CLINICAL STUDY PROTOCOL

A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF TRASTUZUMAB DERUXTECAN (DS-8201A), AN ANTI-HER2-ANTIBODY DRUG CONJUGATE, VERSUS ADO-TRASTUZUMAB EMTANSINE (T-DM1) FOR HER2-POSITIVE, UNRESECTABLE AND/OR METASTATIC BREAST CANCER SUBJECTS PREVIOUSLY TREATED WITH TRASTUZUMAB AND TAXANE (DESTINY-Breast03)

DS8201-A-U302

IND/EudraCT NUMBERS 127553/2018-000222-61

VERSION 6.0, 25 SEP 2020

Daiichi Sankyo Inc.

CRITICAL STUDY CONTACT LIST

Sponsor (United States)	Daiichi Sankyo Inc. 211 Mt Airy Rd Basking Ridge, NJ 07920 USA

DOCUMENT HISTORY

Version Number	Version Date
5.0	23 April 2020
4.0	26 April 2019
3.0	08 Mar 2019
2.0	20 June 2018
1.0	23 March 2018

INVESTIGATOR AGREEMENT

A Phase 3, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (DS-8201a), an anti-HER2-antibody drug conjugate, versus ado-trastuzumab emtansine (T-DM1) for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane (DESTINY-Breast03)

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Director, Global Oncology R&D	25 Sep 2020
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

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

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

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

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

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 6.0 (dated 25 Sep 2020) vs. protocol Version 5.0 (dated 23 Apr 2020) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS8201-A-U302 clinical study protocol (Version 6.0) by section.

Amendment Rationale:

DS8201-A-U302 was recently amended in April 2020 to Version 5.0, which incorporated coronavirus disease 2019 (COVID-19) management updates. This amendment is primarily driven by the addition of biomarker analyses to evaluate the impact of the global pandemic caused by COVID-19 at the subject-level and study-level and a change in the stopping rules for the progression-free survival (PFS) interim analysis. The exploratory endpoints were also revised to include evaluation of progression-free survival on the next line of therapy (PFS2) and withdrawal of consent language was clarified. Other changes are noted in the table below.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/Ethics Committee (EC) of the European Parliament and the Council of the European Union.

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

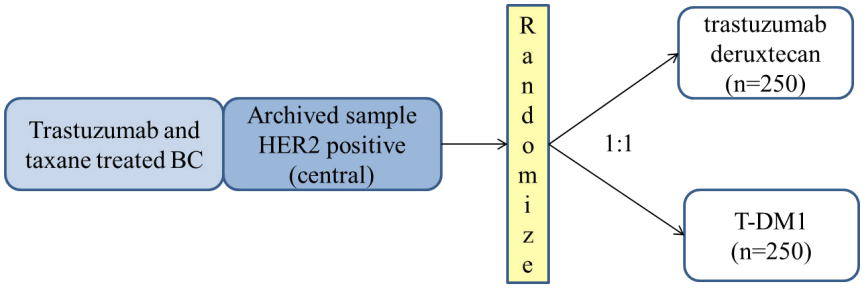
Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis	Destiny number was added	To provide clarification
	The exploratory objective was updated	To provide clarification
	The following exploratory endpoint was added: • Progression on the next line of treatment (PFS2) based on investigator assessment	To explore emerging PFS data
	The efficacy boundary for the interim analysis was updated	To include a change in the stopping rules

2.1.4. Exploratory Objectives 2.3.4. Exploratory Efficacy Endpoints	These subsections were updated	To explore emerging PFS data
5.9. Study Drug Discontinuation and Discontinuation from the Study	The heading and subheadings of this section were updated	To provide clarification
6.2. Screening 6.4.1.2. Day 1; Before Infusion (All Cycles, Unless Otherwise Noted) 6.5. End of Treatment	COVID-19 serology testing was added	To align with the latest safety information
6.4. Treatment Period 6.5. End of Treatment 6.6. Follow-up 10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45	Timing of completion of specific Health Economics and Outcomes Research (HEOR) outcomes questionnaires was specified	To provide clarification
7.1.4. Exploratory Efficacy Endpoints	PFS and PFS2 analyses were added	To explore emerging PFS data
8.1. Pharmacokinetic Assessments Table 17.2 Schedule of Events	Conditions for collecting PK samples from subjects treated with Chloroquine or Hydroxychloroquine were added	To monitor potential drug-drug interactions between investigational/study drug treatment and COVID-19 specific treatment
11.1. General Statistical Considerations	This section was updated	To provide further clarification
Table 11.1. Efficacy Stopping Boundaries for PFS/overall survival (OS) Interim and Final Analyses	This table was updated	To reflect the changes to the efficacy stopping boundaries for PFS interim analysis
Table 11.2. Probability of Study Outcomes Under Various True Hazard Ratios	This table was updated	To reflect the changes to the efficacy stopping boundaries for PFS interim analysis
11.4.1.1. Primary Efficacy Analyses	The description of the interim analysis was updated	To include a change in the stopping rules
11.4.1.3.2. Analyses of Exploratory Efficacy Endpoints	The analysis of PFS2 data was described	To explore emerging PFS data

11.4.3.1. Pharmacokinetic Analyses	This section was updated	To provide further clarification
11.4.4.7. Immunogenicity (Anti-Drug Antibody) Analyses	This section was updated	To provide further clarification
11.5. Interim Analyses	This section was updated	To include a change in the stopping rules
11.6. Sample Size Determination	This section was updated	To include a change in the stopping rules
16. References	This section was updated	To include references for the new stopping rule
Table 17.1. Schedule of Events	The table and footnotes were updated	To provide clarification To align with the latest safety information
17.8. Instructions Related to Coronavirus Disease 2019 (COVID-19)	This section was updated	To align with the latest management guidelines for COVID-19

PROTOCOL SYNOPSIS

EudraCT:	2018-000222-61
IND Number:	127553
NCT Number	NCT03529110
Protocol Number:	DS8201-A-U302
Investigational Product:	Trastuzumab deruxtecan (DS-8201a; also known as fam-trastuzumab deruxtecan)
Active Ingredients:	Trastuzumab deruxtecan consists of an antibody component, MAAL-9001, covalently conjugated via a maleimide tetrapeptide linker, to a drug component MAAA-1181a
Study Title:	A Phase 3, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (DS-8201a), an anti-HER2-antibody drug conjugate, versus ado-trastuzumab emtansine (T-DM1) for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane (DESTINY-Breast03)
Study Phase:	Phase 3
Indication Under Investigation:	Unresectable/metastatic breast cancer with human epidermal growth factor receptor 2 (HER2)-positive expression
Study Objectives:	Primary Objective: • To compare the progression-free survival (PFS) benefit of trastuzumab deruxtecan to T-DM1for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane. Key Secondary Objective: • To compare overall survival (OS) benefit of trastuzumab deruxtecan to T-DM1. Other Secondary Objectives: • To evaluate efficacy of trastuzumab deruxtecan compared to T-DM1 on: – Confirmed objective response rate (ORR); – Duration of response (DoR). • To further determine pharmacokinetics (PK) of trastuzumab deruxtecan. • To further evaluate safety of trastuzumab deruxtecan compared to T-DM1. • To evaluate Health Economics and Outcomes Research (HEOR) endpoints for trastuzumab deruxtecan compared to T-DM1.

	Exploratory Objectives: • To evaluate efficacy of trastuzumab deruxtecan compared to T-DM1 by clinical benefit rate (CBR) and progression-free survival on the next line of therapy (PFS2). • To evaluate potential biomarkers of response/resistance (eg, serum HER2-extracellular domain [HER2ECD]). • To evaluate exposure-response relationships for efficacy and safety endpoints.
Study Design:	This is a randomized, 2-arm, Phase 3, open-label, multicenter study to compare the safety and efficacy of trastuzumab deruxtecan versus T-DM1 in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane. Approximately 500 subjects will be randomized 1:1 to trastuzumab deruxtecan versus T-DM1. Randomization will be stratified by: • Hormone receptor status (positive, negative) • Prior treatment with pertuzumab (yes, no) • History of visceral disease (yes, no) • **Study Design Schema of DS8201-A-U302**  There will be follow-up visits after permanent discontinuation of study treatment to obtain information about subsequent treatment(s) and survival status.
Study Duration:	Enrollment is planned to occur over approximately 22 mo. The end of the study hypothesis-testing period is the date when approximately 250 OS events have been observed. The total anticipated duration of the study is approximately 51 mo. For each subject there will be a 40-Day (+ 7 d) Follow-up after the last study treatment administration or before starting new anticancer treatment, whichever comes first, followed by Long-term/Survival Follow-up every 3 mo (± 14 d) from the date of 40-Day (+ 7 d) Follow-up, until death, withdrawal of consent, loss to follow-up, or study closure, whichever occurs first.
Study Sites and Location:	Approximately 175 sites including but not limited to: North America, Asia, and Europe.

Subject Eligibility Criteria:	Key Inclusion Criteria: • Adults ≥18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old.) • Pathologically documented breast cancer that: – is unresectable or metastatic – has confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines evaluated at a central laboratory. – was previously treated with trastuzumab and taxane in the advanced/metastatic setting or progressed within 6 mo after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane. • Documented radiologic progression (during or after most recent treatment or within 6 mo after completing adjuvant therapy). • Subjects must be HER2-positive as confirmed by central laboratory assessment of most recent tumor tissue sample available. If archived tissue is not available, a fresh biopsy is required. Female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 mo after the last dose of trastuzumab deruxtecan and 7 mo after the last dose of T-DM1. Male subjects must agree to inform all potential female partners that they are participating in a clinical trial of a drug that may cause birth defects. Male subjects must also agree to either avoid intercourse or that they and/or any female partners of reproductive/childbearing potential will use a highly effective form of contraception during and upon completion of the study and for at least 4.5 mo after the last dose of trastuzumab deruxtecan or 4 mo after the last dose of T-DM1. • Adequate renal function, defined as: – Creatinine clearance ≥ 30 mL/min, as calculated using the Cockcroft-Gault equation • Adequate hepatic function, defined as: – Total bilirubin ≤ 1.5 × upper limit of normal (ULN) if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline, and – Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 3 × ULN.

	Key Exclusion Criteria: • Prior treatment with an anti-HER2 antibody drug conjugate (ADC) (such as T-DM1) in the metastatic setting. Prior treatment in the adjuvant/neoadjuvant setting would be allowed if progression of disease did not occur within 12 mo of end of adjuvant therapy. • Uncontrolled or significant cardiovascular disease, including any of the following: – History of myocardial infarction within 6 mo before randomization – History of symptomatic congestive heart failure (New York Heart Association Class II to IV) – Troponin levels consistent with myocardial infarction as defined according to the manufacturer within 28 d prior to randomization – Corrected QT interval prolongation to > 470 ms (females) or > 450 ms (male) based on average of Screening triplicate 12-lead electrocardiogram (ECG) – Left ventricular ejection fraction (LVEF) < 50% within 28 d prior to randomization • Has a history of (noninfectious) interstitial lung disease (ILD)/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening. • Spinal cord compression or clinically active central nervous system (CNS) metastases, defined as untreated or 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. • Prior participation in a study involving an ADC produced by Daiichi Sankyo.
Dosage Form, Dose and Route of Administration:	Trastuzumab deruxtecan for injection 100 mg: A trastuzumab deruxtecan lyophilized powder containing 100 mg of trastuzumab deruxtecan in a glass vial. The starting dose of trastuzumab deruxtecan will be 5.4 mg/kg. T-DM1 for injection lyophilized powder in single-use vials. The starting dose of T-DM1 will be 3.6 mg/kg.

	The drug for intravenous (IV) infusion is prepared by dilution of the required volume of the drug product calculated based on the subject's body weight to a 100 mL or 250 mL infusion bag, by the study site pharmacist. The study treatment will be administered as an IV infusion every 3 wk, initially for approximately 90 min, then, if there is no infusion related reaction, for a minimum of 30 min thereafter.
Study Endpoints:	Primary Efficacy Endpoint: • Progression-free survival (PFS) as determined by blinded independent central review (BICR). Key Secondary Efficacy Endpoint: • OS Other Secondary Efficacy Endpoints: • ORR based on BICR and investigator assessment (confirmation of complete response [CR]/partial response [PR] is required) • DoR based on BICR • PFS based on investigator assessment Exploratory Efficacy Endpoints: • Time to response based on BICR • Best percent change in the sum of the diameter of measurable tumors based on BICR • CBR based on BICR • PFS2 based on investigator assessment Health Economic and Outcomes Research Endpoints: • European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) – C30 – BR45 • EuroQol-5 dimensions-5 levels of severity (EQ-5D-5L) • Hospitalization-related endpoints Pharmacokinetic Endpoints: • Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a Biomarker Endpoints: • Serum biomarkers (eg, HER2 extracellular domain [HER2ECD]) • Other potential biomarkers (eg, cell free deoxyribonucleic acid, RNA profiling) Safety Endpoints: • Serious adverse events (SAEs)

	• Treatment-emergent adverse events (TEAEs), graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0 • Adverse events of special interest (AESIs) • TEAEs associated with discontinuation of study treatment • 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 scan (MUGA) findings • Anti-drug antibodies (ADA)
Planned Sample Size:	The target sample size will be approximately 500 subjects, randomized in a 1:1 ratio into 2 treatment groups (trastuzumab deruxtecan versus T-DM1).
Statistical Analyses:	Efficacy Analyses The primary efficacy endpoint is PFS based on BICR. An interim and a final analysis for PFS is planned in this trial. The interim analysis will be performed when approximately 234 BICR-assessed PFS events (70% information fraction) have been observed. If the trial is not statistically significant at this interim analysis, the final PFS analysis will be performed after observing 335 BICR-assessed PFS events. The primary efficacy analyses will be performed for the Full Analysis Set that consists of all randomized subjects. Following intent-to-treat principles, patients will be analyzed according to the treatment and the strata they were randomized to during the randomization process by Interactive Web/Voice Response System (IXRS). The survival distribution of PFS will be estimated by Kaplan-Meier method for each treatment group and results will be presented graphically. The median PFS times and 2-sided 95% confidence intervals (CIs) for the medians will be provided using Brookmeyer and Crowley method for each treatment group. The primary efficacy analysis will be the comparison of the survival distribution of PFS between the 2 treatment groups, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at an overall 2-sided significance level of 0.05. The treatment effect hazard ratio (HR) and its 95% CIs will be estimated, using stratified Cox proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS. An interim analysis for superiority is planned after at least 234 of the 335 targeted PFS events (70% information fraction) have been documented.

The primary intent of the interim analysis is to demonstrate superiority of the primary efficacy endpoint of PFS only and a formal futility evaluation is not planned. A group sequential design, utilizing a Haybittle-Peto efficacy boundary[36, 37] will be used to control the type I error rate for the primary efficacy analysis.

The key secondary efficacy endpoint, OS, will be compared between the 2 treatment groups using stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at 2-sided significance level of 0.05, provided superiority in PFS is demonstrated at either interim or final analysis. A hierarchical testing procedure will be adopted in this study and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant. Up to three analyses for OS could be performed:

- First interim analysis at the time of the interim analysis for PFS (provided PFS is significant), at which point a total of 96 OS events (38.4% information fraction) are expected.
- If the OS interim analysis is not significant, a second interim analysis for OS is planned at the time of the final analysis for PFS when approximately 153 OS events (61.2% information fraction) are expected.
- If the second OS analysis is not significant, a final analysis for OS after approximately 250 OS events have been observed (expected 51 months from date of first subject to be randomized).

OS will be analyzed in the same manner as the primary analysis for PFS. To maintain type I error rate, in addition to the hierarchical testing strategy, a Lan-DeMets alpha spending function with O'Brien-Fleming boundary, independent of the PFS analysis will be utilized.

Other secondary efficacy endpoints are ORR (the proportion of subjects who achieved a best overall response of CR or PR) based on BICR and investigator assessment, DoR based on BICR, and PFS based on investigator assessment.

Cochran-Mantel-Haenszel tests stratified by the randomization stratification factors as recorded by IXRS will be used to compare ORR between the treatment groups. The estimate of ORR and its 2-sided 95% CIs will be provided using Clopper-Pearson method.

Duration of response (based on BICR) will be summarized with median event time and its 2-sided 95% CIs using Brookmeyer and Crowley method for each treatment group.

The survival distribution of PFS based on investigator assessment will be estimated using the Kaplan-Meier method and will be presented graphically by treatment group. The median PFS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS rates at fixed time points (e.g., 3, 6, 9, 12 months)

and the two-sided 95% CIs will be provided for each treatment group. The treatment effect hazard ratio and its two-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with the same stratification factors as the randomization stratification factors taken from IXRS. The survival distribution of PFS based on investigator assessment between the two treatment groups will be compared at a two-sided significance level of 0.05, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at the time when primary analysis of PFS per BICR is statistically significant.

