consistent promising efficacy was observed in the subset of NSCLC subjects with HER2 mutation (N =11). From a safety perspective, trastuzumab deruxtecan dose of 6.4 mg/kg was generally tolerated with an acceptable and manageable safety profile consistent with the safety profile observed in other solid tumors. These results support evaluation of trastuzumab deruxtecan dose of 6.4 mg/kg in subjects with NSCLC in current study.

Trastuzumab deruxtecan dose of 5.4 mg/kg has been evaluated in Study DS8201-A-J101 and a Phase 2 study (DS8201-A-U201) in subjects with HER2-positive, unresectable and/or mBC. The dose of 5.4 mg/kg has shown robust efficacy with confirmed ORR (by Independent Central Review) of 58.3% (137/235; 95%CI: 51.7% - 64.7%) in subjects with mBC. From safety perspective, a numeric trend for better safety profile was seen at the 5.4 mg/kg dose compared to higher doses (≥ 6.4 mg/kg). The trastuzumab deruxtecan dose of 5.4 mg/kg is currently being evaluated in the ongoing Phase 3 studies in subjects with mBC. Based on these efficacy and safety data in subjects with mBC, trastuzumab deruxtecan dose of 5.4 mg/kg was also selected for evaluation in this study in subjects with HER2-expressing NSCLC to assess the benefit/risk profile of the 5.4 mg/kg dose in this patient population.

From the PK perspective, the systemic exposures parameters (Cmax, AUC0-21d [AUC over 21 days of dosing cycle] and trough serum concentration in Cycle 1) of intact trastuzumab deruxtecan and MAAA-1181a were comparable across subjects with mBC and HER2-expressing or -mutant NSCLC at 6.4 mg/kg dose of trastuzumab deruxtecan. The systemic exposure of intact trastuzumab deruxtecan at 5.4 and 6.4 mg/kg doses in patients with solid tumors in Cycle 1 were observed to exceed the systemic efficacious exposure observed during the nonclinical pharmacology evaluation. Based on the exposure response (ER) analyses for efficacy, the mean (90% CI) probability of ORR in subjects with mBC was predicted to be 63% (55%- 70%) and 68% (58% - 77%) for the 5.4 and 6.4 mg/kg dose groups, respectively. Hence, the ER analyses support clinically meaningful efficacy for trastuzumab deruxtecan at both the 5.4 and 6.4 mg/kg doses and a small improvement in ORR at 6.4 mg/kg compared to the 5.4 mg/kg dose level in subjects with mBC. The ER analyses for safety estimated, a numerically higher incidence (approximately 1% to 7%) of the safety endpoints (adverse event [AE] related discontinuation, dose reduction or drug interruption), AEs ≥ Grade 3, SAE, anemia, neutropenia or thrombocytopenia and ILD (any grade and ≥ Grade 3), and decreased LVEF (≥ Grade 2) at

6.4 mg/kg dose compared to 5.4 mg/kg dose. Overall, these ER results for efficacy and safety indicate that while both 5.4 and 6.4 mg/kg doses showed a positive benefit/risk profile, the 6.4 mg/kg dose showed a numerical trend for an increase in the ORR as well as a numerical increase in the incidence of adverse events compared to the 5.4 mg/kg dose. These findings along with the observed efficacy and safety data in subjects with NSCLC in Study DS8201-A-J101 support the selection of 5.4 and 6.4 mg/kg doses in subjects with NSCLC in the current study.

Based on the efficacy, tolerability and PK profile of trastuzumab deruxtecan, doses of 5.4 mg/kg and 6.4 mg/kg were evaluated in previous Phase 2 studies as well as in the ongoing Phase 2 and Phase 3 studies in patients with solid tumors. These doses have demonstrated to be efficacious and have a manageable safety profile. On the basis of these data, trastuzumab deruxtecan doses of 5.4 mg/kg and 6.4 mg/kg administered Q3W were selected for this study.

3.4. Interim Analyses

Efficacy and safety interim analyses will be performed on cohorts 1 and 2 when approximately 20 subjects in cohort 2 have had at least 18 weeks of follow-up after initiation of therapy [usually three computed tomography [CT] scans post baseline] or discontinued treatment. The purpose of the interim analysis is to guide the future strategy for trastuzumab deruxtecan in this patient population.

A second interim analysis will be conducted when at least 60 subjects in Cohort 2 have had at least 12 weeks of follow-up after initiation of therapy or discontinued treatment. This interim analysis will also be performed on Cohorts 1 and 2.

A third interim analysis will be performed when at least 20 subjects in Cohort 1a have had at least 18 weeks of follow-up after initiation of therapy [usually 3 CT scans post baseline] or discontinued treatment. This interim analysis will be performed on cohorts 1, 1a, and 2.

The main purpose of this interim analysis is to get an early idea about the safety and efficacy of the administered dose in Cohort 1a.

4. STUDY POPULATION

Each subject will sign a study Main ICF provided by the site. A subject is considered enrolled in the study upon the Investigator or designee obtaining written Main ICF from the subject at the time of screening and upon determination that all inclusion and exclusion criteria have been satisfied.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited subject information (initials, age, gender, date) and outcome of screening process (ie, enrollment in the study, reason for ineligibility, withdrew consent).

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

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

4.1. Inclusion Criteria

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

1. Must have provided informed consent for study participation (see Section 14.3) before performance of any study-specific procedure or test.
2. Age ≥20 y old in Japan, ≥18 y old in other countries.
3. Pathologically documented unresectable and/or metastatic non-squamous NSCLC.
4. Has relapsed from or is refractory to standard treatment or for which no standard treatment is available.
5. For Cohort 1 and Cohort 1a only: HER2-overexpression status must be assessed and confirmed by Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or equivalent, from an archival tumor tissue sample.

   For Cohort 2 only: suject has any known documented activating HER2 mutation from an archival tumor tissue sample analyzed by Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory or equivalent, specifically exon 20 insYVMA (Y772_A775dup), insGSP (G778_P780dup), insTGT (G776delinsVC), single base pair substitutions L755S, V777L, or S310F or another HER2 mutation listed in the appendix (see Table 16.5). Note: HER2 mutation documented only from a liquid biopsy sample cannot be used for enrollment.
6. Presence of at least one measurable lesion assessed by the investigator based on RECIST version 1.1.
7. Is willing and able to provide an adequate archival tumor tissue sample. Fine needle aspirates are not acceptable
8. Is willing to undergo a tissue biopsy, taken after the completion of the most recent treatment regimen.
9. Has ECOG PS of 0 to 1.
10. Has adequate organ function within 14 d before enrollment, defined as:

Parameter	Laboratory value
Adequate bone marrow function	
Platelet count	≥ 100 000/mm^3 (Platelet transfusion is not allowed within 1 wk prior to screening assessment)
Hemoglobin	≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 wk prior to screening assessment)
Absolute neutrophil count (ANC)	≥ 1500/mm^3 (G-CSF administration is not allowed within 1 wk prior to screening assessment)
Adequate renal function	
Creatinine Clearance	Creatinine clearance ≥ 30 mL/min as calculated using the Cockcroft-Gault equation: CLcr (mL/min) = (140 - age [years]) × weight (kg) {× 0.85 for females} (72 × serum creatinine [mg/dL])
Adequate hepatic function	
ALT/AST	< 2.5 × ULN per institutional standards or < 5 × ULN if liver metastases are present
Total bilirubin (TBL)	≤ 1.5 × ULN if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline
Adequate blood clotting function	
International normalized ratio (INR)/Prothrombin time (PT) and either partial thromboplastin (PTT) or activated partial thromboplastin time (aPTT)	≤ 1.5 × ULN

11. Has adequate treatment washout period before enrollment, defined as:

Treatment	Washout Period
Major surgery	≥ 4 wk
Radiation therapy including palliative stereotactic radiation to chest	≥ 4 wk (palliative stereotactic radiation therapy to other areas, ≥ 2 wk)
Anti-cancer chemotherapy [Immunotherapy (non antibody based therapy)] retinoid therapy	≥ 3 wk (≥ 2 wk or 5 half-lives, whichever is longer, for small-molecule targeted agents such as 5-fluorouracil-based agents, folinate agents, weekly paclitaxel; ≥ 6 wk for nitrosureas or mitomycin C, ≥1 wk for TKIs approved for the treatment of NSCLC - baseline CT scan must be completed after discontinuation of TKI)
Antibody-based anti-cancer therapy	≥ 4 wk
Chloroquine/Hydroxychloroquine	>14 d

12. 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 4.5 mo for male subjects, for at least 7 mo for female subjects, after the last dose of study drug.

    Methods considered as highly effective methods of contraception include:

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

  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 4.5 mo for male subjects, for at least 7 mo for female subjects after the last dose of study drug. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not an acceptable method of contraception.

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

13. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 4.5 mo after the final study drug administration. Preservation of sperm should be considered prior to enrollment in this trial.
14. 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 mo after the final study drug administration.
15. Subjects should be willing and able to comply with protocol visits and procedures.

4.2. Exclusion Criteria

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

1. Had been previously treated with HER2-targeted therapies, except for pan-HER class tyrosine kinase inhibitors.
2. For Cohort 1 and Cohort 1a only: Has known HER2 mutation.
3. Has uncontrolled or significant cardiovascular disease, including any of the following:
    a. Medical history of myocardial infarction within 6 months before enrollment
    b. Symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV) 28 d prior to enrollment
    c. Troponin levels consistent with myocardial infarction (as defined by the manufacturer) 28 d prior to enrollment
    d. History of unstable angina, or serious cardiac arrhythmia requiring treatment
    e. LVEF < 50% within 28 d prior to enrollment
    f. Has a QT interval corrected by Fridericia's Formula (QTcF) prolongation to > 470 ms (females) or >450 ms (males) based on average of the screening triplicate 12-lead ECG.
4. Has a history of (non-infectious) ILD/pneumonitis that required steroids, has current ILD, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
5. Has 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 wk must have elapsed between the end of whole brain radiotherapy and study enrollment.
6. Has multiple primary malignancies within 3 y, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumors curatively treated.
7. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
8. Has history of severe hypersensitivity reactions to other monoclonal antibodies.
9. Has an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
10. Has substance abuse or any other medical conditions such as clinically significant cardiac 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.
11. Has known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects should be tested for HIV prior to randomization/enrollment if required by local regulations or institutional review board (IRB)/ethics committee (EC).

12. Has unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Subjects with chronic Grade 2 toxicities may be eligible per the discretion of the investigator after consultation with the Sponsor Medical Monitor or designee (eg, Grade 2 chemotherapy-induced neuropathy).
13. Is a female subject who is pregnant or breastfeeding or planning to become pregnant.
14. 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 study enrollment, 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.
15. Has undergone prior treatment with an ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor.
16. Has social, familial, or geographical factors that would interfere with study participation or follow-up.
17. Has a concomitant medical condition that would increase the risk of toxicity, in the opinion of the investigator.
18. Is a family member of the study site personnel or of the Sponsor personnel.
19. Is otherwise considered inappropriate for the study by the investigator.