Health Economic and Outcomes Research Analyses

A detailed analysis plan of quality of life (QoL) endpoints, including control of type I error regarding QoL analyses, will be provided in the Statistical Analysis Plan (SAP).

Descriptive analyses of the HEOR endpoints based on the following patient reported outcome (PRO) questionnaires will be analyzed by treatment arm and compared using appropriate statistical methods. For the European Organization for Research and Treatment of Cancer quality of life questionnaires (EORTC QLQ)-C30 and EORTC QLQ-BR45: changes from baseline over time on the global QoL scale, the functioning scales, symptom scales, and single-item scales of the QLQ-C30 and in each of the subscales of EORTC QLQ-BR45. For the EQ-5D-5L visual analogue scale, all 5 dimensions and associated utility scores; and for hospitalization-related endpoints: time to hospitalization as well as reason, discharge diagnosis, intensive care unit stay, and length of stay will be reported.

Time to definitive deterioration on the ‘breast symptoms’ and ‘arm symptoms’ subscales of the EORTCQLQ-BR45, and the pain symptom subscale of the EORTC QLQ-C30 will also be assessed. Time to definitive deterioration will be compared between the 2 treatment groups using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at a two-sided significance level of 0.05. The survival distributions will be estimated by Kaplan-Meier method and results will be presented graphically. The median time to definitive deterioration and the proportion of patients without definitive deterioration at specific time points will be reported as well as the 2-sided 95% CIs for the medians. A stratified Cox regression model will be used to estimate the HR of time to definitive deterioration, along with 95% CI.

Pharmacokinetic Analyses

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

The population PK (pop-PK) analysis to evaluate the effect of intrinsic and extrinsic factors of trastuzumab deruxtecan, and if appropriate, total anti-HER2 antibody, and MAAA-1181a will be characterized including

available PK data. 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 results of the nonlinear mixed effects pop-PK and pop-PK/pharmacodynamic models may be reported separately from the clinical study report.

Biomarker Analyses

Archived tissue will be requested for re-analysis of HER2 status by immunohistochemistry and/or in situ hybridization as well as for exploratory biomarkers analyses. Biomarkers will be summarized by treatment group using descriptive statistics.

Safety Analyses

Safety endpoints will include SAEs, TEAEs, AESIs, discontinuations due to AEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings, and ADAs. TEAEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 5.0. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

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 cellular cytotoxic
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0\text{-}21d}$	area under the concentration-time curve from time 0 to 21 days
AUC_{∞}	area under the concentration-time curve from 0 extrapolated to infinity
BI	before infusion
BICR	blinded independent central review
CBR	clinical benefit rate
cfDNA	cell free deoxyribonucleic acid
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
C_{max}	maximum plasma/serum concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAE	discontinuation due to adverse event
DCR	disease control rate
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DoR	duration of response

ABBREVIATION	DEFINITION
EC	Ethics Committee
ECD	extracellular domain
ECG	electrocardiogram
Echo	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOI	end of infusion
EORTC QLQ	European Organization for Research and Treatment of Cancer quality of life questionnaire(s)
EOT	End of Treatment
EQ-5D-5L	EuroQol-5 dimensions-5 levels of severity
FAS	Full Analysis Set
GCP	Good Clinical Practice
HCV	hepatitis C virus
HEOR	health economics and outcomes research
HER2	human epidermal growth factor receptor 2
HER2ECD	HER2 extracellular domain
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	intensive care unit
ILD	interstitial lung disease
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	Interactive Web/Voice Response System
LVEF	left ventricular ejection fraction
Lyo-DP	lyophilized powder

ABBREVIATION	DEFINITION
mAb	monoclonal antibody
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MUGA	multigated acquisition (scan)
NAB	Neutralizing anti-drug antibody
NCI	National Cancer Institute
NSAIDs	nonsteroidal anti-inflammatory drugs
OATP	organic anion transporting polypeptide
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PFS2	Progression-free survival on the next line of therapy
PK	pharmacokinetic
pop-PK	population pharmacokinetic
PPS	Per-protocol Analysis Set
PR	partial response
PRO	patient reported outcome
PT	preferred term
QoL	quality of life
QTc	corrected QT interval
QTcF	QT intervals corrected for heart rate by Fridericia's formula
RT-PCR	real-time polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	stable disease
SID	subject identification

ABBREVIATION	DEFINITION
SMQ	Standardised MedDRA Query
SOC	system organ class
SOP	Standard Operating Procedure
SpO2	peripheral oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T-DM1	ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum plasma/serum concentration (C_{max})
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
V_{ss}	volume of distribution at steady state

1. INTRODUCTION

1.1. Background

Breast cancer remains the most common cancer and the second leading cause of cancer mortality in women both in the United States (US) and globally. In 2015, there were 2.4 million new cancer cases leading to 523,000 deaths worldwide. Breast cancer was also the leading cause of morbidity in women, resulting in an estimated burden of 15.1 million disability-adjusted life years.[1]

In approximately 20% of breast cancer cases, overexpression of human epidermal growth factor receptor 2 (HER2) occurs.[2] Compared to HER2-negative breast cancer, these HER2-positive breast cancers have historically been associated with more aggressive disease and worse outcomes. Although anti-HER2 targeted therapies have improved outcomes, they are not curative in the metastatic setting. Based on results of the CLEOPATRA study, current guidelines recommend the regimen of trastuzumab/pertuzumab/taxane for first line therapy for HER2-positive disease.[3] The only anti-HER2 agent specifically approved for second line therapy is ado-trastuzumab emtansine (T-DM1).

T-DM1 obtained approval based on the results of the EMILIA study in which T-DM1 was compared with the combination of lapatinib and capecitabine for the treatment of patients who had progressed after treatment with the combination of trastuzumab and taxane chemotherapy.[4] It is important to note that this study was conducted prior to the introduction of pertuzumab to first line therapy. Although the mechanism remains unclear, there is a suggestion that response rates to second line T-DM1 are lower when given after pertuzumab-containing regimens.[5]

Trastuzumab deruxtecan is an antibody drug conjugate (ADC) composed of an anti-HER2 antibody conjugated to a drug-linker carrying a topoisomerase I payload. Trastuzumab deruxtecan was studied in the Phase 1 DS8201-A-J101 study in HER2-expressing solid tumors and the DS8201-A-U201 study in HER2-positive metastatic breast cancer previously treated with T-DM1. Based on the results of these studies, trastuzumab deruxtecan (Enhertu®) obtained accelerated approval in the US on 20 December 2019 for the treatment of adults with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting based on the results of Study DS8201-A-U201. On 25 March 2020, trastuzumab deruxtecan (Enhertu) on second use, obtained approval under the conditional early approval system in Japan for the treatment of patients with HER2-positive unresectable or recurrent breast cancer after prior chemotherapy (limit the use to patients who are refractory or intolerant to standard treatments).

1.1.1. Investigational Product

1.1.1.1. Name

Trastuzumab deruxtecan (DS-8201a)

1.1.1.2. Description

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 (IgG1) monoclonal antibody (mAb) 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 (the active metabolite of irinotecan).[6,7,8] This ADC achieves a high drug-to-antibody ratio (approximately 8) with homogeneous conjugation with MAAA-1181a.[9] After binding to HER2 and internalization, trastuzumab deruxtecan is cleaved by lysosomal enzymes and releases MAAA-1181a in the cytoplasm.

The lyophilized powder (Lyo-DP) form of trastuzumab deruxtecan will be administered in this study.

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 new clinical studies, as well as commercial development, transition was made to MAAL-9001 production using a CHO[CCI] cell line (FL-DP2). 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/serum concentration (C_{max}) of trastuzumab deruxtecan was similar, while the area under the concentration-time curve (AUC) was about 22% lower for FL-DP2 material as compared to FL-DP1 material. However, in a xenograft study, no difference was seen in cytotoxicity between the 2 products.

1.1.1.3. Intended Use Under Investigation

This study will compare the efficacy and safety of trastuzumab deruxtecan versus T-DM1 in subjects with HER2-positive, unresectable and/or metastatic breast cancer (mBC) previously treated with trastuzumab and taxane.

1.1.1.4. Comparator (T-DM1)

T-DM1 is a HER2-targeted antibody and microtubule inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive mBC who previously received trastuzumab and a taxane, separately or in combination. T-DM1 is described in the approved regulatory documents in each respective country.

1.1.1.5. Nonclinical Studies of Trastuzumab Deruxtecan

The pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology of trastuzumab deruxtecan have been examined in nonclinical studies. For details of these experiments, please see the latest version of the Investigator's Brochure (IB).[10]

1.1.1.6. 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), with an estimated 1036 subjects exposed to at least 1 dose of trastuzumab deruxtecan. [10] Three studies are complete (have finalized clinical study reports presenting the results for the study primary

objective), and 9 studies are ongoing. [10]For updated results, please refer to the latest version of the IB.[10]

The trastuzumab deruxtecan study, Protocol DS8201-A-U201, is a 2-part, open-label, single-group, multicenter, phase 2 study in adults with pathologically documented HER2-positive metastatic breast cancer who had received previous treatment with trastuzumab emtansine. In the first part of the study, 3 different doses of trastuzumab deruxtecan were evaluated to establish a recommended dose and in the second part of the study, efficacy and safety were evaluated at the recommended dose of 5.4 mg/kg.

Results as of 01 August 2019 were reported in The New England Journal of Medicine. [11] Among the 184 subjects who received trastuzumab deruxtecan at the recommended dose of 5.4 mg/kg, the BICR confirmed response rate was 60.9% (95% CI: 53.4, 68.0); of these subjects, 6.0% had a complete response, and 54.9% had a partial response. [11] The disease control rate was 97.3% (95% CI: 93.8, 99.1). [11] The median time to response was 1.6 months (95% CI: 1.4, 2.6) and the median duration of response was 14.8 months (95% CI: 13.8, 16.9). [11] The median PFS was 16.4 months (95% CI: 12.7, not reached). [11] Estimated OS was 93.9% (95% CI: 89.3, 96.6) at 6 months and 86.2% (95% CI: 79.8, 90.7) at 12 months; the median overall survival was not reached. [11]

As of 01 August 2019, among 184 subjects who received 5.4 mg/kg trastuzumab deruxtecan, 99.5% had at least one AE and 57.1% had an AE of grade 3 or higher. [11] The most common grade 3 or higher AEs were neutrophil count decreased (20.7%), anemia (8.7%), nausea (7.6%), white blood cell count decreased (6.5%), lymphocyte count decreased (6.5%), and fatigue (6.0%).[11] AEs led to dose interruption in 35.3%, dose reduction in 23.4%, and dose discontinuation in 15.2% of subjects.[11] A total of 25 deaths were reported, including 7 that occurred during treatment as a result of either disease progression (in 3 subjects) or adverse events (hemorrhagic shock, general physical health deterioration, pneumonia, and acute organ failure in 1 subject each). [11] During survival follow-up (which was defined as 47 days after the end of treatment), 18 of the 25 deaths occurred, 2 of which were caused by events associated with interstitial lung disease (ILD) that started during treatment; the remaining 16 deaths were considered by investigators to be unrelated to trastuzumab deruxtecan. [11] For further details related to the efficacy and safety of trastuzumab deruxtecan reported from clinical studies, please see the latest version of the IB.[10]

1.1.1.7. Summary of Clinical Pharmacokinetics

Pharmacokinetics were evaluated in 24 subjects who received trastuzumab deruxtecan. Following a single IV administration, the systemic exposure increased approximately in proportion to the dose. The PK parameters at 5.4, 6.4, and 8.0 mg/kg are shown in Table 1.1. The C_{max} of trastuzumab deruxtecan at 6.4 mg/kg was achieved with a median time to C_{max} (T_{max}) of 2.16 hours. The C_{max} and AUC from time 0 to 21 d ($AUC_{0\text{-}21d}$) at 6.4 mg/kg were 181 µg/mL and 901 µg•d/mL, respectively (Table 1.1). The systemic exposure at 6.4 mg/kg in subjects in Cycle 1 was observed to exceed the systemic efficacious exposure observed during the nonclinical pharmacology evaluation. At this dose, the mean terminal elimination half-life ($t_{½}$) of trastuzumab deruxtecan was 7.33 d at 6.4 mg/kg, and the volume of distribution at steady state (V_{ss}) was 58.6 mL/kg which is similar to the serum volume.

The PK parameters of total antibody were close to that of trastuzumab deruxtecan (Table 1.2).

The C_{max} and AUC for the dosing interval ($AUC_{0\text{-}21d}$) of MAAA-1181a, which were quite low, were 6.80 ng/mL and 31.0 ng•d/mL at 6.4 mg/kg, respectively (Table 1.3). The $t_{½}$ of MAAA-1181a was similar to that of trastuzumab deruxtecan.

Table 1.1: Mean Pharmacokinetic Parameters of Trastuzumab Deruxtecan (± Standard Deviation)

Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (h) Median (range)	$AUC_{0\text{-}21d}$ (µg•d/mL)	AUC_{∞} (µg•d/mL)	$t_{½}$ (d)	CL (mL/d/kg)	V_{ss} (mL/kg)
5.4 (N=6)	127 ± 17.2	1.92 (1.92, 2.16)	544 ± 165	590 ± 186	6.03 ± 0.603	10.1 ± 3.90	75.2 ± 24.2
6.4 (N=6)	181 ± 33.1	2.16 (1.44, 4.08)	901 ± 155	1030 ± 209	7.33 ± 1.64	6.41 ± 1.12	58.6 ± 11.0
8.0 (N=3)	216 ± 52.0	1.92 (1.92, 2.16)	914 ± 235	1020 ± 279	6.97 ± 0.357	8.17 ± 1.93	69.7 ± 13.1

AUC = area under the concentration-time curve; $AUC_{0\text{-}21d}$ = AUC from the time 0 to 21 d; AUC_{∞} = AUC from 0 extrapolated to infinity; CL = clearance; C_{max} = maximum plasma/serum concentration; d = day, N = number of evaluable subjects; $t_{½}$ = terminal elimination half-life; T_{max} = time to C_{max}; V_{ss} = volume of distribution at steady state.

Table 1.2: Mean Pharmacokinetic Parameters of Total Antibody (±Standard Deviation)

Trastuzumab Deruxtecan Dose (mg/kg)	C_{max} (µg/mL)	T_{max} (h) Median (range)	$AUC_{0\text{-}21d}$ (µg•d/mL)	AUC_{∞} (µg•d/mL)	$t_{½}$ (d)
5.4 (N=6)	116 ± 13.9	1.92 (1.92, 6.96)	609 ±151	682 ± 172	6.78 ± 2.39
6.4 (N=6)	146 ± 18.9	3.84 (2.16, 6.96)	878 ± 97.1	1050 ± 149	8.25 ± 2.16
8.0 (N=3)	178 ± 18.5	2.16 (1.92, 6.72)	1090 ± 213	1270 ± 296	7.35 ± 0.417

AUC = area under the concentration-time curve; $AUC_{0\text{-}21d}$ = AUC from the time 0 to 21 d; AUC_{∞} = AUC from 0 extrapolated to infinity; C_{max} = maximum plasma/serum concentration; d = day; N = number of evaluable subjects; $t_{½}$ = terminal elimination half-life; T_{max} = time to Cmax.

Table 1.3: Mean Pharmacokinetic Parameters of MAAA-1181a (±Standard Deviation)

Trastuzumab Deruxtecan Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h) median (range)	$AUC_{0\text{-}21\ d}$ (ng·d/mL)	AUC_{∞} (ng·d/mL)	$t_{½}$ (d)
5.4 (N=6)	10.8 ± 7.56	5.28 (3.84, 23.76)	40.6 ± 19.8	43.6 ± 21.2	6.11 ± 0.811
6.4 (N=6)	6.80 ± 1.72	6.72 (4.08, 7.20)	31.0 ± 5.11	34.2 ± 5.63	6.28 ± 1.17
8.0 (N=3)	9.25 ± 3.18	6.72 (6.72, 6.96)	39.4 ± 6.43	43.4 ± 9.16	6.36 ± 1.53

AUC = area under the concentration-time curve; $AUC_{0\text{-}21d}$ = AUC from time 0 to 21 d; AUC_{∞}= AUC from 0 extrapolated to infinity; C_{max} = maximum plasma/serum concentration; d = day; N = number of evaluable subjects; $t_{½}$ = terminal elimination half-life; T_{max} = time to Cmax.