4.3. Subject Rescreening Procedures

Rescreening is permitted for any subject who failed to meet the eligibility criteria in the initial screening. The limit of re-screening is 1 time. The site SID must remain the same at the time of re-screening. The initial screening information and the reason why the subject was ineligible for the initial evaluation will be recorded in the Screening Log. No data from the initial evaluation will be entered into the clinical database for a subject who is rescreened.

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group(s)/Sequences

There will be subjects allocated to 2 different cohorts (see Section 3.1) according to the centrally confirmed HER2 IHC status and documented HER2 mutation status. All subjects will receive trastuzumab deruxtecan treatment at the 6.4 mg/kg Q3W or 5.4 mg/kg Q3W dosages.

5.1.2. Method of Treatment Allocation

Subjects are enrolled in Interactive Web/Voice Response System (IXRS) for Cohort 1 and Cohort 1a (HER2-overexpressing [IHC 3+ or IHC 2+]) and for Cohort 2 (HER2 mutation) after signing the tissue screening ICF for Cohort 1 and Cohort 1a subjects or the Main ICF for Cohort 2 subjects.

5.1.3. Blinding

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

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug

5.2.1. Description

Lyophilized powder (Lyo-DP)

Trastuzumab deruxtecan for injection 100 mg will be provided as a sterile lyophilized powder containing 100 mg of Trastuzumab deruxtecan in a glass vial (Lyo-DP). Each glass vial should be reconstituted with 5 mL water for injection to a concentration of 20 mg/mL (ie, 100 mg/5 mL). Trastuzumab deruxtecan will be administered with 5% dextrose as an IV infusion. Each vial is designed for single use only and is not to be used to treat more than one subject.

5.2.2. Labeling and Packaging

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

5.2.3. Preparation

The study drug for IV infusion is prepared by dilution of the required volume of the study drug calculated on the basis of the subject's body weight in a volume of 100 mL, by the study site pharmacist. Prepared study drug solutions should be used as directed in the pharmacy instructions. The preparation will be conducted in accordance with the pharmacy instructions provided by the Sponsor. Procedures for proper handling and disposal of anticancer drugs

should be followed in compliance with the standard operating procedures (SOPs) of the study site.

5.2.4. Administration

The study drug will be administered as an IV infusion over 30 to 90 min every 3 wk ±2 d. The initial dose of study drug will be infused for 90±10 min. If there is no infusion-related reaction, after the initial dose, the next dose of trastuzumab deruxtecan may be infused over 30 ±5 min. The subject's weight at screening (baseline) will be used to calculate the initial dose. If during the course of treatment, the subject's weight changes by ≥10% of the baseline weight, the subject's dose will be recalculated on the basis of the subject's updated weight. Refer to the pharmacy instructions for detailed information about administration of study drug.

5.2.5. Storage

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

- Stored at 2 to 8 °C (protected from light) for lyophilized powder

If storage conditions are not maintained per specified requirements, the Sponsor or Contract Research Organization (CRO) should be contacted.

See pharmacy instructions for storage conditions of the infusion solution.

5.2.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and acknowledge receipt in IXRS. In addition, the investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for study drug (trastuzumab deruxtecan). The record must be kept current and should contain the following:

- Dates and quantities of drug received,
- SID and/or initials or supply number (as applicable),
- The date and quantity of study drug dispensed and remaining (if from individual subject drug units),
- The initials or seal of the dispenser.

At the end of the study, as per local laws and/or directed by the Sponsor, all unused study drug will be returned or destroyed as per local laws or site policy and only after the study monitor has completed a final inventory. As applicable, the study site must file a copy of the appropriate institution policy within their investigator site file and provide a copy to the Sponsor. See pharmacy instructions for details.

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 which is traceable to the study drug.

All study drug forms must be made available for inspection by the Sponsor's authorized representative or designee and regulatory agency inspectors.

5.3. Control Treatment

Not applicable.

5.4. Management Guidelines for trastuzumab deruxtecan

The investigator will evaluate which toxicities are attributed to the study drug and adjust the dose of the drug as recommended below for study drug. All dose modifications should be based on the worst preceding toxicity (Common Terminology Criteria for Adverse Events [CTCAE] version 5.0). Specific criteria for interruption, re-initiation, dose reduction and/or discontinuation of trastuzumab deruxtecan are listed in Table 5.2, Table 5.3, Table 5.4, Table 5.5, which are 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. Appropriate clinical experts should be consulted as deemed necessary.

Investigators may consider dose reductions or discontinuations of the study drug according to the subject's condition and after discussion with the Sponsor Medical Monitor.

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

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. Dose Reduction and Interruption Guidelines

Note: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified in Section 5.4.1.1.

One initial starting dose of trastuzumab deruxtecan will be used in this study. This starting dose of trastuzumab deruxtecan Lyo-DP formulation will be 6.4 mg/kg or 5.4 mg/kg. A dose can be delayed for up to 28 d (49 d from the last infusion date) from the planned date of administration. If a subject is assessed as requiring a dose delay of longer than 28 d, 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 of the last trastuzumab deruxtecan dose.

Up to two dose reductions will be permitted. The adjustments for reduced dosing of trastuzumab deruxtecan depending on the initial starting dose are shown in Table 5.1.

Table 5.1: Sample Dose Reduction Levels of Trastuzumab Deruxtecan

Starting Dose	Dose Level -1	Dose Level -2
6.4 mg/kg	5.4 mg/kg	4.4 mg/kg
5.4 mg/kg	4.4 mg/kg	3.2 mg/kg

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

Dose can be interrupted for up to 28 d from the planned date of administration. If a subject requires a dose delay longer than 28 d, the subject will permanently discontinue study drug, but will be followed for survival.

Treatment cycles for a subject for whom study drug dosing was temporarily withheld for any reason may have future cycles scheduled based on the date of the last study drug dose.

All confirmed or suspected COVID-19, adverse events must be recorded in the eCRF. Please refer to Section 16.7 for additional information on dose modification.

Investigators may contact the Sponsor's Medical Monitor or designee to discuss questions regarding dose modification or discontinuation of study drug.

5.4.1.1. Dose Modifications

5.4.1.1.1. Cardiac Toxicities

Table 5.2: Management Guidelines for Cardiac Toxicities

CTCAE v5.0 Grade	Management Guidelines for trastuzumab deruxtecan
Left Ventricular Ejection Fraction	
Symptomatic CHF	Discontinue subject from study drug
Decrease in LVEF 10 to 20% (absolute value), but LVEF > 45%	Continue treatment with study drug
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	Continue treatment with study drug Repeat LVEF assessment within 3 wk
LVEF 40% to ≤ 45% and decrease is 10-20% (absolute value) from baseline	Interrupt study drug dosing Repeat LVEF assessment within 3 wk. If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study drug If LVEF recovers to within 10% from baseline, resume treatment with study drug
LVEF < 40% or > 20% (absolute value) drop from baseline	Interrupt study drug dosing Repeat LVEF assessment within 3 wk. If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue subject from study drug

CTCAE v5.0 Grade	Management Guidelines for trastuzumab deruxtecan
Electrocardiogram QT 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, then if attributed to study drug, reduce by one dose level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue subject from study drug
Troponin	
Grade 1 (Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer)	If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3. For newly diagnosed Grade 1 events, repeat troponin testing at 3 ± 1 hours (h) after initial troponin test. If repeat troponin level at 3 ± 1 h rises significantly per institutional guidelines, - perform ECG in triplicate; - repeat troponin testing at 6 ± 1 h after initial troponin test; - follow institutional guidelines for management of detectable troponin testing. If repeat troponin level at 3 ± 1 h does not rise significantly per institutional guidelines, - repeat troponin testing at 6 ± 1 h or at 24 ± 2 h after initial troponin test. Continue treatment with trastuzumab deruxtecan.
Grade 3 (Levels consistent with myocardial infarction as defined by the manufacturer)	Perform ECG in triplicate. Repeat troponin testing at 6 h (±1 h) and 12 h (±1 h) after initial troponin test. Follow institutional guidelines for management of detectable troponin testing. If AMI confirmed, discontinue subject from study therapy. Otherwise, delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, maintain dose. If resolved in > 7 d from day of onset, reduce dose 1 level.

AMI = acute myocardial infarction; CHF = congestive heart failure; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; QTc = corrected QT interval; ULN = upper limit of normal

5.4.1.1.2. Hematologic Toxicity

Table 5.3: Management Guidelines for Hematologic Toxicities

CTCAE v5.0 Grade	Management Guidelines for trastuzumab deruxtecan
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, Reduce by one dose level
Febrile Neutropenia (absolute neutrophil count < 1 × 10^9/L, fever > 38.3°C or a sustained temperature of ≥ 38 °C for more than one h)	Delay dose until resolved, Reduce by one dose 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 d from day of onset, maintain dose If resolved in > 14 d from day of onset, reduce dose one level
Anaemia	
Grade 3 (Hemoglobin <8.0 g/dL); transfusion indicated	Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 (Hemoglobin <8.0 g/dL) Life-threatening consequences; urgent intervention indicated	Delay dose until resolved to ≤ Grade 2, then reduce dose one level
Platelet Count Decreased	
Grade 3 (<50 to 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose one level
Grade 4 (< 25 × 10^9/L)	Delay dose until resolved to ≤ Grade 1, then reduce dose one level

CTCAE = Common Terminology Criteria for Adverse Events

5.4.1.1.3. Non-Hematologic Toxicity

The following guidelines should be followed for subjects who develop Grade 3 or 4 non-hematologic toxicity unless otherwise noted in Table 5.4.

Other Laboratory and Non Laboratory TEAEs:

- Grade 3: delay dose until resolved to ≤ Grade 1 or baseline level:
  - If resolved in ≤ 7 d from day of onset, maintain dose
  - If resolved in > 7 d from day of onset, reduce by one dose level
- Grade 4: discontinue subject from study drug

5.4.1.1.3.1. Hepatic Toxicity

Dose and schedule modifications for hepatic toxicities in subjects with normal hepatic function and mild/moderate hepatic impairment at baseline (ie, the last measurement prior to study drug administration on Cycle 1 Day 1) should be followed as outlined in Table 5.4.