1.2. Study Rationale

A member of the HER superfamily, HER2 initiates signal transduction via the PI3K/Akt and RAS/MAPK pathways.[12,13] In human advanced solid tumors, expression of HER2 protein has been reported in various tumor tissues and a variety of cultured tumor cell lines including breast cancer,[13,14] gastric cancer,[15,16] pancreatic cancer,[17] lung cancer,[18] colorectal cancer,[19] and ovarian cancer.[20] There are also many reports demonstrating an association between expression of HER2 protein and poor clinical prognosis. In normal human tissue, low expression of HER2 protein has been reported on cell membranes of epithelial cells in the gastrointestinal, respiratory, reproductive, and urinary tract as well as in the skin, breast, and placenta.[21]

The current first line standard of care for HER2-positive mBC, with the addition of pertuzumab to trastuzumab and chemotherapy, was established based on results of the CLEOPATRA study. Like trastuzumab, pertuzumab is a humanized mAb that binds HER2 at a separate epitope in the extracellular domain. In addition to ADCC activity, pertuzumab adds a novel mechanism of action by inhibiting dimerization of HER2, a process thought to be important for HER2 activation. The CLEOPATRA study randomized subjects to receive trastuzumab plus docetaxel with or without the addition of pertuzumab as first line therapy for metastatic HER2-positive breast cancer. The addition of pertuzumab improved median progression-free survival (PFS) from 12.4 to 18.5 mo and median overall survival (OS) from 40.8 to 56.5 mo, leading to a new standard of care for patients with mBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.[5]

In the setting of HER2-positive breast cancer following treatment with a trastuzumab containing regimen, the EMILIA study established T-DM1 as the standard for subsequent anti-HER2 therapy. T-DM1 is an ADC linking the trastuzumab antibody to emtansine, a tubulin inhibitor. In the EMILIA study, T-DM1 was compared with the combination of lapatinib and capecitabine for the treatment of subjects who had progressed after treatment with a trastuzumab and taxane combination. In this study, T-DM1 improved median PFS from 6.4 to 9.6 mo and median OS from 25.1 to 30.9 mo.[22] It is important to note that this study was conducted prior to the introduction of pertuzumab to first line therapy.

In contrast to T-DM1, trastuzumab deruxtecan is a HER2-targeting ADC with a high drug-to-antibody ratio (7 to 8), and a novel topoisomerase I inhibitor as payload. Trastuzumab deruxtecan is expected to inhibit tumor growth on the basis of the following reasons: like trastuzumab, it induces ADCC activities and inhibits Akt phosphorylation 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 nonclinical models, trastuzumab deruxtecan showed a much broader antitumor spectrum than T-DM1, including efficacy against T-DM1 resistant and HER2 low-expressing tumors. In vivo studies using a tumor-bearing mouse model suggest that administration of trastuzumab deruxtecan results in the regression of HER2-positive tumors.

In the Phase 1 clinical study DS8201-A-J101, preliminary results from HER2-positive breast cancer subjects pretreated with T-DM1 showed that almost all subjects experienced tumor shrinkage and durable treatment duration. Subjects evaluable for confirmed responses (at least 2 post-baseline scans, total n=33) showed ORR of 60.6% (20 of 33). The current Kaplan-Meier estimate for median PFS reaches 10.4 mo (95% confidence interval [CI]: 32.1, not applicable). In the combined Part 1 and Part 2 population of HER2-positive breast cancer subjects who received pertuzumab pretreatment (a subset of the T-DM1 treated population), an ORR of 60.0% (total of 18 responders out of 30 subjects in Part 1 and Part 2) and a DCR of 96.7% was observed. Of 7 subjects with a minimum of 2 post-baseline scans who did not have prior pertuzumab therapy, 4 (57.1%) achieved PR when treated with trastuzumab deruxtecan suggesting that trastuzumab deruxtecan maintains efficacy in this patient population. In addition, the response rate does not seem to differ between this patient population and those who received prior pertuzumab (57.1% vs. 62.0%).

DS8201-A-U302 is designed to compare trastuzumab deruxtecan versus T-DM1 in the same line of therapy for which T-DM1 was approved.

1.3. Risks and Benefits for Study Subjects

Trastuzumab deruxtecan is under development for the treatment of HER2-expressing cancers and HER2-mutant tumors. The DS8201-A-U201 study was initiated based on preliminary clinical observations in the Phase 1 study (DS8201-A-J101) (see Section 1.1.1.6). In this study, trastuzumab deruxtecan demonstrates antitumor activity in HER2 expressing cancers including breast cancer and gastric cancer.

As of 01 Feb 2019, from the ongoing DS8201-A-J101 study, 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 Independent Committee Review (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%.

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, anemia, neutrophil count decrease including febrile neutropenia, and platelet count decrease are classified as important

identified risks. LVEF decrease is classified as an important potential risk. Infusion related reactions, which were previously classified as an important potential risk, are reclassified as an identified risk. QT prolongation is no longer considered an important potential risk and has been removed from the list of safety concerns for trastuzumab deruxtecan.

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

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

Other identified risks of trastuzumab deruxtecan in order of descending frequencies are nausea, decreased appetite, alopecia, vomiting, fatigue, constipation, diarrhoea, WBC count decrease, stomatitis, aspartate aminotransferase increased, cough, headache, abdominal pain, alanine aminotransferase increased, hypokalaemia, epistaxis, dyspnoea, dyspepsia, dizziness, dry eye, upper respiratory tract infection, asthenia, and infusion related reactions.

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

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

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

For current assessments of risks and benefits to subjects, please refer to the current IB for trastuzumab deruxtecan.[10]

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective is to compare the PFS benefit of trastuzumab deruxtecan to T-DM1 for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane.

2.1.2. Key Secondary Objective

The secondary objective is to compare the OS benefit of trastuzumab deruxtecan to T-DM1.

2.1.3. Other Secondary Objectives

Other secondary objectives are:

- To evaluate efficacy of trastuzumab deruxtecan compared to T-DM1 on:
  - Confirmed ORR;
  - DoR.
- To further determine PK of trastuzumab deruxtecan;
- To further evaluate safety of trastuzumab deruxtecan compared to T-DM1;
- To evaluate Health Economic and Outcomes Research (HEOR) endpoints for trastuzumab deruxtecan compared to T-DM1.

2.1.4. Exploratory Objectives

The exploratory objectives are:

- To evaluate efficacy of trastuzumab deruxtecan compared to T-DM1 by clinical benefit rate (CBR) and progression-free survival on the next line of therapy (PFS2).
- To evaluate potential biomarkers of response/resistance (eg, serum HER2-extracellular domain [HER2ECD]).
- To evaluate exposure-response relationships for efficacy and safety endpoints.

2.2. Study Hypothesis

Trastuzumab deruxtecan confers a significant benefit in PFS compared with T-DM1 in HER2-positive breast cancer patients who have previously received trastuzumab and taxane.

2.3. Study Endpoints

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

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS as determined by blinded independent central review (BICR).

2.3.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is OS.

2.3.3. Other Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- ORR based on BICR and investigator assessment (confirmation of complete response [CR]/partial response [PR] is required)
- DoR based on BICR
- PFS based on investigator assessment

2.3.4. Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Time to response based on BICR
- Best percent change in the sum of the diameter of measurable tumors based on BICR
- CBR based on BICR
- PFS2 based on investigator assessment

2.3.5. Health Economic and Outcomes Research Endpoints

The HEOR endpoints include:

- European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30
- EORTC QLQ-BR45
- EuroQol-5 dimensions-5 levels of severity (EQ-5D-5L)
- Hospitalization-related endpoints

2.3.6. Pharmacokinetic/Biomarker Endpoints

2.3.6.1. Pharmacokinetic Endpoints

The PK endpoints include:

- Serum concentrations of trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a

2.3.6.2. Biomarker Endpoints

The biomarker endpoints include:

- Serum biomarkers (eg, HER2ECD)
- Other potential biomarkers (eg, cell free deoxyribonucleic acid [cfDNA], RNA profiling)

2.3.7. Safety Endpoints

The safety endpoints include:

- Serious adverse events (SAEs)
- TEAEs
- Adverse events of special interest (AESIs)
- TEAEs associated with discontinuation of study treatment
- Physical examination findings (including Eastern Cooperative Oncology Group Performance Status [ECOG PS])
- Vital sign measurements
- Standard clinical laboratory parameters
- Electrocardiogram (ECG) parameters
- Echocardiogram (Echo)/multigated acquisition scan (MUGA) findings
- Anti-drug antibodies (ADA)

3. STUDY DESIGN

3.1. Overall Design

This is a randomized, 2-arm, Phase 3, open-label, multicenter study designed to compare the safety and efficacy of trastuzumab deruxtecan versus T-DM1 in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane. Figure 3.1 shows the study design.

Trastuzumab deruxtecan for injection, 100 mg, will be administered IV at a starting dose of 5.4 mg/kg.

Randomization will be stratified by:

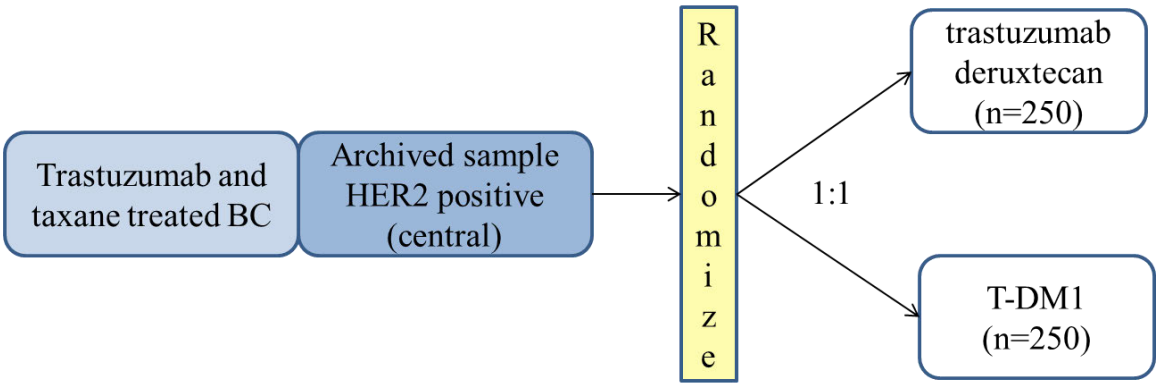
- Hormone receptor status (positive, negative)
- Prior treatment with pertuzumab (yes, no)
- History of visceral disease (yes, no)

For subjects randomized to T-DM1, the treatment will be in accordance to the approved label.

The study treatment will be continued according to the dosing criteria in the absence of withdrawal of subject consent, progressive disease (PD), or unacceptable toxicity (see Section 5.9). If the study treatment is delayed more than 28 d from the planned date of administration, the subject will be withdrawn from study treatment.

History of past treatment with pertuzumab will be collected for all study subjects.

Figure 3.1: Study Design Schema



BC = breast cancer; HER2 = human epidermal growth factor receptor 2; T-DM1 = ado-trastuzumab emtansine.

3.1.1. Duration of the Study

Enrollment is planned to occur over approximately 22 mo. The end of the study hypothesis-testing period is the date when approximately 250 OS events have been observed. The total anticipated duration of the study is approximately 51 mo.

The study team will monitor number of PFS events. The study statistician will make projections of the data cutoff date for PFS analysis, first quarterly and then monthly. The projection date will be made at a time when the number of reported PFS events is 90% or less of the planned

required number of events. PFS analysis will use all events accrued on or before the cutoff date. All data before or on the cutoff date will be used for analysis. Similar projections on data cutoff date will be performed for the OS analysis (as needed), and all data up to the data cutoff date will be used for OS analysis.

For each subject there will be a 40-Day (+ 7 d) Follow-up after the last study treatment administration or before starting new anticancer treatment, whichever comes first, followed by Long-term/Survival Follow-up every 3 mo (± 14 d) from the date of 40-Day (+ 7 d) Follow-up, 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).

3.1.2. Duration of Subject Participation

The Screening period is up to 28 d. Each cycle of treatment will be 21 d. The number of treatment cycles with trastuzumab deruxtecan is not fixed. Upon commencing study treatment, subjects may continue receiving study treatment until the occurrence of any of the events defined in Section 5.9.1.

After study treatment discontinuation, all subjects may be contacted every 3 mo until death 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 (Section 5.9.2).

3.1.3. Definition of the End of the Study

The end of the study hypothesis-testing period is defined as the date when approximately 250 OS events have been observed. The study closure is defined as the date when the last subject discontinues study treatment and applicable follow-up occurs, or the study is ended by the Sponsor.

3.2. Discussion of Study Design

This study will be conducted in approximately 175 study sites including but not limited to: North America, Asia, and Europe.

The target sample size will be approximately 500 subjects, randomized in a 1:1 ratio into 2 treatment groups (trastuzumab deruxtecan versus T-DM1).

4. STUDY POPULATION

Each subject will sign Study Informed Consent Form(s) (ICF) provided by the site. A subject is considered enrolled in the study upon the investigator or designee obtaining written informed consent from the subject (Section 15.3) 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 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 be competent and able to comprehend, sign, and date an Institutional Review Board (IRB) or Ethics Committee (EC) approved ICF before performance of any study-specific procedures or tests.
2. Adults ≥18 y old. (Please follow local regulatory requirements if the legal age of consent for study participation is >18 y old.)
3. Pathologically documented breast cancer that:
    a. is unresectable or metastatic.
    b. has confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines evaluated at a central laboratory.[23]
    c. was previously treated with trastuzumab and taxane in the advanced/ metastatic setting or progressed within 6 mo after neoadjuvant or adjuvant treatment involving a regimen including trastuzumab and taxane.
4. Documented radiologic progression (during or after most recent treatment or within 6 mo after completing adjuvant therapy).
5. Subjects must be HER2-positive as confirmed by central laboratory assessment of most recent tumor tissue sample available. If archived tissue is not available, a fresh biopsy is required.
6. Presence of at least 1 measurable lesion per modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1 (see Section 17.4).[24]
    a. Brain lesions will be considered as non-target lesions only.
7. ECOG PS 0 or 1.

8. Adequate bone marrow function, within 14 d before randomization, defined as:
   - Absolute neutrophil count ≥ 1.5×10^9/L (granulocyte colony-stimulating factor administration is not allowed within 1 wk prior to Screening assessment);
   - Platelet count ≥ 100×10^9/L (Platelet transfusion is not allowed within 1 wk prior to Screening assessment);
   - Hemoglobin level ≥ 9.0 g/dL (Red blood cell transfusion is not allowed within 1 wk prior to Screening assessment).
9. Adequate renal function within 14 d before randomization, defined as:
   - Creatinine clearance ≥ 30 mL/min, as calculated using the Cockcroft-Gault equation ($\text{CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ {× 0.85 for females}; Section 17.2).
10. Adequate hepatic function within 14 d before randomization, defined as:
    - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) if no liver metastases or < 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia) or liver metastases at baseline, and
    - Aspartate transaminase (AST)/alanine transaminase (ALT) ≤ 3 × ULN
11. Adequate blood clotting function within 14 d before randomization, defined as:
    - International normalized ratio/prothrombin time ≤ 1.5 × ULN and either partial thromboplastin or activated partial thromboplastin time ≤ 1.5 × ULN
12. Female subjects of reproductive/childbearing potential must agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 mo after the last dose of trastuzumab deruxtecan and 7 mo after the last dose of T-DM1. Male subjects must agree to inform all potential female partners that they are participating in a clinical trial of a drug that may cause birth defects. Male subjects must also agree to either avoid intercourse or that they and/or any female partners of reproductive/childbearing potential will use a highly effective form of contraception during and upon completion of the study and for at least 4.5 mo after the last dose of trastuzumab deruxtecan or 4 mo after the last dose of T-DM1. Methods considered as highly effective methods of contraception include:
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
      – Oral
      – Intravaginal
      – Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
      – Oral
      – Injectable
      – Implantable

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence defined as refraining from heterosexual intercourse during and upon completion of the study and for at least 7 mo for female subjects (4.5 mo for male subjects)after the last dose of trastuzumab deruxtecan or 7 mo after the last dose of T-DM1. True abstinence must be in line with the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods) is not an acceptable method of contraception.

Non-childbearing potential is defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 mo of spontaneous amenorrhea (in questionable cases, a blood sample with simultaneous follicle-stimulating hormone > 40 mIU/mL and estradiol < 40 pg/mL [< 147 pmol/L] is confirmatory). Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the contraception methods outlined for women of childbearing 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 throughout the study period beginning at Cycle 1 Day 1 and for at least 4.5 mo after the last dose of trastuzumab deruxtecan or 4 mo after the last dose of T-DM1. Preservation of sperm should be considered prior to enrollment in this study.
14. Female subjects must not donate ova or retrieve them for their own use from the time of Screening and throughout the study treatment period, and for at least 7 mo after the last dose of trastuzumab deruxtecan or 7 mo after the last dose of T-DM1.
15. Has adequate treatment washout period before randomization/enrollment, defined as chloroquine/hydroxychloroquine >14 days

4.2. Exclusion Criteria

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

1. Prior treatment with an anti-HER2 ADC (such as T-DM1) in the metastatic setting. Prior treatment in the adjuvant/neoadjuvant setting would be allowed if progression of disease did not occur within 12 mo of end of adjuvant therapy.
2. Uncontrolled or significant cardiovascular disease, including any of the following:
   a. History of myocardial infarction within 6 mo before randomization;

b. History of symptomatic congestive heart failure (New York Heart Association Class II to IV);
c. Troponin levels consistent with myocardial infarction as defined according to the manufacturer within 28 d prior to randomization;
d. Corrected QT interval (QTc) prolongation to > 470 ms (females) or >450 ms (male) based on average of Screening triplicate 12-lead ECG;
e. LVEF < 50% within 28 d prior to randomization

3. Has a history of (noninfectious) ILD/pneumonitis that required steroids, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at Screening.
4. Spinal cord compression or clinically active central nervous system (CNS) metastases, defined as untreated or 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.
5. Has a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
6. History of severe hypersensitivity reactions to other mAbs.
7. Substance abuse or medical conditions such as clinically significant cardiac or pulmonary diseases or psychological conditions, that may, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
8. Social, familial, or geographical factors that would interfere with study participation or follow-up.
9. Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
10. Known human immunodeficiency virus (HIV) infection or active hepatitis B or C infection. Subjects 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 if required by local regulations or IRB/EC.
11. Multiple primary malignancies within 3 y, except adequately resected non-melanoma skin cancer, curatively treated in situ disease, or contralateral breast cancer.
12. 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. Therapeutic radiation therapy or major surgery within 4 wk before randomization or palliative stereotactic radiation therapy within 2 wk before randomization.
14. Systemic treatment with anticancer therapy (immunotherapy [non-antibody-based therapy], retinoid therapy, or hormonal therapy) within 3 wk before randomization; antibody-based-anticancer-therapy within 4 wk before randomization; or treatment with nitrosoureas or mitomycin C within 6 wk before randomization; or treatment with small-molecule targeted agents within 2 wk or 5 half-lives before randomization, whichever is longer.
16. Participation in a therapeutic clinical study within 3 wk before randomization (for small-molecule targeted agents, this non-participation period is 2 wk or 5 half-lives, whichever is longer), or current participation in other investigational procedures.
17. Pregnant, breastfeeding, or planning to become pregnant.
18. Subject must not be an immediate family member of study site personnel working for the investigator or of Sponsor personnel.
19. Otherwise considered inappropriate for the study by the investigator.
20. Prior participation in a study involving an antibody drug conjugate produced by Daiichi Sankyo.
21. Clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, but not limited to, any underlying pulmonary disorder (ie, pulmonary emboli within 3 months of the study enrollment, severe asthma, severe chronic obstructive pulmonary disease [COPD], restrictive lung disease, pleural effusion etc), and any autoimmune, connective tissue or inflammatory disorders with pulmonary involvement (ie, rheumatoid arthritis, Sjögren's, sarcoidosis etc), or prior pneumonectomy

5. STUDY TREATMENTS

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Groups

There will be 2 treatment groups: trastuzumab deruxtecan and T-DM1

5.1.2. Method of Treatment Allocation

Prior to randomization of a subject, all eligibility criteria must be met and a signed informed consent obtained.

Subjects will be randomized into 1 of the 2 treatment groups (trastuzumab deruxtecan versus T-DM1) in a 1:1 ratio. The randomization will be stratified by hormone receptor status (positive, negative), prior treatment with pertuzumab (yes, no), and history of visceral disease (yes, no). Randomization will be managed through an Interactive Web/Voice Response System (IXRS) for subjects meeting all eligibility criteria. The directions on how to use the system will be provided in the IXRS Quick Reference Manual.

The system will assign a unique SID number and treatment arm for that subject (ie, trastuzumab deruxtecan versus T-DM1).

5.1.3. Blinding

It is not feasible to blind treatment allocations for individual subjects because of different administration protocols and different AE profiles between trastuzumab deruxtecan and T-DM1. The primary endpoint of BICR-assessed PFS is a robust endpoint and bias due to lack of blinding should be minimal. The study team will not perform or have access to efficacy analysis/summary during the study.

An independent biostatistician, not otherwise part of the Sponsor study team, will generate the randomization schedule.

5.1.4. Emergency Unblinding Procedure

Not applicable

5.2. Trastuzumab Deruxtecan

5.2.1. Description

Lyophilized powder (Lyo-DP)

Trastuzumab deruxtecan for injection 100 mg will be provided as a lyophilized powder containing 100 mg of trastuzumab deruxtecan in a glass vial. Each glass vial should be reconstituted to a concentration of 20 mg/mL. Each vial is designed for single-use only and is not to be used to treat more than 1 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 packaged and labeled in compliance with regulatory requirements. The packaging will clearly display the name of the study treatment, the lot number, storage condition, and other required information in accordance with local regulations.

5.2.3. Preparation

Trastuzumab deruxtecan for IV infusion is prepared by dilution of the required volume of the study treatment calculated based on the subject's body weight to a 100 mL or 250 mL infusion bag. 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. Storage

Trastuzumab deruxtecan for injection 100 mg must be stored in a secure, limited access storage area under the storage conditions listed below:

- Stored at 2°C to 8°C (protected from light) 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.

5.3. Control Treatment (T-DM1)

5.3.1. Description

Lyophilized powder in single-use vials containing 100 mg per vial.

5.3.2. Labeling and Packaging

T-DM1 will be packaged and labeled in compliance with local regulatory requirements.

5.3.3. Preparation

T-DM1 should be prepared following the pharmacy instructions.

5.3.4. Storage

Storage for all medications must follow the locally approved label.

T-DM1 lyophilized powder must be stored in a secure, limited access storage area under the storage conditions listed below:

- Stored at 2°C to 8°C

5.4. Administration of either Trastuzumab Deruxtecan or T-DM1

The study treatment will be administered initially as an IV infusion over 30 to 90 min every 21 d (± 2 d). The initial dose of study treatment will be infused for approximately 90 min. If there is no infusion related reaction, after the initial dose, the next doses of study treatment will be infused for a minimum of 30 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 based on the subject's updated weight. Refer to the pharmacy instructions for detailed information about administration of study treatment.

Trastuzumab deruxtecan should only be initiated by a physician or healthcare professional experienced in the administration of cytotoxic chemotherapy. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment, should be available for immediate use.

For subjects randomized to T-DM1, the treatment administration and monitoring of subjects will be in accordance with the locally approved label.

5.5. Drug Accountability

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

A Drug Accountability Record will be provided for study treatment (trastuzumab deruxtecan/T-DM1). The record must be kept current and should contain the following:

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

At the study closure, as per local laws and/or directed by Sponsor, all unused study treatment 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. At the study closure, a final study treatment reconciliation statement must be completed by the investigator or designee and provided to the Sponsor. See pharmacy instructions for details.

Unused drug supplies may be destroyed by the investigator when approved in writing by Sponsor and 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 treatment.

All investigational product inventory forms must be made available for inspection by a Sponsor authorized representative or designee and Regulatory Agency inspectors.

5.6. Dose Interruptions and Reductions

The investigator will evaluate which toxicities are attributed to the study treatment and adjust the dose of the drug as recommended below for trastuzumab deruxtecan. Dose adjustments for T-DM1 should be made in accordance with the locally approved label. All dose modifications should be based on the worst preceding toxicity (Common Toxicology Criteria for Adverse Events [CTCAE] version 5.0). All interruptions or modifications must be recorded on the AE and drug administration electronic case report form (eCRF). Appropriate clinical experts should be consulted as deemed necessary.

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

For Grade 3 or Grade 4 events assessed as related to use of trastuzumab deruxtecan by the investigator(s), monitoring (including local laboratory tests when appropriate) should be performed at intervals no greater than 7 d until the AE is determined to be resolving.

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

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

5.6.1. Dose Reduction and Interruption Guidelines

NOTE: There will be no dose modifications for Grade 1 or Grade 2 AEs unless specified below in Table 5.3.

The starting dose of trastuzumab deruxtecan Lyo-DP formulation will be 5.4 mg/kg. The starting dose of T-DM1 will be 3.6 mg/kg. Two dose reductions will be permitted (Table 5.1 and Table 5.2).

Table 5.1: Dose Reduction Levels of Trastuzumab Deruxtecan

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

Table 5.2: Dose Reduction Levels of T-DM1

Starting Dose	Dose Level -1	Dose Level -2
3.6 mg/kg	3.0 mg/kg	2.4 mg/kg

Once the dose of study treatment has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. If toxicity continues after 2 dose reductions, then the subject will be withdrawn from study treatment. Study treatment 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 is assessed as requiring a dose delay longer than 28 d (49 d from the last infusion date), the subject will permanently discontinue study treatment and will be followed for survival.

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

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

5.6.1.1. Dose Modifications

Dose adjustments for T-DM1 should be made in accordance with the approved label for T-DM1.

Specific criteria for interruption, re-initiation, dose reduction, and/or discontinuation of trastuzumab deruxtecan are listed in table below, 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.

All confirmed or suspected coronavirus disease 2019 (COVID-19) infection events must be recorded in the eCRF. Please refer to Section 17.8 for additional information on dose modification.

Dose adjustments guidelines for trastuzumab deruxtecan are shown in Table 5.3.

Table 5.3: Dose Modification for Trastuzumab Deruxtecan

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	**Management Guideline for trastuzumab deruxtecan**
No Toxicity	Maintain dose and schedule
Infusion related Reaction	
Grade 1 (Mild transient reaction; infusion interruption not indicated; intervention not indicated)	• If infusion related reaction (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, hypotension) is observed during administration, the infusion rate should be reduced by 50% and subjects should be closely monitored. • If no other reactions appear, the subsequent infusion rate could be resumed at the initial planned rate.

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Grade 2 (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h)	• Administration of trastuzumab deruxtecan should be interrupted and symptomatic treatment started (eg, antihistamines, NSAIDs, narcotics, IV fluids). • If the event resolves or improves to Grade 1, infusion can be re-started at a 50% reduced infusion rate. • Subsequent administrations should be conducted at the reduced rate.
Grade 3 or 4 (Prolonged or life-threatening consequences, urgent intervention indicated)	• Administration of trastuzumab deruxtecan should be discontinued immediately and permanently. • Urgent intervention indicated. Antihistamines, steroids, epinephrine, bronchodilators, vasopressors, IV fluid therapy, oxygen inhalation etc, should be administered.
Hematologic Toxicity	
Neutrophil Count Decreased and/or White Blood Cell Count Decreased	
Grade 3 (Neutrophils: <1.0 to 0.5 × 10^9/L, WBCs: <2.0 to 1.0 × 10^9/L)	• Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 (Neutrophils: <0.5 × 10^9/L, WBCs: <1.0 to 1.0 × 10^9/L)	• Delay dose until resolved to ≤ Grade 2 • Reduce dose 1 level
Febrile Neutropenia (absolute neutrophil count < 1 × 10^9/L, fever > 38.3°C or a sustained temperature of ≥ 38°C for more than 1 h)	• Delay dose until resolved • Reduce dose by 1 level
Lymphocyte Count Decreased	
Grade 1 to Grade 3 lymphopenia	• No dose modification
Grade 4 (< 0.2 × 10^9/L)	• Delay dose until resolved to ≤ Grade 2: – If resolved in ≤ 14 d from day of onset, maintain dose – If resolved in > 14 d from day of onset, reduce dose 1 level

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Anaemia	
Grade 3 (Hemoglobin [Hb] <8.0 g/dL); transfusion indicated	• Delay dose until resolved to ≤ Grade 2, then maintain dose
Grade 4 (Hb <8.0 g/dL) Life-threatening consequences; urgent intervention indicated	• Delay dose until resolved to ≤ Grade 2, then reduce dose 1 level
Platelet Count Decreased	
Grade 3 (platelets <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 1 level
Grade 4 (platelets < 25 × 10^9/L)	• Delay dose until resolved to ≤ Grade 1, then reduce dose 1 level
Cardiac Toxicity	
Symptomatic congestive heart failure	• Discontinue subject from study treatment
Decrease in LVEF 10-20% (absolute value), but LVEF > 45%	• Continue treatment with trastuzumab deruxtecan
LVEF 40% to ≤ 45% and decrease is < 10% (absolute value) from baseline	• Continue treatment with trastuzumab deruxtecan • Repeat LVEF assessment within 3 wk
LVEF 40% to ≤ 45% and decrease is 10-20% (absolute value) from baseline	• Interrupt trastuzumab deruxtecan dosing • Repeat LVEF assessment within 3 wk • If LVEF has not recovered to within 10% (absolute value) from baseline, discontinue subject from study treatment • If LVEF recovers to within 10% from baseline, resume study drug treatment and maintain dose
LVEF < 40% or > 20% (absolute value) drop from baseline	• Interrupt trastuzumab deruxtecan dosing • Repeat LVEF assessment within 3 wk • If LVEF < 40% or > 20% drop from baseline is confirmed, discontinue subject from study treatment

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline 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 are any changes in serum electrolytes that can be corrected, then – if attributed to trastuzumab deruxtecan, reduce dose 1 level
Grade 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	• Discontinue subject from study treatment
Troponin Increased	
Grade 1 (Levels above the ULN 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 (CTCAE Grade 1) at baseline, no repeat testing is required if the troponin level is not Grade 3. For new diagnosed Grade 1 detected on study, repeat troponin testing at 3 h ± 1 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 h ± 1 h – 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 6 h ± 1 h or 24 h ± 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 acute myocardial infarction is confirmed, discontinue subject from study treatment. • 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

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Pulmonary Toxicity	If a subject develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the "Other Non-laboratory Adverse Events" dose modification section below. If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluations. Evaluations should include: • High resolution computed tomography (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 (SpO2) • Arterial blood gases if clinically indicated • One blood sample collection for PK (central) analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered as needed. Radiation applications utilized for the monitoring and management of potential ILD are not specific to this study; routine CT scans should be performed. If the AE is confirmed to be ILD/pneumonitis, follow the management guidance as outlined below. All events of ILD regardless of severity or seriousness will be followed until resolution including after drug discontinuation.

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Grade 1	The administration of trastuzumab deruxtecan must be interrupted for any ILD events regardless of grade. • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated). • Consider starting systemic steroids (eg, 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 Grade 1 ILD/pneumonitis occurs beyond cycle Day 22 and has not resolved within 49 d from the last infusion, the study treatment 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 (eg, at least 1 mg/kg/day prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Monitor symptoms closely. • Re-image as clinically indicated. • If worsening or no improvement in clinical or diagnostic observations in 5 days, – Consider increasing dose of steroids (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.

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Grade 3 and 4	Permanently discontinue subject from study treatment. • Hospitalization required. • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks. • Re-image as clinically indicated. • If still no improvement within 3 to 5 days, – Re-consider additional work-up for 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 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 1 level
Grade 4 (> 6.0 × ULN)	• Discontinue subject from study treatment
Hepatic Toxicity	
AST or ALT With Simultaneous Total Bilirubin Increased	
AST/ALT ≥3.0 × ULN with simultaneous total bilirubin >2.0 × ULN	• Delay study medication until drug-induced liver injury can be ruled out. • If drug-induced liver injury is ruled out, the subject should be treated accordingly, and resumption of study treatment may occur after discussion between the investigator and Sponsor. • If drug-induced liver injury cannot be ruled out from diagnostic work-up, permanently discontinue study treatment. • Monitor AST/ALT and total bilirubin twice weekly until resolution or return to baseline.

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
AST or ALT Increased	
Grade 2 (> 3.0 to 5.0 × ULN if baseline was normal; >3.0 to 5.0 × baseline if baseline was abnormal)	• No action for Grade 2 AST/ALT
Grade 3 (> 5.0 to 20.0 × ULN if baseline was normal; >5.0 to 20.0 × 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 to 20.0 × ULN if baseline was normal; >8.0 to 20.0 × 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 × ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	• Discontinue subject from study treatment
Total Bilirubin Increased	
Grade 2 (> 1.5 to 3.0 × ULN if baseline was normal; >1.5 to 3.0 × 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

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
Grade 3 (> 3.0 to 10.0 × ULN if baseline was normal; >3.0 to 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 to 20.0 × ULN if baseline was normal; >5.0 to 20.0 × ULN 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
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 1 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 1 level
Grade 4	• Discontinue subject from study treatment

Table 5.3: Dose Modification for Trastuzumab Deruxtecan (Continued)

Worst toxicity CTCAE version 5.0 Grade (unless otherwise specified)	Management Guideline for trastuzumab deruxtecan
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
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

All dose modifications should be based on the worst preceding toxicity.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CT = high resolution computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; Hb = hemoglobin; ILD = interstitial lung disease; IV = intravenous; LVEF = left ventricular ejection fraction; NSAID = nonsteroidal anti-inflammatory drug; PK = pharmacokinetic; QTc = corrected QT interval; SpO2 = peripheral oxygen saturation; ULN = upper limit of normal; WBC = white blood cell.