Table 5.4: Management Guidelines for Hepatic Toxicity

CTCAE v5.0 Grade	Management Guidelines for trastuzumab deruxtecan
Aspartate amino transaminase (AST) or Alanine amino transaminase (ALT) with Simultaneous Blood Bilirubin Increased	
AST/ALT ≥3.0 × ULN with simultaneous TBL >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 workup, 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
Grade 3 (>5.0 - 20.0 × ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal). In subjects without liver metastases and subjects with liver metastases and baseline level ≤ 3 × ULN	Repeat testing within 3 d. Delay dose until resolved to ≤ Grade 1, if baseline ≤3 × ULN, otherwise delay dose until resolved to ≤ baseline, then: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 3: (>8.0 - 20.0 × ULN if baseline was normal; >8.0 - 20.0 x baseline if baseline was abnormal). In subjects with liver metastases, if the baseline level was > 3 × ULN	Repeat testing within 3 d. Delay dose until resolved to ≤ baseline level, then: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4 (>20.0 x ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Discontinue subject from study treatment
Total Bilirubin	
Grade 2 (>1.5 - 3.0 × ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal)	If no documented Gilbert's syndrome or liver metastases at baseline delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level If documented Gilbert's syndrome or liver metastases at baseline, continue study treatment

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

ALT = alanine transaminase; AST = aspartate transaminase; CTCAE = Common Terminology Criteria for Adverse Events; d = days; SAE = serious adverse event; TBL = total bilirubin; ULN = upper limit of normal

5.4.1.1.3.2. Other Non-Hematologic Toxicity

Table 5.5: Management Guidelines for Non-Hematologic Toxicities

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
Infusion Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	If infusion-related reaction (such as fever and chills [with and without nausea/vomiting], pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 h)	Administration of study drug 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 restarted 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 study drug should be discontinued immediately and permanently. Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation etc., should be administered.

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
Pulmonary Toxicity	
	If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-Laboratory Adverse Events" in the dose modification section of the study protocol. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluation. Evaluations should include: • high resolution CT • pulmonologist consultation (Infectious Disease consultation as clinically indicated) • Blood culture and complete blood count (CBC). Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • pulmonary function tests and pulse oximetry (SpO_2) • arterial blood gases if clinically indicated • one blood sample collection for PK analyses as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed. If the AE is confirmed to be ILD/pneumonitis, follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.
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 d for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. • If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines. * For Grade 1 events, trastuzumab deruxtecan can be restarted only if the event is fully resolved to Grade 0: • If resolved in ≤ 28 d from day of onset, maintain dose • If resolved in > 28 d from day of onset, reduce dose 1 level However, if the event of Grade 1 ILD/pneumonitis occurs beyond Day 22 and has not resolved within 49 d from the last infusion, the study drug should be discontinued. * If subject is asymptomatic, then subject 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 d or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks.

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
	• Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 d, - Consider increasing dose of steroids (eg., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg. methylprednisolone). - Re-consider additional work-up for alternative etiologies as described above. - Escalate care as clinically indicated.
Grades 3 and 4	Permanently discontinue subject from study treatment. • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (e.g., 500-1000 mg/day for 3 d), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 d 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 d, - Re-consider additional work-up for alternative etiologies as described above. - Consider other immuno-suppressants and/or treat per local practice.
Ocular	
Grade 3	Delay dose until resolved to ≤ Grade 1: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose by 1 level
Grade 4	Discontinue subject from study treatment
Blood Creatinine Increased	
Grade 3 (> 3.0 to 6.0 × ULN)	Delay dose until resolved to ≤ Grade 2 or baseline, then reduce dose one level
Grade 4 (> 6.0 × ULN)	Discontinue subject from study drug
Gastrointestinal	
Nausea	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose one level
Diarrhea/Colitis	
Grade 3	Delay dose until resolved to ≤ Grade 1 If resolved in ≤ 3 d from day of onset, maintain dose If resolved in > 3 d from day of onset, reduce dose one level
Grade 4	Discontinue subject from study drug
Other Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline level: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan
Other Non-Laboratory Adverse Events	
Grade 3	Delay dose until resolved to ≤ Grade 1 or baseline: If resolved in ≤ 7 d from day of onset, maintain dose If resolved in > 7 d from day of onset, reduce dose 1 level
Grade 4	Discontinue subject from study treatment

AEs = adverse events; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; d = days; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs; SAE = serious adverse event; ULN = upper limit of normal; SpO2 = peripheral oxygen saturation

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

5.5. Method of Assessing Treatment Compliance

Trastuzumab deruxtecan will be administered IV only to subjects participating in the study and under the supervision of clinical study personnel at the study site. Therefore, treatment compliance will be guaranteed as long as the subject attends each visit for administration of the study treatment. Start and stop date/time of injection, amount of drug administered, and reason for change or interruption (if applicable) must be recorded in medical record by clinical study personnel. These data will be recorded in the eCRF.

5.6. Prior and Concomitant Medications

Medications used from the time the subject signs the Main ICF for study participation to the visit 40-Day Follow-up (+7 d) after the last administration of trastuzumab deruxtecan will be recorded. Prophylactic treatment for the study treatment and all concomitant medications will be recorded in the eCRF.

Permitted Therapies/Products:

1. Hematopoietic growth factor may be used for prophylaxis or treatment based on the clinical judgment of the investigator.
2. Concomitant use of dietary supplements, medications not prescribed by the Investigator, and alternative/complementary treatments is discouraged, but not prohibited.
3. Prophylactic or supportive treatment of study-drug induced AE will be otherwise as per investigator's discretion and the institutional guidelines.
4. Based on the currently available clinical safety data, it is recommended that subjects patients 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 (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

5.7. Prohibited Medications and Treatments

The following medications and products will be prohibited during the treatment period:

1. Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anti-cancer hormonal treatment [concurrent use of hormones for noncancer-related conditions (e.g. insulin for diabetes and hormone replacement therapy) is acceptable].
2. Other investigational therapeutic agents.
3. 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).
4. Concomitant use of chronic systemic (IV or oral) corticosteroids or other immunosuppressive medications except for managing AEs; (Inhaled steroids or intra articular steroid injections are permitted in this study.)
    - Subjects with bronchopulmonary disorders who require intermittent use of bronchodilators (such as albuterol) will not be excluded from this study.
5. Radiotherapy to the thorax.
6. Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. Refer to Section 16.7 for further details.

5.7.1. Restricted products

1. 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 Drug

Subjects may be withdrawn from study drug for the following reasons:

- PD per RECIST version 1.1 assessed by the investigator;
- Clinical progression (definitive clinical signs of disease progression, but a recent radiographic assessment did not meet the criteria for PD according to RECIST version 1.1);
- AE;
- Death;
- Pregnancy;
- Protocol deviation;
- Withdrawal of consent by subject;
- Lost to follow-up;
- Physician decision;

- Study terminated by the Sponsor;
- Other, specify.

All subjects who are withdrawn from the study treatment should complete protocol-specified withdrawal procedures (Section 5.8.3) and follow-up procedures (Section 6.6).

Record the reason for any subject who discontinues study treatment. Discontinued subjects will be followed for survival, either through direct contacts or by collecting public records (eg, death certificates) unless prohibited by local laws.

5.8.2. Reasons for Discontinuation of Study Participation

The duration of subject participation in the study will be until one of the following occurs:

- Subject dies;
- Study is terminated by the Sponsor;
- Subject withdraws consent to participate in study procedures;
- Subject is lost to follow-up;
- Others, specify.

Note: 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.

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 due to an AE, the investigator will follow the subject until the AE has resolved or stabilized, post-cancer treatment, or lost to follow-up.

All subjects who are withdrawn from the study drug should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be obtained during the EOT visit (within +7 d) and the 40-Day Follow-up Visit (within +7 d) conducted after date that Principal Investigator decides subject discontinuation of treatment (Section 6.5 and Section 6.6).

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Section 16.1. A signed and dated Main ICF will be obtained before any study-related procedures or assessments are conducted. For Cohort 1 and Cohort 1a, a separate tissue screening ICF may be used to obtain consent to send the sample to the central laboratory.

After signing the tissue screening ICF for Cohort 1 and Cohort 1a subject or the Main ICF for Cohort 2 subjects, the investigator or designee will assign an SID and enter subject's background data in the IXRS.

Informed consent for optional pharmacogenomics study will be obtained separately.

6.1. Tissue Screening (For Cohort 1 and Cohort 1a Only)

To determine eligibility, subjects must meet tumor biomarker criteria.

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

Please refer to the study laboratory manual for required tumor tissue sample specifications and shipping instructions.

The following procedures will be conducted:

- Obtain a signed and dated written consent from the subject to collect archival tumor tissue sample.
- Register the subject in the IXRS and assign an SID.
- Obtain adequate archival tumor tissue sample for HER2 IHC testing. Slides or adequate paraffin-embedded tissue blocks of formalin-fixed tissue specimens can be submitted for this analysis. Fine needle aspirates are not acceptable.
- Send the sample to the central laboratory to assess and confirm HER2 IHC status

If subject is ineligible during the tissue screening period, the subject is not eligible for screening.

6.2. Screening

A signed and dated Main ICF will be obtained before any study-related procedures or assessments are conducted. After eligibility is confirmed, the subject will be enrolled to IXRS as ineligible or eligible and assigned to the cohort.

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

- For Cohort 1, Cohort 1a and Cohort 2, fresh tumor biopsy must be obtained after discontinuation of the most recent treatment regimen and before treatment with trastuzumab deruxtecan. The detailed procedures for preparing and submitting tumor tissue samples will be provided in the laboratory manual. There is no need to perform fresh tumor biopsy if a subject already has an adequate tumor tissue sample which was taken after the completion of the most recent treatment regimen and available to be submitted.

- For Cohort 1, Cohort 1a and Cohort 2, tumor tissue samples for the specimen used to determine HER2 status for screening should be provided. Central laboratory confirmation is required prior to enrollment for Cohort 1 and Cohort 1a, but not for Cohort 2. Further details will be provided in the laboratory manual.

Within 28 d before enrollment:

- Perform ophthalmologic assessment, including visual acuity testing, slit lamp examination, and fundoscopy.
- Perform an ECHO or MUGA (Note: The same test must be used for the subject throughout the study).
- Perform tumor assessment by CT or magnetic resonance imaging (MRI) scans of the chest, abdomen, pelvis, and any other sites of disease. A CT or MRI of the brain is to be included for all subjects. Baseline CT scan must be completed after discontinuation of TKI.
- Perform an HIV antibody test. It is optional unless required by local regulations or IRB/ECs.
- Perform hepatitis B surface antigen test, and hepatitis C antibody test.

Note: To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use it as comparator for subsequent measurement. Therefore, all lesions (target and non-target) have to be assessed at Screening according to RECIST version 1.1.

The following activities and/or assessments will be performed during the Screening period within 14 d before enrollment except as indicated:

- Record concomitant medications and AEs, (from the time the subject signed the Main ICF). For details on AE collection and reporting, refer to Section 9.
- Confirm subject eligibility
- Obtain demographics (eg, birth date, sex, race, ethnicity), medical and surgical history, including all previous, now resolved, significant medical conditions, smoking history, histology (eg, adenocarcinoma, large cell carcinoma) date of diagnosis, extent of disease, disease staging, primary tumor site (eg, right upper lobe, right middle lobe, right lower lobe, left upper lobe, left lower lobe), previous cancer therapies (including prior radiation therapy), historical gene abnormality status (eg, EGFR, proto oncogene B-raf mutation, ALK, ROS proto-oncogene 1 fusion, microsatellite instability status) and oncology surgical history.
- Perform a complete physical examination (see Section 9.11) including weight and height.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and peripheral oxygen saturation (SpO_2).
- Assess functional status using the ECOG PS (see Section 16.4).

- Collect and send blood and urine samples to the laboratory for the following tests:
  - Hematology;
  - Chemistry;
  - Troponins (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;
  - Coagulation;
  - Urinalysis
- Perform triplicate 12-lead ECG.
  - ECGs will be taken in close succession, initiated approximately 3 min apart, after the subject has been in a supine/semi-recumbent position.

Within 72 h prior to enrollment:

- For women of childbearing potential, perform a serum or urine pregnancy test and document the results. Test must be confirmed negative within 72 h prior to enrollment. For subjects who are of non-childbearing potential, no pregnancy test will be required.

6.3. Randomization

Not applicable.

6.4. Treatment Period

Treatment will begin as soon as possible after a subject is enrolled to IXRS.

6.4.1. Cycle 1 to Cycle 4 and Subsequent Cycles

Treatment and procedures performed on Cycle 1 Day 1 and beyond are specified in Section 16.1 and further described below. Procedures are to be performed within 3 d of the Day 1 visit of each cycle unless otherwise specified.

Note: Vital sign (including SpO_2) evaluations, 12-lead ECG, hematology, chemistry, physical examination, weight, and ECOG PS determination need not be repeated if they were performed within 3 d of the first dose of Cycle 1, Day 1.

6.4.1.1. Day 1; Before Infusion (All Cycles, Unless Otherwise Noted):

- Perform a physical examination (Section 9.11), including weight. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Perform ophthalmologic assessment, including visual acuity testing, slit lamp examination, and fundoscopy on Day 1: Cycles 2, 6, 10, 14, etc (- 7 d). If the planned date of study drug administration is delayed after examination of ophthalmologic assessments, and there are no abnormal findings on the examination,

it is up to the investigator's judgment as to whether ophthalmologic assessments need to be repeated.

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and SpO_2). More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Collect blood samples for the following tests (see Section 9.8)
  - Hematology;
  - Chemistry
- Perform an ECHO or MUGA scan assessment (Note: The same test must be used for the subject throughout the study) every 4 cycles (-7 d) starting with Cycle 5 (ie, Cycle 5, 9, 13, etc). If the planned date of study drug administration is delayed after examination of ECHO or MUGA, and there are no abnormal findings on the examination, it is up to the investigator's judgment as to whether ECHO or MUGA need to be repeated.
- Assess functional status using the ECOG PS (see Section 16.4)
- Perform triplicate 12-lead ECG. ECGs will be taken in close succession, initiated approximately 3 minutes apart, while in a supine/semi-recumbent position. ECGs should be performed before PK blood draws
- Obtain blood samples for:
  - Serum will be obtained before infusion (BI) (within -8 h) on Day 1: Cycles 1, 2, 3, 4, and 6 for PK assessments;
  - Pharmacogenetic assessment, Cycle 1 only, if the subject provides consent by signing the pharmacogenetics sample banking ICF. (This sample is not required for study participation.)
  - ADA will be obtained BI (within -8 h) at Cycles 1, 2 and 4, then every 4 cycles (ie, Cycles 8, 12, 16, etc.)
- If a subject provides consent once protocol version 7.0 is applied, leftover samples after ADA testing would be used for future central laboratory analysis for COVID-19 testing at Cycles 1, 4 and every 4 cycles thereafter. For subjects with suspected or confirmed COVID-19, follow the dose modifications in Section 16.7
- Obtain blood samples for exploratory biomarkers, such as cfDNA analysis, before treatment on Day 1 of every cycle.
- Record concomitant medications and AEs at every visit
- Serum or urine sample for pregnancy testing in women of childbearing potential. Test must be confirmed negative within 72 h prior to drug administration.

6.4.1.2. Day 1; Dosing and End of Infusion (All Cycles, unless otherwise noted):

- Administer trastuzumab deruxtecan IV infusion 90±10 min for the initial dose and, if no infusion-related reaction after the initial dose, infuse subsequent doses over 30±5 min. Record start and stop times. Trastuzumab deruxtecan is to be administered every 3 wk ±2 d.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and SpO_2). More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Collect blood samples for:
  - Serum will be obtained within 15 min after the end of infusion (EOI) on Day 1: Cycles 1, 2, 3, 4, and 6 for PK assessments.
  - Serum will be obtained 5 h after the start of drug administration (±2 h), Cycle 1 only.

6.4.1.3. Cycle 1 - Day 8 and Day 15 (±1 d):

- Collect blood samples for serum on Cycle 1 Day 8 (±1 d); and Day 15 (±1 d) for PK assessments.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and SpO_2). More frequent examinations may be performed at the discretion of the investigator and if medically indicated.

6.4.2. Every 6 Wk (±7 d)

- Tumor assessments, based on sites of disease identified at Screening and any additional newly suspected sites of PD, will be conducted every 6 wk (±7 d) from Cycle 1 Day 1, independent of treatment cycle. A CT and/or MRI (spiral CT or MRI with ≤ 5 mm cuts) of chest, abdomen, and pelvis should be used for tumor assessment unless another modality of disease assessment is necessary for the lesions. The same assessment modality should be used throughout the study for all assessments for each subject unless prior approval is obtained from the Sponsor or its designee. Unscheduled tumor assessments may be performed if progression is suspected.
- A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need additional brain scans for tumor assessment unless clinically indicated.

Note: Imaging results will be reviewed by an independent radiologic facility. Copies of CT and/or MRI images should be provided after the images are taken.

6.4.3. Fresh Tumor Biopsy During Treatment

An optional fresh tumor biopsy specimen will be obtained from a subject at Day 43 from Cycle 1 Day 1 (±7 d) if a subject agrees. Tumor tissue will be sent to the central laboratory for exploratory biomarker analysis. Further details will be provided in the laboratory manual. If the tumor is not taken, document the reason why the fresh tumor tissue sample is unavailable.

6.5. End of Treatment

The EOT visit should be conducted within 7 d after Investigator decides to discontinue study drug. The following procedures will be performed as specified in the Schedule of Events (Table 16.1). However, if the EOT assessments have been performed within 40 (+7 d) of their last treatment, they can be considered to be the EOT data and there is no need to repeat them; otherwise, these assessments need to be repeated:

- Perform a physical examination (Section 9.11), including weight.
- Perform ophthalmologic assessment, including visual acuity testing, slit lamp examination, and fundoscopy.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and SpO_2).
- Perform triplicate 12-lead ECG. ECGs will be taken in close succession, initiated approximately 3 minutes apart, while in a supine/semi-recumbent position.
- Perform an ECHO or MUGA (Note: The same test must be used for the subject throughout the study).
- Collect sample for ADA
- Collect blood samples for the following tests:
  - Hematology;
  - Chemistry;
  - Troponin (local testing: preferably high-sensitivity troponin-T). An additional sample should be submitted for central lab troponin-T testingIf troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is <Grade 3.
- Blood sample for exploratory biomarkers, such as cfDNA analysis, will be collected.
- Serum or urine sample for pregnancy testing in women of childbearing potential.
- 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 Version 1.1. If the previous scan was within the last 6 wk, this assessment does not need to be performed at the EOT Visit. If investigator makes a clinical diagnosis that there has been progression, imaging examinations should be performed as promptly as possible, and effort should be made to obtain an image based assessment of PD.
- A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Subjects without brain metastases do not need brain scan for tumor assessment unless clinically indicated.
- Assess functional status using the ECOG PS.
- Obtain an optional fresh tumor specimen from a subject at the EOT if a subject agrees. Tumor tissue will be sent to the central laboratory for an exploratory

biomarker analysis. Further details will be provided in the laboratory manual. If the tumor is not taken, document the reason why the fresh tumor tissue sample is unavailable.

- Record concomitant medications and AEs.

6.6. Follow-up

6.6.1. 40-Day Follow-up (within + 7 d)

Forty days (within +7 d) 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 16.1). If EOT is > 40 d after last treatment, then the EOT assessments can also function as the 40-Day Follow-up visit.

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and SpO_2).
- Perform a physical examination (Section 9.11), including weight.
- Assess functional status using the ECOG PS.
- Collect blood samples for the following tests:
  - Hematology
  - Chemistry
- Serum or urine sample for pregnancy testing in women of childbearing potential.
- Obtain blood samples for ADA

  For subjects with positive ADA at the 40-Day Follow-up visit, additional blood ADA samples may be collected every 3 mo (±14 d) up to 1 y from the last dose of study drug, or until the ADA becomes negative, or until the ADA titer becomes less than baseline (applicable when preexisting ADA is observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
- Record concomitant medications and AEs.

6.6.2. Long-Term Follow-up Visits

After completion of the 40-Day Follow-up Visit, the Long-Term Follow-up Visits will be performed every 3 mo (±14 d), from the date of 40-Day Follow-up Visit, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first or until follow-up data collection is no longer of scientific value or otherwise needed (at the Sponsor's discretion), to obtain information about subsequent treatment(s) and survival status.

This information may be collected in a visit or via phone contact, or (as necessary for survival status, in the case of withdrawal of consent or loss to follow-up) from public records (eg, death certificates) in accordance with local laws.

Further follow-up may be required for ongoing AEs (see Section 9.2)

6.7. Additional PK assessments due to COVID-19 infection

In case of chloroquine or hydroxychloroquine administration for SARS CoV-2 infection, additional PK samples should be collected at the following time points (See Table 8.2).

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoint(s)

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is ORR, defined as the sum of CR rate; PR rate, assessed by ICR based on RECIST Version 1.1. Efficacy assessments will be based on tumor assessments to be performed at screening and every 6 wk while the subject remains on study drug.

7.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints noted below that will be assessed by the investigator and/or ICR review will be based on RECIST version 1.1. Secondary efficacy endpoints include:

- DoR, defined as time from the initial response (CR or PR) until documented tumor progression or death from any cause, based on ICR and investigator assessment. DoR is only defined for subjects who achieved confirmed CR or PR. Censoring is the same as for PFS analysis and will be detailed in SAP.
- DCR, defined as the proportion of subjects who achieved CR, PR, or SD during study treatment, based on ICR and investigator assessment
- PFS, defined as the time from date of enrollment until first objective radiographic tumor progression or death from any cause, based on ICR and investigator assessment. Detailed censoring rules will be provided in SAP.
- ORR, defined in Section 7.1.1, based on investigator assessment
- OS, defined as the time from date of enrollment until death from any cause (based on records in clinical database and public records where it is allowed by law). Subjects last known to be alive are censored at the date of last contact.