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

5.7. Method of Assessing Treatment Compliance

Trastuzumab deruxtecan and T-DM1 will be administered by IV only to subjects participating in the study and under the supervision of clinical study personnel at the site. Start and stop times of injection and amount of drug administered are to be recorded by clinical study personnel.

5.8. Concomitant Medications (Drugs and Therapies)

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

Hematopoietic growth factors may be used for prophylaxis or treatment based on the clinical judgment of the investigator, except for within 1 wk prior to Screening (see Section 4.1).

Prophylactic or supportive treatment of study treatment-induced AEs will be otherwise as per investigator's discretion and institutional guidelines.

Based on the currently available clinical safety data, it is recommended that subjects receive prophylactic anti-emetic agents prior to infusion of trastuzumab deruxtecan and on subsequent

days. Antiemetics such as 5-hydroxytryptamine receptor antagonists or Neurokinin-1 receptor antagonists and/or steroids (eg, dexamethasone) should be considered and administered in accordance with the prescribing information or institutional guidelines.

Concomitant use of dietary supplements, medications not prescribed by the investigator, and alternative/complementary treatments is discouraged, but not prohibited. Concomitant use of e-cigarettes and vaping is strongly discouraged but not prohibited.

Prohibited Medications and Treatments

With the exception of medications that are under investigation in the study (eg, standard of care, comparators, or combination therapies), the following medications, treatment and procedures will be prohibited during the treatment period (see Section 4.2 for required washout periods). The Sponsor must be notified if a subject receives any of these during the study.

- Other anticancer therapy, including cytotoxic, targeted agents, immunotherapy, antibody, retinoid, or anticancer hormonal treatment (concurrent use of hormones for noncancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable);
  - Use of bisphosphonates or RANKL pathway inhibitors for the prevention or treatment of skeletal-related events is acceptable.
- Concomitant treatment with chloroquine or hydroxychloroquine is not allowed during the study treatment. Refer to Section 17.8 for further details.;
- Other investigational therapeutic agents;
- Radiotherapy (except for palliative radiation to known metastatic sites as long as it does not affect assessment of response or interrupt treatment for more than the maximum time specified in dose modification section);
- Radiotherapy to the thorax;
- 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.

For subjects randomized to T-DM1:

- Refer to the approved local label for T-DM1 for medications prohibited during treatment with the applicable product.

5.9. Study Drug Discontinuation and Discontinuation from the Study

5.9.1. Discontinuation of Study Drug

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

- PD per criteria set forth in mRECIST version 1.1 (Section 17.4);

- Clinical progression (definitive clinical signs of PD), but a recent radiographic assessment did not meet the criteria for PD according to mRECIST version 1.1;
- AE;
- Death;
- Pregnancy;
- Withdrawal of consent by subject (to discontinue study drug) Note: this section only refers to withdrawal from treatment with study drug, which is not the same thing as a complete withdrawal from the study. Discuss with the subject that they will remain in the study (ie, continue with study visits and assessments, including survival follow-up);
- Lost to follow-up;
- Protocol deviation;
- Physician decision;
- Study terminated by Sponsor;
- Other, specify.

Procedures for Discontinuation from Study Drug

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

All subjects who are withdrawn from study treatment should complete protocol-specified withdrawal procedures (Section 5.9.2) and follow-up procedures (Section 6.6). The investigator or sub-investigator must discuss with the subject that even though study treatment has stopped, the subject will continue into the follow-up period for study visits. If a subject withdraws consent from study treatment, the investigator or sub-investigator must discuss with the subject that their decision to permanently discontinue study treatment does not mean follow-up visits should be discontinued as well.

Record the reason for any subject who discontinues study treatment on the eCRF. Discontinued subjects will be followed for survival, either through direct contact or by collecting public records (eg, death certificates) as allowed by local laws. If a subject discontinues treatment for reasons other than disease progression or death, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review even if the subject has started another anticancer therapy.

If the subject is withdrawn because of an AE, the investigator will follow the subject until the AE has resolved or stabilized.

If a subject does not agree to continue to come to the study site, then a modified follow-up must be arranged to ensure the continued collection of endpoints and safety information. Options for modified follow-up are noted below.

Modified Follow-up Options

The following modified follow-up options can be offered to the subject who does not agree to study visits at the study site.

- Study personnel contacting the subject by telephone to collect study information based on the follow-up schedule
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider)
- Study personnel accessing and reviewing the subject's medical information (eg, doctor's notes, hospital records) at the study site or other location)

Dates of the modified follow-up contact(s) should be recorded. See Section below, (Subject Withdrawal/Discontinuation from the Study) for definition of withdrawal by subject from the study (ie, withdrawal of consent).

Subject Withdrawal/Discontinuation from the Study The duration of subject participation in the study will be until 1 of the following occurs:

- Subject dies;
- Study termination;
- Withdrawal by subject (from the study) Note: This indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for long-term survival;
- Subject is lost to follow-up;
- Other, specify.

Only subjects who refuse all of the following methods of follow-up will be considered to have withdrawn consent from study participation (ie, from the interventional portion and follow-up):

- Attendance at study visits per protocol
- Study personnel contacting the subject by telephone
- Study personnel accessing and reviewing the subject's medical information (at study site or other location)

If the subject refuses all of the above methods of follow-up, the investigator or sub-investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the investigator or sub-investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

5.9.2. 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.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures. Protocol-specified withdrawal procedures will be obtained during the End of Treatment (EOT) assessments (+ 7 d) and the 40-Day (+ 7 d) Follow-up assessments conducted after the last administration of study treatment (Section 6.5 and Section 6.6.1).

5.9.3. Subject Replacement

Randomized subjects will not be replaced.

5.9.4. Subject Re-screening Procedures

Re-screening is permitted for any subject who failed to meet eligibility criteria upon initial screening. The SID number **must remain the same** at the time of re-screening. The initial screening information and the reason why the subject was ineligible for the initial evaluation will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for a subject who was re-screened (see Study Manual for details).

6. STUDY PROCEDURES

A study visit schedule in tabular format is provided in Table 17.1 for the Tissue Screening and Screening period and in Table 17.2 for the treatment and follow-up periods.

6.1. Tissue Screening

To determine eligibility, subjects must have breast cancer that has confirmed HER2-positive expression as determined according to American Society of Clinical Oncology – College of American Pathologists guidelines[23] evaluated at a central laboratory.

Note: Subjects may continue on prior therapy while HER2 testing takes place.

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

The following procedures will be conducted:

- Obtain a signed and dated written Tissue Screening ICF from the subject prior to collecting tissue. .
- Obtain adequate archived or recent tumor tissue sample for HER2 testing. Refer to study laboratory manual for preparation, number of slides required, storage, and shipment procedures. If the most recent tissue sample is unavailable:
  - Document the reason why the most recent tissue sample is unavailable and submit another prior tissue specimen.
- If archival tissue is not available, collect fresh tissue sample.
- If a tumor biopsy is needed, report any SAEs directly related to tissue screening procedure (ie, tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.
- Send the samples to the central laboratory to confirm HER2 status.
- Assign SID.

6.2. Screening

Obtain a signed and dated Main ICF before any study-related procedures or assessments are conducted.

The following activities and/or assessments will be performed **within 28 d before randomization** during the Screening period:

- Perform an HIV antibody test if required by local regulations or IRB/ECs.
- Perform hepatitis B surface antigen/hepatitis C antibody test.
- Perform ophthalmologic assessments 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 computed tomography (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.
  - Note: Radiation applications utilized to assess tumor burden are not specific to this study. Scans will be performed per the normal course of subject care
- Additional slides for optional exploratory biomarker assessment are requested (see study laboratory manual). It is preferred if the slides are from the same block as the tissue sample sent for central laboratory HER2 testing.

If there are screening procedures that are performed within 28 days of randomization during the standard treatment of the subject, these procedure results can be used for the study even if conducted prior to consent because they were performed during the normal course of subject care.

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 mRECIST version 1.1 (Section 17.4).

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

- Confirm subject eligibility.
- Obtain demographics (eg, birth date, sex, race, ethnicity), medical and surgical history, including all previous, now resolved, significant medical conditions, date of diagnosis, extent of disease, disease staging, estrogen/progesterone receptor status, previous cancer therapies (including prior radiation therapy) and oncology surgical history.
- Perform a complete physical examination (see Section 9.11) including weight and height.
- Assess functional status using the ECOG PS (Section 17.3).
- Record concomitant medications, AEs, and hospitalization-related records at every visit (from the time the subject signed the Main ICF). For details on AE collection and reporting, refer to Section 9.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature; Section 9.9) and peripheral oxygen saturation (SpO2; Section 9.12.2).
- Perform triplicate 12-lead ECG. ECGs will be taken in close succession while in a supine/semi-recumbent position (Section 9.10). ECG should be performed prior to blood draws.

  - Note that subsequent ECGs will be performed in triplicate only if an abnormality is noted.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology;
  - Chemistry;
  - Coagulation (should also be performed as clinically indicated throughout the study);
  - 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. In addition to the troponin sample that is tested locally, a sample should also be submitted for central laboratory troponin-T testing.
  - Serum biomarkers (eg, HER2ECD; Section 8.3.2; COVID-19 serology, Table 17.2).
- Obtain urine sample for urinalysis (protein, glucose, blood, microscopy assessment [if indicated], and specific gravity; Section 9.8).
- For women of childbearing potential (criteria for non-childbearing potential are defined in Section 4.1) perform a serum or urine pregnancy test and document the results. A positive urine pregnancy test result must be confirmed immediately using a serum test, with a confirmed negative test result within 72 hours prior to drug administration. For subjects who are of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.

6.3. Randomization

Eligible subjects will be randomized by the IXRS in a 1:1 ratio into 1 of 2 treatment groups (trastuzumab deruxtecan versus T-DM1).

Randomization will be stratified by hormone receptor status (positive, negative), prior treatment with pertuzumab (yes, no), and history of visceral disease (yes, no).

A subject's first dose/Cycle 1 Day 1 should occur within 7 d from the date the subject is randomized.

6.4. Treatment Period

6.4.1. Cycle 1 to 4 and Subsequent Cycles

Treatment and procedures performed on Day 1 of Cycle 1 and beyond are specified in Table 17.2 and further described below. Cycles for trastuzumab deruxtecan and T-DM1 are both 21 d in duration.

6.4.1.1. Between -3 Days Through Immediately Before Infusion (All Cycles)

- The subject must complete the HEOR outcomes, EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or

procedures are done that day . Complete at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and then every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc).

- Perform 12-lead ECG.
  - If an abnormality is noted, perform triplicate ECG. ECGs will be taken in close succession while in a supine/semi-recumbent position. ECGs should be performed before blood draws at respective time points.
- 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.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Record concomitant medications, AEs, and hospitalization-related records at every visit.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology
  - Chemistry
- For all female subjects of childbearing potential (as defined in Section 4.1) perform a serum or urine pregnancy test within 72 h prior to the beginning of the infusion and document the results. A positive urine pregnancy test result must be confirmed immediately using a serum test, with a confirmed negative test result within 72 hours prior to drug administration. For subjects who are of non-childbearing potential (as defined in Section 4.1), no pregnancy test will be required.
- **Note:** Vital signs (including SpO2) evaluations, clinical laboratory tests, physical examination, weight, ECG, HEOR outcomes, and ECOG PS determination need not be repeated if they were performed within 3 d of the first dose in each cycle.

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

- Obtain blood samples for:
  - Pharmacogenetic assessment, Cycle 1 only, if the subject provides consent by signing the pharmacogenetics sample banking consent form. (This sample is not required for study participation.);
  - Serum biomarkers (eg, HER2ECD, COVID-19 serology [refer to Section 17.8]) assessment which will be collected on Cycle 3 Day 1 and every 2 cycles thereafter (Cycles 5, 7, 9, etc).

  - COVID-19 testing will be performed only on the serology samples from Cycle 5 and every 4 cycles thereafter. For subjects with suspected or confirmed COVID-19, follow the dose modifications in Section 17.8.
  - Only subjects randomized to trastuzumab deruxtecan:
  - PK assessment before infusion (BI) (within 8 h) on Day 1 of Cycles 1, 2, 3, 4, 6, and 8;
  - ADA at Cycles 1, 2 and 4, then every 4 cycles (Cycles 8, 12, 16, etc);

- Obtain blood samples for exploratory biomarkers, such as cfDNA analysis in plasma, before treatment on Day 1 of Cycle 1 and every 3 cycles thereafter until EOT (Cycles 4, 7, etc).
- Record concomitant medications, AEs, and hospitalization-related records at every visit.

6.4.1.3. Day 1: Dosing and End of Infusion (All Cycles, Unless Otherwise Noted)

- Administer study treatment IV infusion approximately 90 min for the initial dose and, if no infusion related reaction after the initial dose, infuse subsequent doses over a minimum of 30 min. Record start and stop times and amount of drug administered. Study treatment is to be administered every 21 d ± 2 d.
  - Trastuzumab deruxtecan should only be initiated by a physician or healthcare professional experienced in the administration of cytotoxic chemotherapy. Medicinal products to treat allergic/anaphylactic infusion reactions, as well as emergency equipment, should be available for immediate use.
  - Trastuzumab deruxtecan arm only: During and following the first infusion (Cycle 1 Day 1), subjects will be observed for infusion related reaction until the PK collection time point, which is about 5 h (± 2 h) after the start of infusion of trastuzumab deruxtecan.
- Administration and monitoring of subjects randomized to T-DM1 should occur per the locally approved label. Blood samples for PK analyses are not required at the end of infusion (EOI)/treatment for subjects randomized to T-DM1 as part of this study protocol.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Trastuzumab deruxtecan arm only: At Cycle 1 Day 1, perform ECG testing at 5 h after the start of drug administration (± 2 h).
  - If an abnormality is noted, perform triplicate ECG. ECGs will be taken in close succession while in a supine/semi-recumbent position. ECG should be performed prior to blood draws.
- Trastuzumab deruxtecan arm only: Collect blood samples for:

  - PK analysis samples on Day 1 of Cycles 1, 2, 3, 4, 6, and 8 should be collected as soon as possible after EOI and the actual time of sampling should be accurately recorded. In addition, for Cycle 1 Day 1 only, collect sample at 5 h after the start of drug administration (± 2 h).

- If at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis, collect blood samples for troponin (preferably high-sensitivity troponin-T) testing and perform ECG in triplicate. If ECG is abnormal, follow institutional guidelines. See details in Table 5.3.

6.4.1.4. Day 8 (± 1 d) and Day 15 (± 1 d) (Cycle 1 Only)

- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2. More frequent examinations may be performed at the discretion of the investigator and if medically indicated.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology
  - Chemistry
- Record concomitant medications, AEs, and hospitalization-related records at every visit.

6.4.2. Every 2 Cycles after Cycle 3

- The subject must complete the HEOR outcomes, EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day . Collect HEOR outcomes on Day 1 at Cycles 1, 2, and 3; thereafter, collect every 2 cycles (eg, Cycle 5, Cycle 7, Cycle 9, etc).

6.4.3. Every 4 Cycles (± 7 d) after Cycle 1

- Perform an Echo or MUGA every 4 cycles after Cycle 1 (Cycle 5, 9, 13, etc). (note: the same test must be used for the subject throughout the study).

6.4.4. Every 6 Weeks (± 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 randomization, independent of treatment cycle. A CT and/or MRI (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 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.

Imaging results will be reviewed by an independent radiologic facility.

6.5. End of Treatment

The EOT is defined as the date the investigator decides to discontinue study treatment (+ 7 d). All assessments required as part of EOT must occur within 7 days from the date the Investigator decides to discontinue study treatment. The following procedures will be performed as specified in the Schedule of Events (Table 17.2). However, if the EOT assessments have been performed within 30 d (± 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.