Detailed censoring rules for secondary efficacy endpoints will be specified in the SAP.

7.1.3. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- TTR, defined as the time from the date of enrollment to the date of the first documentation of objective response (CR or PR), based on ICR and investigator assessment. TTR will be measured for responding subjects (CR or PR) only
- Best percent change from baseline in the sum of the diameters for all target lesions based on ICR and investigator assessment
- Analysis of biopsied materials for mechanisms of resistance to trastuzumab deruxtecan
- Exposure-response relationships for efficacy and safety endpoints

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Assessment(s)

Blood samples for PK assessments will be collected at multiple time points in the study, as outlined in Table 8.1.

Table 8.1: Blood Sampling for Pharmacokinetic Analysis

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI 5 h after the start of drug administration (±2 h)
	Day 8	7 d after the start of drug administration (±1 d)
	Day 15	14 d after the start of drug administration (±1 d)
	(Day 22)	If the schedule on Day 1 of the next cycle is delayed for 3 d or more, including if the subject cannot continue onto the next cycle, collect blood sample 21 d after the start of drug administration (±2 d). If the next schedule is not delayed, sampling at this point is not necessary
Cycle 2	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI
Cycle 3	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI
Cycle 4	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI
Cycle 6	Day 1	BI (– 8 to 0 h) EOI: Within 15 min after EOI

BI = before infusion; EOI = end of infusion
Note: Obtain one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible.

In case of chloroquine or hydroxychloroquine administration for COVID-19, additional PK samples should be collected at the following time points

Table 8.2: Schedule of PK Sample Collection in Case of Chloroquine or 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 h)
EOT with chloroquine or hydroxychloroquine	Prior to chloroquine or hydroxychloroquine dose (within 4 h)
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 times of study drug administration and the exact time of blood sampling for PK analysis must be recorded on the eCRF, including those samples collected in case of chloroquine or hydroxychloroquine administration for SARS CoV-2 infection.

Details for blood sampling, processing, storage and shipment for PK samples will be provided in the study laboratory manual.

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

8.2. Biomarker Assessment(s)

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

HER2 gene mutations in tissue are planned to be analyzed in a central laboratory as exploratory biomarkers when tissue samples are available.

Detailed instructions for the collection, handling, and shipping of biomarker samples are outlined in the study laboratory manual.

8.2.1. Tumor and Blood Biomarker Assessments

Tumor specimens will be used to assess the HER2 expression using IHC and ISH, HER2 mutation using NGS technology or other methods. Blood samples for exploratory biomarkers, such as cfDNA, are planned with intent of monitoring the antitumor impact of treatment with trastuzumab deruxtecan.

8.2.2. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, other exploratory biomarker research may be conducted on tissue and/or soluble 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.

If the patient agrees, the remaining biomarker samples (tumor tissue, blood, or other specimen obtained in the study) may be stored for up to 15 y and further analyzed to address scientific questions related to trastuzumab deruxtecan and/or cancer.

8.3. Immunogenicity

Blood samples for ADA analyses will be collected at the time points specified in Section 16.1. A blood sample will be drawn at each time point. Instructions for the handling and shipping of

ADA serum samples are included in a separate document (ie, laboratory manual). The ADA samples will be shipped to a central laboratory for forwarding to the Sponsor-designated bioanalytical laboratory.

The immunogenicity testing will be performed using validated ADA assay following tiered assay steps including screening, confirmatory as well as titer determination. Samples confirmed positive will be analyzed with the neutralizing antibody assay. Serum concentrations of trastuzumab deruxtecan and/or total anti-HER2 antibody may be measured using the same ADA samples as part of ADA assessment.

For subjects with positive anti-trastuzumab deruxtecan antibodies on the blood sample drawn at the F/U Visit, additional serum samples will be obtained every 3 mo (± 14 d) for ADA measurement for up to 1 year from the last dose of trastuzumab deruxtecan, or until the subject has a negative ADA result or started another cancer therapy, whichever occurs first.

8.4. Pharmacogenomic Analysis

8.4.1. Genomic or Genetic Banking and Analysis

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

The following procedures will be used for the long-term preservation (banking) of DNA specimens extracted from subjects' blood samples. Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, 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 DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, 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.

8.4.1.1. Disclosure of the Results of Genomic or Genetic Analysis

See the Main ICF for details on disclosure.

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

Samples will be retained until the genetic material has been exhausted or until the Sponsor instructs the genotyping contractor to destroy the sample (in accordance with laboratory procedures). During the period of storage, the genetic 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 genetic analysis has been completed before the subject withdraws consent.

9. SAFETY EVALUATION AND REPORTING

9.1. Assessment of Safety Endpoint(s)

Safety endpoints will include SAEs, TEAEs, adverse events of special interest (AESIs), ECHO/MUGA findings; ophthalmologic findings, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters (central laboratory; troponin), ADAs, and ECG parameters. All AEs will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events and abnormal laboratory test results, if applicable, will be graded using CTCAE version 5.0. 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

All clinical AEs (see Section 9.4.1 for definitions) occurring after the subject signs the ICF and up to 40 (within + 7) d after last treatment (ie, the 40-Day Follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. All SAEs occurring after subject signs the ICF and up to 40 (within + 7) d after last treatment will be recorded on the eCRF. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history.

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

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

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

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

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

For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and, consequently, should not be reported as an AE/SAE. However, when a subject dies from PD with no other immediate causes, "disease progression" should be reported as an SAE.

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

9.3. Adverse Events of Special Interest

9.3.1. LVEF Decrease

Clinical Summary: LVEF decrease in association with trastuzumab deruxtecan is considered to be an important potential risk based on the available pre-clinical data in association with trastuzumab deruxtecan is considered to be an important potential risk based on the available nonclinical data, literature, and available safety information for drugs of similar class. Refer to the current IB for a summary of preliminary clinical trial data.

Management Guidance: LVEF will be measured by either ECHO or MUGA scan. All ECHOs/MUGAs will be evaluated by the investigator or delegated physician for monitoring cardiac function.

Troponin will be measured at screening and EOT, and as needed based on subject reported cardiac signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. An additional sample will be submitted for central lab troponin-T testing, and ECG will be performed in triplicate. If ECG is abnormal, follow institutional guidelines.

ECGs will be performed and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by Investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter is to be recorded in the eCRF.

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

9.3.2. Interstitial Lung Disease

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

Management Guidance:

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

an etiology other than ILD/pneumonitis, follow the management guidance outlined in the designated "Other Non-Laboratory Adverse Events" dose modification section of the study protocol.

If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include high-resolution CT, pulmonologist consultation (infectious disease consultation as clinically indicated), blood culture and CBC (other blood tests could be considered as needed), bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible should be considered, pulmonary function tests and pulse oximetry (SpO_2), arterial blood gases if clinically indicated, and one blood sample collection for PK as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered as needed. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification section of the study protocol. All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after study drug discontinuation.

Additional relevant information regarding the AESI, ILD/pneumonitis for the trastuzumab deruxtecan clinical program is to be collected through the targeted questionnaires within the clinical study database, regardless of seriousness.

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

9.3.2.1. Interstitial Lung Disease Adjudication Committee

An independent ILD Adjudication Committee (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 and 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 adverse events reported using selected 42 Preferred Terms (all from the ILD Standard MedDRA Query [SMQ]) plus 2 PTs of acute respiratory failure and respiratory failure.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

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

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

9.4.2. Serious Adverse Event

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

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

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

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

Note:

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

9.4.3. Severity Assessment

All AEs will be graded (1 to 5; see below) according to the latest CTCAE version 5.0:

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

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe

headache). Seriousness of an event is based upon a universal and global regulatory definition for reporting SAEs to regulatory agencies. For example, 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 may or may not be assessed as serious based on the seriousness criteria. Overall, the severity of an event may be graded by the investigator as Grade 1 or 2, but if the subject presents to the emergency facility for evaluation and is hospitalized overnight for observation that immediately makes the event serious based upon hospitalization without regard to the investigator assessment of severity.

9.4.4. Causality Assessment

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

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

or

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

9.4.5. Action Taken Regarding Study Drug(s)

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

9.4.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.

  - Prescription and/or over-the-counter medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

9.4.7. Adverse Event Outcome

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

9.5. Serious Adverse Events Reporting–Procedure for Investigators

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

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

Any SAEs directly related to a tumor biopsy procedure should also be reported.

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

- SAEs (see Section 9.4.2 for definition)

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

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

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow- up. In the event that eCRF is unavailable, report SAEs 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.

See Section 14.10 for contact information for SAE reporting. Please call the local SAE Hotline or your study monitor for any questions on SAE reporting.

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

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

In the United States, 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 the Sponsor's instruction.

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

In Japan, it is the Sponsor's responsibility to report SUSARs to the IRB/ECs.

9.7. Exposure In Utero During Clinical Studies

The Sponsor must be notified of any female subject who becomes pregnant within 7 mo of the last dose of study drug or the female partner of a male subject who becomes pregnant while receiving or within 4.5 mo of, the last dose of the study drug.

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

9.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

1. Hematology tests
    a. Red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).
2. Blood chemistry tests
    a. Total protein, albumin, alkaline phosphatase, ALT, AST, TBL, blood urea nitrogen (BUN)/urea, calcium, chloride, serum creatinine, lactate dehydrogenase (LDH), potassium, sodium, and magnesium.

b. A coagulation test (prothrombin time and activated partial thromboplastin time) will be performed at screening and thereafter as needed.
c. Creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation (see Section 16.2).

3. Troponin T will be analyzed at the local and central laboratory for each sample. Local laboratory values will be used for treatment decisions and narratives, the central laboratory values will be stored within the central database.
4. Urinalysis
   a. Protein, glucose, blood, microscopy assessment (if indicated), and specific gravity.

In addition, the following parameters will be analyzed at the visits indicated in the Schedule of Events (see Section 16.1).

5. Pregnancy test (serum or urine) for all female subjects of childbearing potential must be performed during the Screening Period and on Day 1 of each cycle before infusion.

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 (see Section 9.5). Abnormal laboratory values (CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, pulse rate, respiratory rate, SpO_2 and body temperature.

9.10. Electrocardiograms

Standard supine/semi-recumbent 12-lead ECGs in triplicate (taken in close succession, initiated approximately 3 min apart) will be performed as described in the Schedule of Events. Standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnormalities.

9.11. Physical Examinations

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

9.12. Other Examinations

9.12.1. Cardiac Assessments

Either ECHO or MUGA, will be performed as described in the Schedule of Events (Section 16.1); LVEF will be measured.

9.12.2. Pulmonary Assessments

Computed tomography or MRI of the chest will be performed as described in Section 6.2 and Section 6.4.2. Additionally, SpO_2 will be measured at Screening, before administration and end of infusion on Day 1 of each cycle, and at the EOT and the 40-Day Follow-up Visits. For more details please refer to Section 6.

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

10. STATISTICAL METHODS

10.1. General Statistical Considerations

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

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

Efficacy analyses will be performed on the Full Analysis Set (FAS). In addition, select efficacy analyses will also be performed on the Response Evaluable Set (RES). Safety analyses will be performed using the Safety Analysis Set. Analysis of PK parameters will be based on the PK Analysis Set. All other exploratory analyses will be performed based on the RES.

Efficacy and safety interim analyses will be performed on cohorts 1 and 2 when approximately 20 subjects in cohort 2 have had at least 18 weeks of follow up after initiation of therapy (usually three CT scans post baseline) or have discontinued treatment. The purpose of the interim analysis is to guide the future strategy for trastuzumab deruxtecan in this patient population.

A second interim analysis will be conducted when at least 60 subjects in Cohort 2 have had at least 12 weeks of follow-up after initiation of therapy or discontinued treatment. This interim analysis will also be performed on cohorts 1 and 2.A third interim analysis will be performed when at least 20 subjects in Cohort 1a have completed at least 18 weeks of follow up after initiation of therapy (usually three CT scans post baseline) or have discontinued treatment. This interim analysis will be performed on cohorts 1, 1a, and 2.

A primary analysis will be performed when subjects in Cohort 2 have sufficient follow-up for the assessment of primary efficacy endpoint. This primary analysis will include all available data, but the results of Cohort 2 will be the focus. A Clinical Study Report (CSR) will be based on this primary analysis.

At the time of this primary analysis, the data for Cohort 1a may not be sufficiently mature. An additional analysis will be performed when subjects have sufficient follow-up. Additional analyses may be performed to address COVID-19 impact.

10.2. Analysis Sets

10.2.1. Full Analysis Set

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

10.2.2. Safety Analysis Set

The Safety Analysis Set will include all enrolled subjects who received at least one dose of study drug.

10.2.3. Response Evaluable Set

The RES will include all enrolled subjects who received at least 1 dose of study drug and had measurable disease at baseline per ICR.

10.2.4. Pharmacokinetic Analysis Set

The PK Analysis Set will include all enrolled subjects who received at least one dose of study drug and had measurable serum concentrations of trastuzumab deruxtecan.

10.3. Study Population Data

Subject disposition will be summarized for subjects in the FAS. 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 and RES. Study drug exposure and treatment duration will be summarized using descriptive statistics for the FAS.

10.4. Efficacy Analyses

The primary efficacy analysis will be performed for the FAS. All efficacy analyses will be performed for FAS. In addition, select efficacy analyses will also be performed on the Response Evaluable Set (RES). All CIs will be 2-sided 95% CIs, unless stated otherwise.

10.4.1. Primary Efficacy Analyses

The primary efficacy endpoint is ORR assessed by ICR. Primary analysis of ORR will be summarized by cohort for FAS. Their corresponding 2-sided 95% exact CI will be provided.

10.4.2. Key Secondary Efficacy Analyses

The secondary efficacy endpoints are: DoR, DCR, and PFS, which will be determined based on ICR and based on investigator assessment , as well as ORR based on investigator assessment, and OS will be the other secondary endpoints.

ORR and DCR will be summarized by cohort, and their 95% exact CIs will be provided.

For time to event endpoints (DoR, PFS, OS), Kaplan-Meier estimates of medians and their corresponding 95% CIs will be computed using Brookmeyer and Crowley method will be provided by cohort. Kaplan-Meier estimates of survival curves will be plotted.

10.4.3. Exploratory Efficacy Analyses

Exploratory efficacy endpoints include TTR, best percent change from baseline in the sum of the diameters for all target lesions, analysis of biopsies for mechanisms of resistance to trastuzumab deruxtecan and exposure-response relationships.

Summary statistics (n, mean, standard error, median, min, max) will be provided by cohort for TTR and for best percent change from baseline in the sum of the diameters for all target lesions, respectively.

10.4.4. Pharmacokinetic and Pharmacodynamic Analyses

10.4.4.1. Pharmacokinetic Analyses

Analysis of PK parameters (serum concentrations and PK parameters of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181) will be based on the PK analysis set. Descriptive statistics will be provided by cohort for all serum concentration data at each time point and PK parameter as appropriate.

The population pharmacokinetic 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 Phase 1 study. After establishment of the pop-PK model, a pop-PK/pharmacodynamic model may be developed to evaluate the relationship between exposure and efficacy and toxicity. The population PK and PK/pharmacodynamic modeling analyses may be reported separately from the clinical study report.

10.4.4.2. Pharmacodynamic Analyses

Not applicable.

10.4.5. Biomarker Analyses

Biomarkers will be listed and summarized by cohort using descriptive statistics.

10.4.6. Immunogenicity (Anti-Drug Antibody [ADA]) Analyses

Immunogenicity will be assessed through characterization of incidence and titer of the 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 least one time point post-study drug treatment as positive. The raw values and change from baseline for ADA titers will be summarized by time point and cohort using descriptive statistics. The raw values and change from baseline for ADA titers will be summarized by time point and cohort using descriptive statistics. The treatment-emergent ADA incidence will also be calculated. Treatment-emergent ADA positive subjects will be defined as subjects who are ADA negative at baseline and become ADA positive post-treatment, or who are ADA positive at baseline and post-treatment, but have an increase in ADA titer from baseline to post-treatment, or those who have missing ADA data at baseline but become ADA positive post-treatment. The number and percentage of subjects positive for neutralizing antibody (Nab) of trastuzumab deruxtecan will also be assessed.

10.5. Safety Analyses

Safety analysis will be performed using the Safety Analysis Set.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics by cohort. Listings of safety data will be provided and details will be specified in SAP.

10.5.1. Study drug exposure

Treatment duration, total dose, dose intensity and relative dose intensity will be summarized by cohort using descriptive statistics. In addition, the total number of cycles initiated will be summarized by cohort using descriptive statistics.

10.5.2. 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.

Adverse events will be coded using MedDRA and graded using CTCAE version 5.0. The number and percentage of subjects reporting TEAEs will be tabulated by system organ class (SOC), PT, relationship to the study drug, the worst CTCAE grade and by cohort. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by cohort, as well as TEAEs leading to discontinuation of the study drugs.

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

10.5.3. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory test results and changes from baseline by cohort at each scheduled time of evaluation.

Abnormal clinical laboratory results will be graded according to CTCAE version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting 2-way frequency tabulation for baseline and the worst posttreatment value according to CTCAE grade, will be provided for clinical laboratory tests.

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

10.5.4. Vital Sign Analyses

Descriptive statistics will be provided by cohort for vital sign measurements and changes from baseline by scheduled time of evaluation. The baseline value is defined as the last non-missing value before the initial administration of study treatment.

10.5.5. Electrocardiogram Analyses

Descriptive statistics will be provided by cohort for ECG parameters and changes from baseline by scheduled time of evaluation. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (QTc ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms). Maximum change from baseline will be tabulated (≤30 ms, >30 to ≤60 ms, >60 ms). The QT intervals will be corrected for heart rate by Fridericia's formula (QTcF). ECG data will also be listed.

10.5.6. Other Safety Analysis

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

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

10.5.7. Other Analyses - Assessment of the Impact of 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 statistical analysis plan.

10.6. Interim Analyses

Efficacy and safety interim analyses will be performed on Cohorts 1 and 2, when approximately 20 subjects in cohort 2 have had at least 18 weeks of follow -up after initiation of therapy (usually three CT scans post baseline) or have discontinued treatment.

A second interim analysis will be conducted when at least 60 subjects in Cohort 2 have had at least 12 weeks of follow-up after initiation of therapy or discontinued treatment. Safety data related to adverse events will be summarized with descriptive statistics by each cohort. This interim analysis will also be performed on cohorts 1 and 2.

A third interim analysis will be performed when approximately 20 subjects in cohort 1a have had at least 18 weeks of follow-up after initiation of therapy (usually three CT scans post baseline) or have discontinued treatment. This interim analysis will be performed on cohorts 1, 1a, and 2.

For each cohort, the primary efficacy endpoint of ORR will be summarized using descriptive statistics including 2-sided exact 95% CI (Clopper-Pearson). Other efficacy endpoints based on response rates will be summarized by cohort using the same methodology as the primary efficacy endpoint. For time to event endpoint PFS, Kaplan-Meier estimates of medians and their corresponding 95% CIs using Brookmeyer and Crowley method will be provided by cohort. Safety data related to adverse events will be summarized with descriptive statistics by each cohort.

In addition, PK endpoints of trastuzumab deruxtecan and MAAA-1181a, Cmax, Tmax, AUClast, and $AUC_{0\text{-}21d}$ for each cohort may be summarized using descriptive statistics. The relationship between trastuzumab deruxtecan or MAAA-1181 exposure and efficacy or safety may be explored.

The results of any interim efficacy or PK analysis, if performed, will not be used to change the conduct of the study.

10.7. Sample Size Determination

There will be approximately 40 subjects in Cohort 1, approximately 40 subjects in Cohort 1a (to be enrolled after protocol V6.0), and approximately 90 subjects in Cohort 2, of which 50 will be enrolled following Protocol Amendment Version 5.0. Thus, in all the total number of subjects on the study will be approximately 170.

A sample size of 40 response evaluable subjects each in Cohorts 1 and 1a is required so that the average distance from the limits of the respective 95% CIs to the observed ORR is approximately 0.14, assuming the expected ORR is 0.3.

A sample size of 90 subjects in Cohort 2 ensures that the average distance from the limits of a 95% CI to the observed ORR is approximately 0.09, assuming the expected ORR is 0.3. With this sample size, the probability of the lower bound of the 95% CI exceeding 0.3 is more than 49% when the true ORR is 0.4 and the probability increases to more than 96% when the true ORR is 0.5. The operating characteristics for a few other scenarios are included in the following table.

Table 10.1: Operating Characteristics for Single Arm Expansion Design with 90 Subjects

True ORR	Observed ORR	95% confidence interval (CI)	Probability of lower confidence limit exceeding 30% under the true ORR
30%	30% (27 out of 90)	(20.79%, 40.57%)	2.50%
40%	40% (36 out of 90)	(29.81%, 50.87%)	49.06%
50%	50% (45 out of 90)	(39.27%, 60.73%)	96.67%
60%	60% (54 out of 90)	(49.13%, 70.19%)	99.99%
70%	70% (63 out of 90)	(59.43%, 79.21%)	100.00%

ORR = Overall Response Rate

The upper 95% confidence limit of the ORR for the current standard of care (SOC) Docetaxel was observed to be under 0.2 or 20% [33]. The threshold of 0.3 or 30% was decided by benchmarking against this estimate of the upper limit of 20% and allowing a further increment of 10% to account for the sparseness of the available data.