- The subject must complete the HEOR outcomes, EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day.
- Perform a physical examination (Section 9.11), including weight.
- Ophthalmologic assessments to include visual acuity testing, slit lamp examination, and fundoscopy.
- Assess functional status using the ECOG PS (Section 17.3).
- Record concomitant medications, AEs, and hospitalization-related records at every visit.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2.
- Perform 12-lead ECG.
  - If an abnormality is noted, perform triplicate ECG. Triplicate ECGs will be taken in close succession while in a supine/semi-recumbent position. ECG should be performed prior to blood draws.
- Echo or MUGA (note: the same test must be used for the subject throughout the study).
- Blood sample for troponin (preferably high-sensitivity troponin-T); in addition to the troponin sample that is tested locally, a sample should also be submitted for central laboratory troponin-T testing:
  - If troponin levels are consistent with myocardial infarction as defined according to manufacturer (CTCAE Grade 3), perform ECG testing in triplicate, repeat troponin testing 6 h (± 1 h) and 12 h (± 1 h) after initial troponin test was drawn, and follow institutional guidelines.
  - If troponin levels are new CTCAE Grade 1 (ie, levels at baseline were ≤ULN), repeat troponin testing at 3 h (± 1 h) after initial troponin test was drawn. If troponin level at 3 h after initial troponin test was drawn significantly increases

per institutional guidelines, then perform ECG in triplicate, repeat troponin testing at 6 h (± 1 h) and follow institutional guidelines. Otherwise, repeat troponin testing at 6 h (±1 h) or at 24 h (±2 h) after initial troponin test.

  - If at any time a subject reports signs or symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis, collect blood samples for troponin (preferably high-sensitivity troponin-T) testing and perform ECG in triplicate.

- Collect sample for ADA, only in subjects randomized to trastuzumab deruxtecan.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology;
  - Chemistry;
  - Serum biomarkers (eg, HER2ECD; Section 8.3.2; COVID-19 serology; Section 17.8);
  - Coagulation.
- Blood sample for exploratory biomarkers, such as cfDNA analysis in plasma, 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 where PD is suspected (eg, MRI of the brain if brain metastases are suspected) should also be imaged, per mRECIST version 1.1 (Section 17.4). If the previous scan was within the last 6 wk (± 7 d) from the date of EOT, this assessment does not need to be performed at EOT. If a subject discontinues treatment for reasons other than disease progression, every attempt should be made to collect tumor assessments until disease progression and the scans be sent for central review even if the subject has started another anti-neoplastic therapy.
- 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.

6.6. Follow-up

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

Forty d (+ 7 d) after last study treatment administration or before starting new anticancer treatment, whichever comes first, the following procedures will be performed as specified in the Schedule of Events (Table 17.2). If EOT is > 40 d (+ 7 d) after last treatment, then the EOT assessments can also function as the 40-Day (+ 7 d) Follow-up assessments.

- The subject must complete the HEOR outcomes, EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day.

- Perform a physical examination (Section 9.11), including weight.
- Assess functional status using the ECOG PS Scale (Section 17.3).
- Record concomitant medications, AEs, and hospitalization-related records.
- Obtain vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) and SpO2.
- Collect and send blood samples to the laboratory for the following tests (Section 9.8):
  - Hematology;
  - Chemistry;
  - Coagulation.
- Obtain blood samples for ADA, only for subjects randomized to trastuzumab deruxtecan.
- For subjects with positive ADA at the follow-up visit, additional serum ADA samples may be collected every 3 mo (± 1 mo) up to 1 y from the last dose of study treatment, 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.
- Serum or urine sample for pregnancy testing in women of childbearing potential.

6.6.2. Long-term/Survival Follow-up Visits

After completion of the 40-Day (+ 7 d) Follow-up assessments, the Long-term/Survival Follow-up assessments will be performed every 3 mo (± 14 d), from the date of 40-Day (+ 7 d) Follow-up assessments, until death, withdrawal of consent from the study, loss to follow-up, or study closure, whichever occurs first.

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

- The subject must complete the HEOR outcomes, EORTC QLQ-C30 and EORTC QLQ-BR45, and EQ-5D-5L questionnaires before any other assessments or procedures are done that day (only at first 3 mo, which will be the last data collection point for both questionnaires);
- Record subsequent anticancer treatments, their outcomes, and survival;
- Further follow-up may be required for ongoing AEs (see Section 9).

If direct contacts are not possible due to withdrawal of consent or the subject becomes lost to follow-up, the site must make every effort to collect survival status from public records (eg, death certificates) in accordance with local laws. See Section 5.9.2 for further details on how subjects will be followed for survival status if they withdraw consent.

7. EFFICACY ASSESSMENTS

7.1. Assessments for Efficacy Endpoints

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is PFS based on BICR. Progression-free survival based on BICR is defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression per BICR according to mRECIST version 1.1 or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the data cutoff date for PFS analysis will be censored at the date of their last evaluable tumor assessment. Detailed censoring rules for PFS based on BICR will be specified in the Statistical Analysis Plan (SAP).

7.1.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is OS, defined as the time from the date of randomization to the date of death for any cause. If there is no death reported for a subject before the data cutoff for OS analysis, OS will be censored at the last contact date at which the subject is known to be alive. The definition and additional details for the last contact date will be specified in the SAP.

7.1.3. Secondary Efficacy Endpoints

Other secondary efficacy endpoints noted below will be assessed by BICR review based on mRECIST version 1.1. Secondary efficacy endpoints include:

- ORR, defined as the proportion of subjects who achieve a best overall response of CR rate and PR rate, based on BICR and based on investigator assessment. Confirmation of CR/PR is required for this study;
- DoR, defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression, based on BICR. Duration of response will be measured for responding subjects (PR or CR) only. Subjects who are progression-free at the time of the analyses will be censored at the date of the last evaluable tumor assessment;
- PFS (based on investigator assessment), defined as the time from the date of randomization to the earliest date of the first objective documentation of radiographic disease progression via investigator-assessed disease progression according to mRECIST version 1.1 (Section 17.4) or death due to any cause. Subjects who are alive with no objective documentation of (radiographic) disease progression by the data cutoff date for PFS analysis will be censored at the date of their last evaluable tumor assessment.

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

7.1.4. Exploratory Efficacy Endpoints

- Time to response, defined as the time from the date of randomization to the date of the first documentation of objective response (CR or PR), based on BICR. Time to response will be measured for responding subjects (CR or PR) only.
- Best percent change in the sum of the diameter of measurable tumors based on BICR.
- CBR, defined as the sum of CR rate, PR rate, and more than 6 mo SD rate, based on BICR.
- PFS2, defined as the time from date of randomization to the first documented progression on next line therapy* or death due to any cause, whichever occurs first. The first documented progression on next-line therapy is based on investigator assessment of PD. PFS2 will be censored if no PFS2 event is observed during next line therapy before the analysis cutoff date; censoring date will be the last contact date. In case a second anti-neoplastic therapy is introduced prior to a PFS2 event, the PFS2 date will be censored at the end date of the first next line therapy.
  - Any death occurring prior to the start of next line therapy will be considered a PFS2 event.
  - Any death following the next line of therapy will be a PFS2 event if no second new line of therapy is initiated.
  - PFS and PFS2 may be identical in the case that a patient starts the next line anti-neoplastic therapy prior to progression on the trial therapy and tumor assessments continue after start of the new therapy.

* Next line therapy is defined as the first new systemic anti-neoplastic therapy initiated after discontinuation of study treatment, regardless of EOT reason.

7.2. Appropriateness of Selected Efficacy Assessments

The primary endpoint of this study is PFS based on mRECIST version 1.1 which will be determined by independent review of baseline and follow-up assessments obtained every 6 wk. Progression-free survival has served as the basis of several recent approvals in the mBC setting including pertuzumab (CLEOPATRA study),[3] palbociclib (PALOMA studies),[25,26] ribociclib (MONALEESA-2),[27] and abemaciclib (MONARCH 2).[28] While PFS is a well-accepted measure to demonstrate clinical benefit in this setting, OS provides additional evidence of clinical efficacy and is the key secondary endpoint. Sample size has been calculated to ensure the study is adequately powered to detect a clinically meaningful PFS and OS benefit.

Patients with mBC face an illness associated with significant symptoms. Moreover, they are also aware that despite the availability of various treatments, it is ultimately incurable. The success of modern therapies in achieving better disease control and prolonged survival means that more women with mBC can receive several lines of treatment and in the process the key goals are to prolong survival and to improve health-related quality of life (QoL) (Section 10). That is why it is particularly valuable to involve subjects in clinical studies by asking them to provide assessment of their health and quality of life. In recent years a growing number of clinical studies in mBC have been reporting on health-related QoL, the most common patient reported outcome

(PRO) being used is the EORTC QLQ-C30 with or without the breast cancer supplement EORTC QLQ-BR45, followed by FACT-B.[29]

The index scores from the PROs will be used to show changes in overall health-related quality of life and clinically meaningful changes in specific aspects of subject's well-being over time. In addition, the outcomes will be used in additional analyses and economic models to generate evidence to support access and reimbursement.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Assessments

Blood samples for PK assessments will be collected only from subjects randomized to trastuzumab deruxtecan at multiple time points in the study, as outlined in Table 8.1 and Table 17.2. In addition, if feasible, a blood sample should be collected for PK analysis as soon as possible when a subject is suspected of having ILD/pneumonitis.

Table 8.1: Blood Sampling for Pharmacokinetic Analysis

Cycle	Day	Sampling Time Point (Acceptable Ranges)
Cycle 1	Day 1	BI (within 8 h) EOI [a] 5 h after the start of drug administration (± 2 h)
Cycles 2, 3, 4, 6, and 8	Day 1	BI (within 8 h) EOI [a]

BI = before infusion; EOI = end of infusion

[a] The tissue sample should be collected as soon as possible after EOI and the actual time of sampling should be accurately recorded.

At each time point, blood will be collected for trastuzumab deruxtecan, total anti-HER2 antibody, and MAAA-1181a PK analysis. The actual time of study treatment administration and the exact time of blood sampling for PK analysis must be recorded on the eCRF.

Details for blood sampling, processing, storage and shipment to central laboratory 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.

If chloroquine or hydroxychloroquine are administered for COVID-19 infection, additional PK serum samples should be collected from each subject who provides consent and as described in Section 17.8 and at the time points specified in the Schedule of Events (Section 17.1)

8.2. Pharmacodynamic Assessment

Not applicable

8.3. Biomarker Assessments

Samples for biomarker testing will be collected from all subjects at the time points specified in Table 17.2. 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 study laboratory manual.

8.3.1. Tumor Sampling

In addition to the tumor sample required for confirmation of HER2 status, if the subject agrees, additional slides for optional exploratory biomarker analysis are requested. The detailed instructions for the handling and shipping of tumor samples are included in the study laboratory manual.

8.3.2. Blood Sampling

The HER2ECD in serum may be measured by a central laboratory. Other exploratory biomarkers, such as cfDNA in plasma, may be measured.

8.3.3. Additional Biomarker Assessments

During the study, in addition to the biomarkers specified above, optional exploratory biomarker research may be conducted on available additional samples. These studies would extend the search for other potential biomarkers that may correlate with clinical benefit. 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 subject agrees, the remaining samples (tumor tissues, blood and plasma) may be stored for up to 15 y and further analyzed to address scientific questions related to trastuzumab deruxtecan and/or cancer.

8.3.4. Disclosure of the Results of Additional Biomarker Assessments

See ICF for details on disclosure.

8.4. Immunogenicity

Blood samples for ADA analyses will be collected only for subjects randomized to trastuzumab deruxtecan and at the time points specified in Table 17.2. A blood sample will be drawn at each time point. Serum concentrations of trastuzumab deruxtecan and/or total anti-HER2 antibody may be measured using the same ADA samples for purpose of ADA assessment.

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

The ADA testing will be performed using a validated ADA assay following tiered assay steps including screening, confirmatory, and titer determination testing. Samples confirmed positive will be analyzed by neutralizing antibody assay.

8.5. Pharmacogenetic Analysis

8.5.1. Genomic or Genetic Banking and Analysis

A single blood sample for pharmacogenetics analysis will be collected from each subject, who consents to this test, predose on Day 1 of Cycle 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. Pharmacogenetic 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 treatment, as well as helping in the development of new drugs or improvement of existing drugs.

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

8.5.1.1. Disclosure of the Results of Genomic or Genetic Analysis

See ICF for details on disclosure.

8.5.1.2. 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 laboratory for sample storage and/or analysis 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 Endpoints

Safety endpoints will include SAEs, TEAEs, AESI, DAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, Echo/MUGA findings, and ADAs. 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 National Cancer Institute (NCI)-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 Main ICF and up to 40 d (+ 7 d) after last treatment (ie, the 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 Main ICF and up to 40 d (+ 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.

If a tumor biopsy is needed, report any SAEs directly related to tissue screening procedure (ie, tumor biopsy) along with any associated treatment. Unless documentation of other AEs is required by local law, only SAEs directly related to tumor biopsy will be recorded during tissue screening.

All AEs, SAEs, and AESI 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 treatment discontinuation, dose interruption or 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.

The investigator should always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, the primary sign or symptom should be reported 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, they should be reported 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 treatment should also be reported and managed as an SAE.

9.3. Adverse Events of Special Interest

For the trastuzumab deruxtecan clinical program, based on the available pre-clinical data, review of the cumulative literature, reported toxicities for the same class of agents and biological plausibility, ILD and LVEF decrease are considered to be AESIs.

9.3.1. Interstitial Lung Disease/Pneumonitis

9.3.1.1. Clinical Summary

Interstitial lung disease/pneumonitis is considered an important identified risk based on a comprehensive cumulative review of the available safety data from the clinical development program as well as the results of potential ILD/pneumonitis cases reviewed by the independent ILD AC, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. Refer to the current IB for a summary of preliminary clinical study data.[10]

9.3.1.2. Management Guidance

Interstitial lung disease/pneumonitis should be ruled out if a subject develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough or fever. 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 (Section 5.6).

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 SpO2, arterial blood gases if clinically indicated, and one blood sample collection for PK (central) analysis as soon as ILD/pneumonitis is suspected, if feasible. Other tests could be considered, as needed.

If the AE is confirmed to be ILD/pneumonitis, follow the management guidance outlined in the designated "Pulmonary Toxicity" dose modification section of the study protocol (Table 5.3).

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

9.3.1.3. Interstitial Lung Disease Adjudication Committee

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

9.3.2. Left Ventricular Ejection Fraction Decrease

9.3.2.1. Clinical Summary

LVEF decrease in association with trastuzumab deruxtecan are 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 study data.[10]

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

9.3.2.2. 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 and symptoms suggesting congestive heart failure, myocardial infarction, or other causes of cardiac myocyte necrosis. ECGs will be performed, and standard ECG parameters will be measured, including RR, PR, QT intervals, and QRS duration. All ECGs must be evaluated by investigator or delegated physician for the presence of abnormalities. Whether or not measurement is performed, date performed, results, and findings for each parameter will be recorded in the eCRF.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and 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 Council on Harmonisation [ICH] E2A Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).[30]

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).[30]

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 1 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 hospitalization 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 NCI-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, however, the event itself 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 treatment 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 treatment 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 treatment 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 treatment 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 treatments

- Dose Not Changed
  - No change in study treatment dosage was made.
- Drug Withdrawn
  - The study treatment was permanently stopped.
- Dose Reduced
  - The dosage of study treatment was reduced.

- Drug Interrupted
  - The study treatment was temporarily stopped.
- Not Applicable
  - Subject died, study treatment had been permanently discontinued prior to reaction/event, or reaction/event occurred prior to start of study treatment.

9.4.6. Other Action Taken for Event

- None
  - No treatment was required.
- Medication required
  - Prescription and/or OTC medication was required to treat the AE.
- 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. Adverse Events Reporting–Procedure for Investigators

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

Additional relevant information regarding the AESIs ILD/pneumonitis and LVEF decrease for the trastuzumab deruxtecan clinical program regardless of seriousness is to be collected through the targeted questionnaires built within the clinical study database.

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

For the trastuzumab deruxtecan arm, all targeted questionnaires are to be completed. For the comparator arm, only the ILD/pneumonitis targeted questionnaire is to be completed. For broad surveillance of ILD/pneumonitis, the selected 42 PTs (all from the ILD SMQ) plus the 2 PTs of respiratory failure and acute respiratory failure are included for enhanced data collections.

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

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

- SAEs (see Section 9.4.2 for definition)
- All potential ILD cases should be reported within 24 hours; including both serious and non-serious potential ILD cases (potential ILD is defined by the Event Adjudication Site Manual List of PTs).
- Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT or AST) $\geq 3 \times$ ULN and an elevated total bilirubin $> 2 \times$ ULN that may occur either at different time points or simultaneously during the study. A targeted questionnaire is built within the eCRF to collect relevant additional information for these potential cases.
- Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the investigator to be clinically relevant; ie, poses an actual or potential risk to the subject.
  - Overdose is always serious. By definition, an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. AEs can either be serious or non-serious. Details of the overdose including trastuzumab deruxtecan dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the eCRF within electronic data capture.

All events (serious and non-serious) must be reported with investigator's assessment of the event's seriousness, severity, and causality to the study treatment. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and laboratory data that are relevant

to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

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

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

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

Daiichi Sankyo and/or CRO will inform investigators, IRBs/ECs, and Regulatory Authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in other study sites or other studies of the study treatments, as appropriate per local reporting requirements. Daiichi Sankyo and/or CRO will comply with any additional local safety reporting requirements.

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

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

9.7. Exposure In Utero During Clinical Studies

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

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, including normal delivery and induced abortion. An adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. The investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs outlined in Section 9.5.

9.8. Clinical Laboratory Evaluations

The following clinical laboratory tests will be performed:

1. Hematology tests
    - 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
    - Total protein, albumin, alkaline phosphatase, ALT, AST, TBL, blood urea nitrogen (BUN)/urea, calcium, chloride, serum creatinine, lactate dehydrogenase (LDH), magnesium, potassium, sodium.
    - A coagulation test will be performed (prothrombin time and either partial thromboplastin or activated partial thromboplastin time).
    - Creatinine clearance (mL/min) will be calculated using the Cockcroft-Gault equation (Section 17.2).
    - Troponin will be analyzed for each sample at Screening, EOT, and as needed based on subject-reported signs or symptoms.
3. Urinalysis
    - 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 (Table 17.1 and Table 17.2).

- Pregnancy test (serum or urine) for all female subjects of childbearing potential must be performed during the Screening period within 72 h prior to the beginning of infusion on Day 1 of each cycle, at EOT, and at the 40-Day Follow-up assessments. A positive urine pregnancy test result must be confirmed immediately using a serum test.

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 (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant.

9.9. Vital Signs

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

9.10. Electrocardiograms

ECGs will be taken in triplicate at screening. Thereafter, singular ECGs will be performed. If an abnormality is noted, ECGs should then be performed in triplicate. Standard supine/semi-recumbent 12-lead ECGs will be taken prior to blood draws and will be performed as described in the Schedule of Events (Table 17.1 and Table 17.2). When taken in triplicate, ECGs should be taken in close succession). 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; 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 (Table 17.1 and Table 17.2). LVEF will be measured.

9.12.2. Pulmonary Assessments

The SpO2 will be measured at Screening, BI and EOI on Day 1 of each cycle, Days 8 and 15 of Cycle 1, EOT and at the 40-Day (+ 7 d) Follow-up assessments. For more details please refer to Section 6 of the protocol.

An ILD AC will review all cases of (potential) ILD on an ongoing basis. Description of the ILD AC is available in Section 9.3.1.3.

10. OTHER ASSESSMENTS

10.1. Patient Reported Outcomes

Patient reported outcomes will be used to evaluate study treatment. The impact of breast cancer symptoms will be assessed based upon the EORTC QLQ-BR45 and EORTC QLQ-C30 (version 3.0) and EQ-5D-5L questionnaires (Section 17.6 and Section 17.7, respectively).

10.1.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaires C30 and BR45

The QLQ-C30 is a QoL instrument for cancer patients developed in 1987 by EORTC. Since then it has undergone several revisions and its current version is 3.0.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items. Each of the multi-item scales includes a different set of items - no item occurs in more than 1 scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level.

Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

Due to limitations inherent in its generic focus, the EORTC QLQ-C30 is supplemented by disease specific modules such as the EORTC QLQ-BR45, which are designed to be administered in addition to the core questionnaire. The EORTC QLQ-BR45 is specific for breast cancer.

The EORTC QLQ-C30 with EORTC QLQ-BR45 will be used in the study as the disease-specific instruments to assess the health-related QoL of subjects. They will be administered before any other assessments or procedures are done that day. Complete at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and then every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc) and at the EOT as defined in the protocol. Subjects will be followed up at Day 40 (+ 7 d) and at the first Long-term/Survival Follow-up assessments 3 mo after that (last measurement). Reporting will follow closely the Consolidated Standards of Reporting Trials (CONSORT) extension on reporting PROs.[31]

Changes from baseline over time will be assessed in the global QoL scale, each of the functioning scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain), 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) of the EORTC QLQ-C30 and in each of the subscales (breast symptoms, arm symptoms, body image, sexual functioning, and systemic therapy side effects) of the EORTC QLQ-BR45.

Further, time to deterioration on the ‘breast symptoms’ and ‘arm symptoms’ subscales of the EORTC QLQ-BR45 and the pain symptom subscale of the EORTC QLQ-C30 will be assessed. On the basis of previously published research on clinically meaningful changes in the EORTC QLQ-BR45 and the QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores.

Further details on the scoring of these scales, including missing items, will be provided in the SAP.

10.1.2. EuroQoL Five Dimensions Five Levels (EQ-5D-5L) Patient Reported Outcome Questionnaire

Study subjects will be asked to complete the EQ-5D-5L questionnaire, a generic measure of standardized health status, before any other study procedures are performed at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and then every 2 cycles thereafter (eg, Cycles 5, 7, 9, etc) and at the EOT assessments. Data collection will continue at the 40-Day (+ 7 d) Follow-up assessments and the first Long-term/Survival Follow-up assessments 3 mo later, which will be the last data collection point for both questionnaires.

The EQ-5D-5L is self-administered and consists of 2 parts, the EQ-5D-5L descriptive system, and the EQ-visual analogue scale (VAS). The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.[32] The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. The numerals 1 to 5 have no arithmetic properties and should not be used as a cardinal score.

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

The EQ-5D-5L will be administered before the first cycle and every 2 cycles after that until EOT as defined in the protocol. Subjects will be followed up at Day 40 (+ 7 d) and at the first Long-term/Survival Follow-up visit 3 mo after that (last measurement). Reporting will follow closely the CONSORT extension on reporting PROs.[31]

10.2. Health-related QoL Endpoints

10.2.1. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Endpoints

- Changes from baseline over time will be assessed in the global QoL scale, each of the functioning scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain), and the 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) of the EORTC QLQ-C30.
- Time to deterioration on the pain symptom subscale of the EORTC QLQ-C30 will be assessed.
- Changes from baseline over time will be assessed in each of the subscales (breast symptoms, arm symptoms, body image, sexual functioning, and systemic therapy side effects) of the EORTC QLQ-BR45.

- Time to deterioration on the 'breast symptoms' and 'arm symptoms' subscales of the EORTC QLQ-BR45 will be assessed.
- On the basis of previously published research on clinically meaningful changes in the EORTC QLQ-BR45 and the QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores.[33]

10.2.2. EuroQoL Five Dimensions Five Levels Endpoints

- VAS as a measure of self-rated health status
- Response by dimension
- Index score change from baseline using UK value set
- Index score by disease state

10.3. Pharmacoeconomic Assessments

10.3.1. Hospitalization-Related Endpoint

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

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

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The primary analyses for PFS based on BICR will be performed. An interim and a final analysis for PFS is planned in this trial. The interim analysis will be performed when approximately 234 BICR-assessed PFS events (70% information fraction) have been observed. If the trial is not statistically significant at this interim analysis, the final PFS analysis will be performed after observing 335 BICR-assessed PFS events.

Projections of total number of PFS or OS events for interim or final analysis (as appropriate) will be performed as the trial progresses to monitor the number of PFS events for data cutoff. Data cutoff date for primary analysis will be at approximately the projected date of the 234th event for the interim analysis or the 335th PFS event if the study proceeds to final analysis.

Starting 2 wk before and ending by the projected date for the PFS and OS analysis data cutoff, a data sweep will be conducted to collect information such as survival and clinical progression (to be described in a separate PFS/OS event sweep plan).Analysis of the data will be inclusive of all data collected up to the data cutoff date, and the database will be comprised of the primary analysis and submission data sets.

Long-term/Survival Follow-up, as specified in Section 6.6.2, will continue after primary analysis.

Summary statistics will be presented by treatment group. Continuous variables will be summarized by the number of observations, mean, standard error, median, minimum, and maximum values. 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 treatment will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

Efficacy analyses will be performed on the Full Analysis Set (FAS). Primary efficacy analyses may also be performed on the Per-protocol Analysis Set (PPS). Safety analyses will be performed using the Safety Analysis Set. PK analysis will be based on the PK Analysis Set. All other exploratory analyses will be performed based on the FAS unless otherwise specified.

11.2. Analysis Sets

11.2.1. Full Analysis Set

The FAS will include all randomized subjects. Following the intent-to-treat principle, subjects will be analyzed according to the treatments and strata they were assigned at randomization.

11.2.2. Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who received at least 1 dose of study treatment. Subjects will be summarized according to treatment actually received.

11.2.3. Per-protocol Analysis Set

The PPS will include all subjects from the FAS without any of the SAP-specified major protocol deviations and who received at least one dose of study treatment. Additional details will be specified in the SAP.

11.2.4. Pharmacokinetic Analysis Set

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

11.3. Study Population Data

Subject disposition will be summarized for subjects in the FAS. The total number of subjects for each defined analysis population will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the FAS. Some baseline characteristics may also be summarized for Safety Analysis Set and PPS. Study treatment exposure and treatment duration will be summarized using descriptive statistics for the Safety Analysis Set.

11.4. Statistical Analysis

11.4.1. Efficacy Analyses

11.4.1.1. Primary Efficacy Analyses

The primary efficacy endpoint is PFS based on BICR. An interim and a final analysis for PFS is planned in this trial. The interim analysis will be performed when approximately 234 BICR-assessed PFS events (70% information fraction) have been observed. If the trial is not statistically significant at this interim analysis, the final PFS analysis will be performed after observing 335 BICR-assessed PFS events.

The primary efficacy analyses will be performed for the Full Analysis Set that consists of all randomized subjects. Following Intent-to-Treat principles, patients will be analyzed according to the treatment and the strata they were randomized as recorded in IXRS.

The primary efficacy analysis will be the comparison of the survival distribution of PFS based on BICR between the 2 treatment groups, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at an overall 2-sided significance level of 0.05.

One interim analysis for superiority is planned after at least 234 of the targeted 335 PFS events (70% information fraction) have been documented and after enrollment is completed. The primary intent of the interim analysis is to demonstrate superiority of the primary efficacy endpoint of PFS only and a formal futility evaluation is not planned. If superiority is not demonstrated at the interim analysis, final PFS analysis is planned after approximately 335 PFS events have been documented. A group sequential design, utilizing a Haybittle-Peto efficacy boundary[36, 37], will be used to control the type I error rate for the primary efficacy analysis. Additional details of the interim analysis can be found in Section 11.5.

The survival distribution of PFS will be estimated by Kaplan-Meier method for each treatment group and results will be presented graphically. The median PFS time and the 2-sided 95% CI for the median will be provided using Brookmeyer and Crowley method for each treatment group. In addition, Kaplan-Meier estimates of PFS rate at fixed time points (eg, 3, 6, 9, 12 mo) along with their 2-sided 95% CIs will be provided for each treatment group. The treatment effect hazard ratio (HR) and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS.

11.4.1.2. Secondary Efficacy Analyses

The key secondary efficacy endpoint is OS. Two interim analyses and a final analysis of OS are planned. The first OS interim analysis is planned at time of the PFS interim analysis, and the second OS interim analysis is planned at time of the final PFS analysis. Approximately 96 and 153 of the planned 250 OS events (38.4% and 61.2% of information fractions) will be expected to be documented by time of the first and the second OS interim analyses, respectively. Final OS analysis is planned after approximately 250 OS events have been documented.

A three-look design is considered for OS. OS will be hierarchically tested in the following way:

1. The first potential OS analysis will be at the time of the PFS interim analysis after 96 expected deaths. If PFS is statistically significant at this stage, OS will also be tested. If OS is not statistically significant at this stage, the second OS interim analysis will be planned after 153 deaths. If OS is not statistically significant at the second interim analysis, a final analysis is planned after 250 deaths have been recorded.
2. If PFS is not statistically significant at the time of the interim analysis of PFS, then OS will not be tested at the time of the interim analysis of PFS. If PFS is statistically significant at the time of the final analysis, then OS will also be tested. If OS is not statistically significant at this stage, further testing will be carried out when a total of 250 deaths have been recorded.
3. If PFS is not statistically significant after the final analysis for PFS is performed, then OS will not be tested.

The type I error rate will be controlled by using a separate Lan-DeMets alpha spending function with O'Brien-Fleming boundary independent of the one used for the primary efficacy analysis of PFS at the 2-sided significance level of 0.05. This guarantees the protection of the overall significance level across the 2 hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses.[34]

Overall survival will be compared between the 2 treatment groups, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at 2-sided significance level of 0.05, provided superiority in PFS is demonstrated at either interim or final analysis. The survival distribution of OS will be estimated by Kaplan-Meier method and results will be presented graphically. The median survival time and the 2-sided 95% CI for the median will be provided using Brookmeyer and Crowley method for each treatment group. In addition, Kaplan-Meier estimates of OS rate at fixed time points (eg, 3, 6, 9, 12 mo) along with their 2-sided 95% CIs will be provided for each treatment group. The treatment effect HR and its 95% CI will be estimated, using stratified Cox proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS.

Other secondary efficacy endpoints include ORR based on BICR and investigator assessment, DoR based on BICR, and PFS based on investigator assessment.

Cochran-Mantel-Haenszel tests stratified by the randomization stratification factors will be used to compare ORR (based on BICR and investigator assessment) between the treatment groups. ORR will be summarized by treatment group along with their 2-sided 95% CIs using Clopper-Pearson methods.

Duration of response (DoR, based on BICR) will be summarized with median event time and the 2-sided 95% CI using Brookmeyer and Crowley method for each treatment group. Detailed censoring rules for DoR will be specified in the SAP.

The survival distribution of PFS based on investigator assessment will be estimated using the Kaplan-Meier method and will be presented graphically by treatment group. The median PFS and its two-sided 95% CI using Brookmeyer and Crowley method will be provided for each treatment group. PFS rates at fixed time points (e.g., 3, 6, 9, 12 months) and the two-sided 95% CIs will be provided for each treatment group. The treatment effect hazard ratio and its two-sided 95% CI will be estimated using stratified Cox proportional hazards regression model with the same stratification factors as the randomization stratification factors taken from IXRS. The survival distribution of PFS based on investigator assessment between the two treatment groups will be compared at a two-sided significance level of 0.05, using a stratified log-rank test stratified by the randomization stratification factors as recorded by IXRS, at the time when primary analysis of PFS per BICR is statistically significant.

11.4.1.3. Exploratory Efficacy Analyses

11.4.1.3.1. Subgroup Analyses

Subgroup analyses for PFS (based on BICR) and OS will be performed for the FAS if the primary analysis is statistically significant. Subgroups will include:

- Hormone receptor status (positive, negative)
- ERs (positive, negative)
- Lines of prior systemic therapy not including hormone therapy (<3, ≥3)
- Prior treatment with pertuzumab (yes, no)
- Lines of therapy prior to pertuzumab treatment (<3 line, ≥3 line)
- Renal impairment at baseline (within normal range, mild/moderate impairment)
- Hepatic impairment at baseline (within normal range, mild impairment)
- History of visceral disease (yes, no)
- Clinically inactive CNS metastases (CNS metastases, no CNS metastases)
- Age (< 65, ≥ 65 y)
- Race (Asian, Rest of World)
- Region (Asia, North American, Europe, RoW)
- ECOG PS (0, 1)

The subgroups are based on baseline values (ie, the last non-missing values before the first drug administration). In each subgroup defined above, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint but not adjusted by stratification. No inferential statistics (p-values) will be presented for the subgroups. These results will be considered exploratory because of smaller sample sizes. Subgroup analyses will be performed only if at least 10 events in each subgroup.

11.4.1.3.2. Analyses of Exploratory Efficacy Endpoints

Time to response based on BICR, best percent change in the sum of the diameter of measurable tumors based on BICR, and CBR based on BICR will be evaluated and considered as exploratory efficacy endpoints.

Descriptive statistics for the best percent change from baseline to minimum post-baseline sum of the diameter (based on BICR) and for time to response (based on BICR) will be provided by treatment group. A waterfall plot of the best percent change (baseline to post-baseline minimum) in the sum of the diameter for each subject will be presented for each treatment group with vertical lines representing the sorted values of percent changes.

CBR based on BICR will be summarized by treatment group along with their 2-sided 95% CIs using Clopper-Pearson methods.

The survival distribution of PFS2 will be estimated using the Kaplan-Meier method and will be presented graphically by treatment group. The median PFS2 and its 2-sided 95% CI using the Brookmeyer and Crowley method will be provided for each treatment group. PFS2 rates at fixed time points (eg, 3, 6, 9, 12 months) and the 2-sided 95% CIs will be provided for each treatment group. The treatment effect hazard ratio and its 2-sided 95% CI will be estimated using a stratified Cox proportional hazards regression model with the treatment group as model factor and the randomization stratification factors taken from IXRS as strata variables.