10.8. Statistical Analysis Process

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, unusable, or 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.

Sample size is calculated using EAST software (Cytel, MA 02139), and the open-source R software. All statistical analyses will be performed using SAS® version 9.3 or higher (SAS Institute Inc., Cary, NC 27513).

11. 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.

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

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

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

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

11.2. 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. The information should be entered into the eCRF within 5 d of the visit

and should be completed, reviewed, and signed off by the investigator within 2 wk of the last subject visit. Query resolution should be completed within 48 h.

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedures. For subjects who are screened but not registered, minimal data will be recorded on the eCRF, including demography, subject status, and AEs. 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.

11.3. Data Management

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

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to Sponsor or 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 laboratory will be reconciled to the clinical database.

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

All AEs and medical histories will be coded using MedDRA.

All concomitant medications and prior cancer therapies will be coded using the World Health Organization Drug Reference List Dictionary.

11.4. 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 eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, x-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, 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 [TMF]). 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.

11.5. Record Keeping

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system, Trial Master File (TMF) 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 site, 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 3 y after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 y have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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

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

12. FINANCING AND INSURANCE

12.1. Finances

Prior to starting the study, the 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.

12.2. 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.

13. PUBLICATION AND PUBLIC DISCLOSURE OF CLINICAL TRIAL INFORMATION

14. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

14.1. 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:

- United States Food and Drug Administration GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March, 1997 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;
- Other applicable local regulations.

14.2. 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.

14.3. Informed Consent

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries, and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

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

have their origin in the Declaration of Helsinki. The ICF 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.

14.4. Regulatory Compliance

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

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

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

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

14.5. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the 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. The Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

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

If a subject was ineligible or received the incorrect dose or study drug, and had at least one 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.

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

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study, IRBs/ECs, 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.

14.7. Protocol Amendments

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

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

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

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

14.8. 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).

14.9. Data Monitoring Committee

Not applicable.

14.10. Address List

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

15. REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global Cancer Statistics. CA Cancer J Clin 2011;61(2):69–90.
2. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. v.2.2014. www.nccn.org.
3. Kern JA, Slebos RJ, Top B, et al. C-erbB-2 expression and codon K-ras mutations both predict shortened survival for patients with pulmonary adenocarcinomas. J Clin Invest. 1994; 93(2):516-20.
4. Harpole DH Jr, Marks JR, Richards WG, et al. Localized adenocarcinoma of the lung: oncogene expression of erbB-2 and p53 in 150 patients. Clin Cancer Res. 1995; 1(6):659-64.
5. Shi D, He G, Cao S, Pan W, Zhang HZ, et al. Overexpression of the c-erbB-2/neu-encoded p185 protein in primary lung cancer. Mol Carcinog. 1992; 5(3):213-8.
6. Scheurle D, Jahanzeb M, Aronsohn RS, et al. HER-2/neu expression in archival non-small cell lung carcinomas using FDA-approved Hercep test. Anticancer Res. 2000: 20(3B):2091–6.
7. Mazières J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol. 2013; 31(16):1997–2003.
8. Arcila ME, Chaft JE, Nafa K, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res. 2012; 18(18):4910–8.
9. Li C, Sun Y, Fang R, et al. Lung adenocarcinomas with HER2-activating mutations are associated with distinct clinical features and HER2/EGFR copy number gains. J Thorac Oncol. 2012;7(1):85–9.
10. Tomizawa K, Suda K, Onozato R, et al. Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. Lung Cancer. 2011; 74(1):139–44.
11. Shigematsu H, Takahashi T, Nomura M, et al. Somatic mutations of the HER2 kinase domain in lung adenocarcinomas. Cancer Res. 2005; 65(5):1642–6.
12. Yokoyama T, Kondo M, Goto Y, et al. EGFR point mutation in non-small cell lung cancer is occasionally accompanied by a second mutation or amplification. Cancer Sci. 2006; 97(8):753–9.
13. Stinchcombe T, Stahel RA, Bubendorf L, et al. Efficacy, safety, and biomarker results of trastuzumab emtansine (T-DM1) in patients (pts) with previously treated HER2-overexpressing locally advanced or metastatic non-small cell lung cancer (mNSCLC). J Clin Oncol. 2017; 35(15 Suppl):abstract 8509.
14. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine in patients with HER2 mutant lung cancers: Results from a phase II basket trial. J Clin Oncol. 2017; 35(15 Suppl):abstract 8510.

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

16. Cheverton P, Friess H, Andras C, et al. Phase III results of exatecan (DX-8951f) versus gemcitabine (Gem) in chemotherapy- naïve patients with advanced pancreatic cancer (APC). J Clin Oncol. 2004; 22(14 Suppl):abstract 4005.

17. De Jager R, Cheverton P, Tamanoi K, et al. DX-8951f: summary of phase I clinical trials. Ann N Y Acad Sci. 2000; 922:260-73.

18. Ogitani Y, Aida T, Hagihara K, et al. Trastuzumab deruxtecan, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin Cancer Res. 2016; 22(20):5097-108.

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

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

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

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

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

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

25. Blok EJ, Kuppen PJ, van Leeuwen JE, et al. Cytoplasmic overexpression of HER2: a key factor in colorectal cancer. Clin Med Insights Oncol. 2013; 7:41-51.

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

27. Clamon G, Herndon J, Kern J, et al. Lack of trastuzumab activity in nonsmall cell lung carcinoma with overexpression of erb-B2: 39810: a phase II trial of Cancer and Leukemia Group B. Cancer. 2005; 103(8):1670-5.

28. Kris MG, Camidge DR, Giaccone G, et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann Oncol. 2015; 26(7):1421-7.

29. Hyman DM, Piha-Paul SA, Rodón J, et al. Neratinib for *ERBB2* mutant, HER2 non-amplified, metastatic breast cancer: Preliminary analysis from a multicenter, open-label, multi-histology phase II basket trial. Cancer Res. 2016; 76(4 Suppl):abstract PD5-05.

30. Gandhi L, Besse B, Mazieres J, et al. Neratinib ± temsirolimus in HER2-mutant lung cancers: an international, randomized phase II study. J Thorac Oncol. 2017; 12(1 Suppl):abstract MA04.02.

31. Lai W-CV, Lebas L, Milia J, et al. Afatinib in patients with metastatic HER2-mutant lung cancers: an international multicenter study. J Clin Oncol. 2017; 35(15 suppl):abstract 9071.

32. Tsurutani J, Park H, Doi T, et al. Updated Results of Phase 1 Study of DS-8201a in HER2-Expressing or –Mutated Advanced Non-Small-Cell Lung Cancer. J Thorac Oncol. 2018; 13 (10), supplement: S324

33. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer N Engl J Med. 2015; 373:1627-1639

34. Trastuzumab Deruxtecan Global Investigator's Brochure Version 6.0, September 09, 2019

16. APPENDICES

16.1. Appendix 1: Schedule of Events

Table 16.1: Schedule of Events

Visit/Cycle	Tissue Screen (Cohort 1, Cohort 1a)	SCR	Cycle 1					Cycle 2		Cycle 3		Cycle 4 and subsequent cycles Day 1		EOT[a]	F/U[b]	Long-Term Q3M F/U (±14D)
			Day 1		Day 8	Day 15	Day 22	Day 1		Day 1						
			BI	EOI	(±1 D)	(±1 D)	(±2 D)	BI	EOI	BI	EOI	BI	EOI			
Informed consent	X (Cohort 1, Cohort1a)	X														
Tumor tissue sample for tissue screening[s]	X (Cohort 1, Cohort 1a)															
Tumor tissue sample for HER2 status		X														
Fresh tumor biopsy		X[c]	X[d]													
Administer trastuzumab deruxtecan			X					X		X		X				
Medical history/ Demographic		X[e]														
Vital signs		X[e]	X[f]	X	X	X		X[f]	X	X[f]	X	X[f]	X	X	X	
Physical examination		X[e]	X[f]					X[f]		X[f]		X[f]		X	X	
SpO_2		X[e]	X[f]	X	X	X		X[f]	X	X[f]	X	X[f]	X	X	X	
Height		X[e]														
Weight, ECOG PS		X[e]	X[f]					X[f]		X[f]		X[f]		X	X	
Clinical laboratory tests (Hematology, Chemistry)		X[e]	X[f]		X	X		X[f]		X[f]		X[f]		X	X	
Coagulation		X[e]														
Troponin[g]		X[e]												X		

Visit/Cycle	Tissue Screen (Cohort 1, Cohort 1a)	SCR	Cycle 1					Cycle 2		Cycle 3		Cycle 4 and subsequent cycles Day 1		EOT[a]	F/U[b]	Long-Term Q3M F/U (±14D)
			Day 1		Day 8	Day 15	Day 22	Day 1		Day 1						
			BI	EOI	(±1 D)	(±1 D)	(±2 D)	BI	EOI	BI	EOI	BI	EOI			
cfDNA blood samples			X					X		X		X		X		
Pharmacogenomic blood sample			X[h]													
PK blood sample[v]			X[i]	X[j,k]	X	X	X[l]	X[i]	X[j]	X[i]	X[j]	X[i]	X[j]			
PK Sampling for CQ/HCQ Administration			If subject provides consent, samples should be collected. 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[w], (within 8h BI of trastuzumab deruxtecan).													
ADA Blood Sample			X[m]					X[m]				X[m]		X	X	X[n]
HIV antibody test (as required by local regulation)		X[o]														
Hepatitis B/ / C serology		X[o]														
COVID-19 testing[x]			X									X[y]				
ECHO or MUGA (LVEF)		X[o]										X[o,p]		X		
12-lead ECG in triplicate[r]		X[e]	X					X[q]		X[q]		X[q]		X		
Pregnancy test		X[u]	X[f,u]					X[u]		X[u]		X[u]		X	X	
Ophthalmologic assessment[t]		X[o,t]						X[t]				X[t]		X[t]		

Visit/Cycle	Tissue Screen (Cohort 1, Cohort 1a)	SCR	Cycle 1					Cycle 2		Cycle 3		Cycle 4 and subsequent cycles Day 1		EOT[a]	F/U[b]	Long-Term Q3M F/U (±14D)
			Day 1		Day 8	Day 15	Day 22	Day 1		Day 1						
			BI	EOI	(±1 D)	(±1 D)	(±2 D)	BI	EOI	BI	EOI	BI	EOI			
Urinalysis		X[e]														
Tumor assessment[o]		X	Every 6 wk (±7 d) until PD or starting new anticancer treatment regardless of Post-treatment Follow-up period													
Pulmonary imaging[o]		X	Every 6 wk (±7 d) until PD or starting new anticancer treatment regardless of Post-treatment Follow-up period													
Concomitant medications		← X →														
AEs		← X →														
Survival follow-up																X

ADA = anti-drug antibody; AE = adverse event; BI = before infusion; cfDNA = cell-free deoxyribonucleic acid; COVID-19 = Coronavirus disease 19; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; EOI = end of infusion; EOT = end of treatment; F/U = follow-up; HCQ = hydroxychloroquine; HIV = human immunodeficiency virus; LVEF = left ventricular ejection fraction, MUGA = multigated acquisition; PD = progressive disease; PK = pharmacokinetic; SCR = screening; SpO2 = peripheral oxygen saturation

[a] The date Investigator decides to discontinue study treatment (within + 7 d).
[b] 40 d (+7 d) after the last study drug administration or before starting new anticancer treatment, whichever comes first.
[c] For all Cohort 1, Cohort 1a and Cohort 2, fresh tumor biopsy must be obtained after discontinuation of the most recent treatment regimen and before treatment with trastuzumab deruxtecan. The detailed procedures for preparing and submitting tumor tissue samples will be provided in the laboratory manual. There is no need to perform fresh tumor biopsy if a subject already has an adequate tumor tissue sample that was taken after the completion of the most recent treatment regimen and available to be submitted.
[d] An optional tumor rebiopsy will be taken on Day 43 from Cycle 1 Day 1 (±7 d) and at the EOT if a patient agrees.
[e] Within 14 d before enrollment.
[f] Within 72 h of infusion
[g] Collect blood samples for troponin (local testing: preferably high-sensitivity troponin-T) at screening, EOT, and if at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of myocyte necrosis. An additional sample should be submitted for central lab troponin-T testing, and perform ECG in triplicate. If ECG is abnormal, follow institutional guidelines. If troponin levels are above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3.
[h] Participation in this part of the study is optional for all subjects.
[i] Within -8 h BI on Day 1 of each cycle until Cycle 4 and then at Cycle 6 (ie, Cycle 1, 2, 3, 4, 6).
[j] Within 15 min after EOI on Day 1 of each cycle until Cycle 4 (eg, Cycle 1, 2, 3 and 4) and then at Day 1 of Cycle 6.

[k] Cycle 1 Day 1 only, 5 h (±2 h) after the start of drug administration.
[l] If treatment of next cycle is delayed for 3 d or more, or subject is discontinued, collect PK blood on this day (±2 d).
[m] Within -8 h BI on Day 1 in Cycles 1, 2 and 4, and then every 4 cycles. If subject provides consent and once protocol version 7.0 is applied, leftover samples after ADA testing would be used for future central laboratory analysis for COVID-19 testing at Cycles 1, 4 and every 4 cycles thereafter.
[n] For subjects with positive ADA at F/U visit, additional blood ADA samples may be collected every 3 mo (±14 d) up to 1 y from the last dose of study drug, or until the ADA becomes negative, or until ADA titer becomes less than baseline (applicable when preexisting ADA was observed), or until the subject starts another therapy for cancer, or withdraws consent from the study, whichever occurs first.
[o] Within 28 d before enrollment.
[p] ECHO or MUGA scan assessments will be performed at Screening and every 4 cycles (-7 d) starting with Cycle 5 (ie, Cycle 5, 9, 13…). If the planned date of study drug administration is delayed after examination of ECHO or MUGA, and there are no abnormal findings on the examination, it is up to the investigator's judgment as to whether ECHO or MUGA need to be repeated.
[q] Day 1, before infusion at all cycles.
[r] ECGs will be taken in close succession, approximately 3 minutes apart, while in a supine/semi-recumbent position. ECGs should be performed before PK blood draws
[s] For cohort 1 and Cohort 1a: HER2 IHC 2+ or 3+ status must be determined by central laboratory from an archival tumor tissue sample.
[t] Ophthalmologic assessment, including visual acuity testing, slit lamp examination, and fundoscopy on Day 1: Cycles 2, 6, 10, 14, etc (-7 d) and EOT. If the planned date of study drug administration is delayed after examination of ophthalmologic assessments, and there are no abnormal findings on the examination, it is up to the investigator's judgment as to whether ophthalmologic assessments need to be repeated.
[u] Within 72 h before enrollment and study drug administration.
[v] One blood sample collection for PK analysis as soon as ILD /pneumonitis is suspected, if feasible.
[w] A washout period of more than 14 days is required before restarting trastuzumab deruxtecan
[x] If subject provides consent and once protocol version 7.0 is applied, leftover samples after ADA testing would be used for future central laboratory analysis for COVID-19 testing at Cycles 1, 4 and every 4 cycles thereafter . For subjects with suspected or confirmed COVID-19, follow the dose modifications in Section 16.7
[y] Starting at C4, D1 and every 4 cycles thereafter to align with ADA blood sample collections.

For suspected interstitial lung disease (ILD) /pneumonitis , treatment with study drug should be interrupted pending evaluation. Evaluations should include:

- High resolution computed tomography (CT)
- Pulmonologist consultation (Infectious Disease consultation as clinically indicated)
- Blood culture and CBC. Other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests and pulse oximetry (SpO_2)
- Arterial blood gases if clinically indicated
- One blood sample collection for pharmacokinetic (PK) analyses as soon as ILD /pneumonitis is suspected, if feasible.

Other tests could be considered as needed.

16.2. Appendix 2: Cockcroft-Gault Equation

The estimated creatinine clearance rate (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight:

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;16:31-41.

16.3. Appendix 3: New York Heart Association (NYHA)

Table 16.2: New York Heart Association Functional Classification

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

Source: American Heart Association, Inc. Classification of Functional Capacity and Objective Assessment. Available from: http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

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

Table 16.3: Eastern Cooperative Oncology Group Performance Status Scale

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

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

16.5.1. Measurability of Tumor at Baseline

16.5.1.1. Definitions

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

16.5.1.1.1. Measurable

- Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
  - 20 mm by chest X-ray
- Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline (ie, screening for this study) and in follow-up (ie, all measurements past screening for this study), 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.

16.5.1.1.2. 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, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

16.5.1.1.3. Special Considerations Regarding Lesion Measurability

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

16.5.1.1.3.1. Bone Lesions

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

16.5.1.1.3.2. Lesions

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

16.5.1.1.3.3. Lesions with Prior Local Treatment

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

16.5.1.2. Specifications by Methods of Measurements

16.5.1.2.1. 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 28 d before enrollment.

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

Computed tomography, 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. Magnetic resonance imaging is also acceptable in certain situations (eg, for body scans).

16.5.2. Tumor Response Evaluation

16.5.2.1. 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.

In this study, only subjects with measurable disease at baseline should be included.

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

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (representative of all involved organs) should be identified as target lesions and

will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

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

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

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

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

16.5.2.3. Response Criteria

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

16.5.2.3.1. Evaluation of Target Lesions

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

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

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

Stable disease (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.

16.5.2.3.2. Special Notes on the Assessment of Target Lesions

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

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

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

16.5.2.3.3. Evaluation of Non-target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they

need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

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

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

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

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

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

16.5.2.3.5. New Lesions

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

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

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

16.5.2.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug until the EOT.

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

16.5.2.4.1. Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 16.4 provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, see Table 16.4.

Table 16.4: Overall Response: Subjects with Target (± Non-target) Disease

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

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

16.5.2.4.2. Missing Assessments and Not Evaluable Designation

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

16.5.2.4.3. Best Overall Response: All Time Points

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

Best response is defined as the lesser of the two best responses across two consecutive scans (eg, a subject who has PR at first assessment, SD at second assessment, and PD on last assessment; this would report as a best overall response of SD). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline, 6 wk (±7 d). If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered NE.

16.5.2.4.4. Special Notes on Response Assessment

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

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

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

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 NE) will be recorded as the date of the last radiographic evaluation included in the series for that assessment. The date of progression (PD) will be recorded as the date of the earliest radiographic evaluation included in the series for that assessment.

16.5.2.5. Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted every 6 wk (±7 d) while the subject remains on study until progression of disease, withdrawal of consent, death, or loss to follow-up. Scan dates should not be adjusted or rescheduled due to dose interruption of any type.

Baseline tumor assessments must be performed within 28 d before enrollment.

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

The radiographic evaluation must include CT or MRI scanning of chest, abdomen, and pelvis at screening period. A CT or MRI of the brain is mandatory for all subjects included with baseline stable brain metastases. Any additional suspected sites of disease should also be imaged. Every effort should be made to use the same assessment modality for all assessments for each subject. Follow-up evaluations should include all sites of disease identified at screening and any other locations if PD is suspected (eg, CT or MRI of the brain if brain metastases are suspected) should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

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

16.6. Appendix 6: Relevant HER2 Mutations

Table 16.5: List of HER2 Mutations

HER2 mutations
Glu770 Ala771insAlaTyrValMet
Ala771 Tyr772insTyrValMetAla
Gly776delinsLeuCys
Gly776Ser
Gly776Cys
Gly776delinsValCys
Gly776Val
Gly776Val777insLeu
Val777Leu
Val777Met
Val777 Gly778insCysGly
Gly778 Ser779insLeuProSer
Val777 Gly778insGly
Gly776 Val777insValGlySer
Val777 Gly778insGlySerPro
Ser310Pro
Ser310Tyr
Ser310Phe
Arg678Gln
Thr733Ile
Leu755Met
Leu755Pro
Leu755Ser
Leu755Trp
Asp769Asn
Asp769His
Asp769Tyr

Source: Information extracted from Thermo Fisher's analytical validation summary report

16.7. 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 confirmed COVID-19 infection

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

- If COVID-19 is ruled out, follow dose modification and management guidance as outlined in Section 5.4
- If COVID-19 is confirmed or is still suspected after evaluation follow dose modification as outlined in Table 16.6 below and manage COVID-19 per local guidance until recovery from COVID-19. 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 16.6: COVID-19 Dose Modification Criteria

COVID-19 Worst Toxicity 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 study drug if chest CT findings are **not** 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 16.6 , 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 5.5.

* If PCR testing is not available, the subject must not have any sign/symptoms for at least 2 weeks, in addition to meeting the requirement for chest CT imaging.

Prior and Concomitant Medications - Prohibited Therapies/Products

- Chloroquine or hydroxychloroquine;
  - Concomitant treatment is not allowed during the study treatment (Section 5.6).
  - If treatment is absolutely required for COVID-19 infection trastuzumab deruxtecan must be interrupted.
  - If administered, then a washout period of more than 14 days is required before resumption of 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 Table 16.1.The chloroquine or hydroxychloroquine administration time and the exact time of blood sample collection for PK analysis must be recorded on the eCRF.

COVID-19 Assessment(s)

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, 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 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.