Exposure-response relationships will be explored.

11.4.2. Analyses of Health Economic and Outcomes Research Endpoints

Health economic and outcomes research endpoints based on the hospitalization-related data collection form and the following PRO questionnaires will be summarized by treatment group: EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L.

The global health status/QoL scale of the EORTC QLQ-C30 questionnaire is the primary HEOR measurement. A score of the global health status/QoL at each assessment will be calculated per "EORTC QLQ-C30 Scoring Manual." Primary analysis of the global health status/QoL score will use mixed model for repeated measurements. The primary analysis will be detailed in the SAP. Additional analyses of HEOR endpoints are in Section 11.4.2.1 through Section 11.4.2.3.

11.4.2.1. EuroQoL Five Dimensions Five Levels

Based on results of the EQ-5D-5L assessment, the EQ-5D-5L summary index score across disease states will be assessed. Descriptive statistics for the actual value and change from baseline will be computed for the EQ-5D-5L health profile utilities and EQ-VAS by scheduled

time of evaluation (including EOT) for all subjects using the EQ-5D Analysis Set. Results of the EQ-VAS will be presented as a measure of overall self-rated health status.

11.4.2.2. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 and BR45

Changes from baseline over time will be assessed in the global QoL scale, each of the functioning scales (physical, role, emotional, cognitive, and social), symptom scales (fatigue, nausea/vomiting, and pain), and 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) of the EORTC QLQ-C30 and in each of the subscales (breast symptoms, arm symptoms, body image, sexual functioning, and systemic therapy side effects) of the EORTC QLQ-BR45.

Time to deterioration on the 'breast symptoms' and 'arm symptoms' subscales of the EORTC QLQ-BR45 and the pain symptom subscale of the EORTC QLQ-C30 will also be assessed. On the basis of previously published research on clinically meaningful changes in the EORTC QLQ-BR45 and the QLQ-C30, deterioration is defined as an increase of 10 points or more on these symptom subscale scores. Time to definitive deterioration will be compared between the 2 treatment groups in the FAS using the stratified log-rank test with the same stratification factors as the randomization stratification factors taken from IXRS at 2-sided significance level of 5%. The survival distributions will be estimated by Kaplan-Meier method and results will be presented graphically for each treatment. The median time to definitive deterioration and the proportion of patients without definitive deterioration at specific time points will be reported along with the 2-sided 95% CIs for the medians. The treatment effect HR of time to definitive deterioration and its 95% CIs will be estimated using a stratified Cox proportional hazards regression model stratified by the randomization stratification factors as recorded by the IXRS.

Further details on the scoring of these scales, including missing items, will be provided in the SAP.

11.4.2.3. Hospitalization-Related Endpoints

For hospitalization-related endpoints: time to hospitalization as well as reason, discharge diagnosis, ICU stay, and length of stay will be reported.

11.4.3. Pharmacokinetic/Pharmacodynamic/Biomarker Analyses

11.4.3.1. Pharmacokinetic Analyses

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

The population PK (pop-PK) analysis to evaluate the effect of intrinsic and extrinsic factors of trastuzumab deruxtecan, and if appropriate, total anti-HER2 antibody, and MAAA-1181a will be characterized including available PK data. 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 results of the nonlinear mixed effects of pop-PK and pop-PK/pharmacodynamic models may be reported separately from the clinical study report.

11.4.3.2. Pharmacodynamic Analyses

Not applicable

11.4.3.3. Biomarker Analyses

Archived tissue will be requested for re-analysis of HER2 status by immunohistochemistry and/or in situ hybridization as well as exploratory for biomarker analyses. Biomarkers will be summarized by treatment group using descriptive statistics.

11.4.4. Safety Analyses

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

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

11.4.4.1. Adverse Event Analyses

A TEAE is defined as an AE that occurs having been absent before the first dose of study drug or has worsened in severity or seriousness after initiating study drug up until 47 days after last dose of the study drug. SAEs with an onset 48 days or more after the last dose of study drug, if considered related to the study treatment, are also TEAEs. Treatment-emergent AEs will be coded using MedDRA and assigned grades based on version 5.0 of NCI-CTCAE. The number and percentage of subjects reporting TEAEs will be tabulated by System Organ Class (SOC), PT, relationship to the study treatment, and the worst CTCAE grade. Similarly, the number and percentage of subjects reporting serious TEAEs will be tabulated by treatment group, as well as TEAEs leading to discontinuation of the study treatments.

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

Treatment-emergent AEs will also be summarized by treatment group for the subgroups described in the SAP.

11.4.4.2. Clinical Laboratory Evaluation Analyses

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

Abnormal clinical laboratory results will be graded according to NCI-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 NCI-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.

11.4.4.3. Vital Sign Analyses

Descriptive statistics will be provided by treatment group for the vital sign measurements and changes from baseline by scheduled time of evaluation, including EOT and the maximum and minimum posttreatment values. All vital sign data will also be listed.

11.4.4.4. Electrocardiogram Analyses

Descriptive statistics will be provided by treatment group for ECG parameters and changes from baseline by scheduled time of evaluation, including EOT and the maximum posttreatment value. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms). The QT intervals will be corrected for heart rate by Fridericia's formula (QTcF; $QTcF = QT/[RR]^{1/3}$). ECG data will also be listed.

11.4.4.5. Physical Examination Analyses

Physical examination findings will be listed.

11.4.4.6. Concomitant Medication Analyses

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

11.4.4.7. Immunogenicity (Anti-Drug Antibody) Analyses

Immunogenicity will be assessed through characterization of incidence and titer of ADA. A summary table by scheduled visit will be provided for incidence of ADA. The raw values for ADA titers for ADA positive subjects will be listed and summarized using descriptive statistics by scheduled visit.

The number and percentage of the treatment-emerging ADA incidence will be calculated. Treatment-emergent ADA positive subject will be defined as subjects who are ADA negative at baseline and become ADA positive posttreatment, or who are ADA positive at baseline and posttreatment, but have an increase in ADA titer from baseline to posttreatment, or those who have missing ADA data at baseline but become ADA positive posttreatment. The number and percentage of subjects positive for neutralizing anti-drug antibody (NAB) of trastuzumab deruxtecan, if analyzed, will also be determined. A listing of all ADA/NAB assessments will be provided. Further details will be provided in the SAP.

11.4.4.8. Other Safety Analyses

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

11.5. Interim Analyses

An interim analysis of PFS for superiority is planned after at least 234 PFS events (70% information fraction) have been documented. The primary intent of the interim analysis is to demonstrate superiority of the primary efficacy endpoint of PFS only, and a formal futility

evaluation is not planned. If the study continues to the final PFS analysis, the final PFS analysis will be performed when approximately 335 PFS events have been documented. A group sequential design, utilizing a 2-look Haybittle-Peto stop boundary[36, 37], will be used to construct the efficacy stopping boundaries[35] with an overall 2-sided significance level of 0.05.

If the PFS interim analysis is carried out exactly after 70% of events, the efficacy boundary at the interim analysis is calculated as 0.000204 in p-value (2-sided) scale or 0.615 in HR scale; the observed 2-sided p-value/HR has to be less than these efficacy boundaries to conclude superior efficacy at the interim analysis. If the interim analysis of PFS is carried out exactly after 70% of events, and the study continues until the final analysis with exactly 335 PFS events, the observed 2-sided p-value will have to be less than 0.049998 to declare statistical significance at final analysis.

OS will be compared between the 2 treatment groups, provided superiority in PFS is demonstrated at either interim or final analysis. A hierarchical testing procedure, as described in Section 11.4.1.2, will be adopted in this study and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant. Two interim analyses are planned for OS, at the time of the interim and final analyses for PFS. Approximately 96 and 153 of the planned 250 OS events are expected to be observed (38.4% and 61.2% of information fractions) by time of the first and second OS interim analyses, respectively. Final OS analysis is planned after approximately 250 OS events have been documented if the superiority is not demonstrated at either OS interim analysis.

A group sequential design, utilizing 3-look Lan-DeMets alpha spending function with O'Brien - Fleming stop boundary will be used to construct the efficacy stopping boundaries[35] with an overall 2-sided significance level of 0.05. The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant. The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the significance level for OS already spent at the time of earlier analyses.

If the interim and final analyses are carried out with exactly 96, 153, and 250 OS events respectively, the efficacy boundaries in p-value scale (HR scale) at the interim and final analyses are calculated as p = 0.001, 0.008, and 0.047 (2-sided) and HR = 0.496, 0.652, and 0.778, respectively. Efficacy stopping boundaries and the power at each analysis of the group sequential design for PFS and OS are summarized in Table 11.1.

Table 11.1: Efficacy Stopping Boundaries for PFS/OS Interim and Final Analyses

Endpoint		Median PFS: 13.7 mo for trastuzumab deruxtecan arm, 9.6 mo for T-DM1 arm (HR = 0.7)				Median OS: 42.7 mo for trastuzumab deruxtecan arm, 29.9 mo for T-DM1 arm (HR = 0.7)			
PFS	OS	PFS events (IF)	Boundary		Cumulative Power	OS Events (IF) [b]	Boundary		Cumulative Power [f]
			P-value[a]	HR			P-value[a]	HR	
IA	1st IA	234 (70%)	0.000204	0.615	15.9%	96 (38.4%)[c]	0.001	0.496	4.48%
FA	2nd IA	335 (100%)	0.049998	0.807	90.5%	153 (61.2%)[d]	0.008	0.652	31.89%
	Final	--	--	--		250 (100%)[e]	0.047	0.778	

PFS = progression-free survival; OS = overall survival; IA = interim analysis; HR = hazard ratio; IF: Information Fraction

The interim analysis for PFS at IF = 70% to stop for efficacy with 2-look Haybittle-Peto stop boundary. The interim analyses for OS at IF = 38.4% and 61.2% to stop for efficacy with 3-look Lan-DeMets alpha spending function with O'Brien-Fleming stop boundary. A total of 500 subjects will be enrolled.

[a] P-values are 2-sided

[b] The summary is based on 10,000 simulations in EAST 6.4

[c] To be performed if the interim analysis for PFS was statistically significant

[d] To be performed if the interim analysis for PFS was statistically significant but first interim analysis for OS is not statistically significant or if the final analysis for PFS was statistically significant

[e] To be performed only if either the interim or the final analysis for PFS was statistically significant and neither the interim analyses for OS was statistically significant

[f] Power conditional on PFS being significant

Since the observed number of events at the PFS or OS interim analyses may not be exactly equal to the planned number of events, the efficacy boundaries will need to be recalculated based on the actual number of observed events using the pre-specified alpha spending function. If the study continues to final analysis, the efficacy stopping boundary used to declare statistical significance at the final analysis will be based on the actual number of PFS or OS events documented at the cutoff date for the final analysis and the significance level already spent at the interim analyses.

For the interim analysis of PFS, an independent statistician will perform the analyses for the DMC. At the time of the interim analysis for PFS, an interim analysis for OS will be performed if PFS is significant. Unblinded results from the interim analysis for PFS and corresponding interim analysis for OS will not be communicated to the sponsor's clinical team or to any party involved in the study conduct (apart from the independent statistician and DMC members) until the DMC has determined that PFS analysis has crossed the pre-specified boundary for efficacy. Further details will be described in the DMC Charter.

11.6. Sample Size Determination

This is a prospectively randomized, open-label study comparing the primary endpoint of PFS and the key secondary endpoint of OS between the 2 treatment groups, trastuzumab deruxtecan and T-DM1.

Assuming a median PFS of 9.6 months in the T-DM1 arm based on the results of the EMILIA study, [4] it is hypothesized that treatment with trastuzumab deruxtecan will result in a HR of 0.7, a 30% reduction in the hazard rate of PFS (disease progression or death) that would correspond to a 43% improvement in median PFS from 9.6 months in the T-DM1 arm to 13.7 months in the trastuzumab deruxtecan arm under the exponential model assumption.

A total of approximately 500 subjects will be randomized (250 subjects to trastuzumab deruxtecan and 250 subjects to T-DM1). The final PFS analysis will occur after approximately 335 PFS events have been documented, if superiority is not demonstrated at the interim analysis. An interim analysis that allows the study to declare superiority of the primary efficacy endpoint is planned after approximately 234 (70%) of the targeted PFS events are documented. With 335 PFS events, the study will have approximately 90.4% power to detect an HR of 0.70 in PFS at an overall 2-sided significance level of 0.05 to reject the null hypothesis (HR =1) using a log-rank test and a 2-look group sequential design with Haybittle-Peto efficacy boundary[36, 37].

A Monte-Carlo simulation based on 10,000 samples was carried out to characterize the probability of the study outcomes under various assumptions of the true hazard ratios (Table 11.2). If the alternative hypothesis is true, that is, the true hazard ratio is 0.7, then there is 90. 5% probability that the study will be successful at the time of either the interim analysis or the final analysis.

Table 11.2: Probability of Study Outcomes Under Various True Hazard Ratios

True Hazard Ratio (mPFS)	Power at the Interim Analysis[a]	Cumulative Power at the Final Analysis[a]	% Non-success[a,b]
0.5 (9.6 vs 19.2)	93.6%	100%	0%
0.6 (9.6 vs 16)	57.1%	99.8%	0.2%
0.7 (9.6 vs 13.7)	15.9%	90.5%	9.5%

mPFS = median progression-free survival
The PFS interim analysis at IF = 70% in each scenario to stop for efficacy with 2-look Haybittle-Peto boundary. A total of 500 subjects will be enrolled.
[a] Based on 10,000 simulations using EAST 6.5
[b] The study was not statistically significant at the PFS final analysis

OS will be compared between the 2 treatment groups, provided that the test of the primary endpoint PFS is statistically significant. Assuming a median OS of 29.9 months in the T-DM1 arm based on the results of the EMILIA study[4], it is hypothesized that treatment with trastuzumab deruxtecan will result in a hazard ratio of 0.7 in OS that would correspond to a 43% improvement in median OS from 29.9 months in the T-DM1 arm to 42.7 months in the trastuzumab deruxtecan arm under the exponential model assumption. With 250 OS events, the study will have approximately 80% power (conditional on PFS being significant) to detect a HR of 0.70 in OS at an overall 2-sided significance level of 0.05 to reject the null hypothesis (HR =1) using a log-rank test and a 3-look group sequential design with Lan-DeMets alpha spending function with O'Brien-Fleming efficacy boundary. Based on the same number of subjects that are planned to be enrolled in this study to detect the primary endpoint (PFS), it is estimated that final OS analysis will occur at approximately 51 months from the date of first subject randomized when 250 OS events have been documented. If the true hazard ratio is 0.7, it is

estimated that approximately 96 (38.4%) and 153 (61.2%) of the targeted OS events will be documented at the timing of the 2 OS interim analyses. The sample size calculation was conducted using EAST v6.4 software.

11.7. 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 treatment exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

All statistical analyses will be performed using SAS® version 9.3 or higher (SAS Institute Inc., Cary, NC 27513).

12. DATA INTEGRITY AND QUALITY ASSURANCE

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

12.1. Monitoring and Inspections

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

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical 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 will be 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 may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings. In the event that a Regulatory Authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

12.2. Data Collection

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

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

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

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

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

12.3. Data Management

Each subject will be identified in the database by a unique 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 labs will be reconciled to the clinical database.

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

All AEs will be coded using MedDRA.

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

Data that may potentially unblind the treatment assignment (ie, study treatment serum concentrations, ADA, treatment allocation, and study treatment preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent audits.

12.4. Study Documentation and Storage

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

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

12.5. Record Keeping

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

- Subject files containing completed eCRFs, ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB/EC and the Sponsor.
- Records related to the study treatment(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 2 y after the last approval of a marketing authorization in an ICH region and until there are no pending or contemplated marketing authorizations in an ICH region or at least 2 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 medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. Reimbursement, Indemnity, and Insurance

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

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

14. PUBLICATION POLICY

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics, and Regulatory Compliance

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

- US 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 and/or;
- Other applicable local regulations.

15.2. Subject Confidentiality

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

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

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

15.3. Informed Consent

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study treatments 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 consent form and any revision(s) should be approved by the EC/IRB prior to being provided to potential subjects.

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

15.4. Regulatory Compliance

The study protocol, subject information and consent form, the IB, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the 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 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.

15.5. Protocol Deviations

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

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

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

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

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

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

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

15.7. Protocol Amendments

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

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

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

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

15.8. Study Termination

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

15.9. Data Monitoring Committee

An independent data monitoring committee (DMC) will be created to further protect the rights, safety, and well-being of subjects who will be participating in this study by monitoring the progress and results. The DMC will comprise qualified physicians and scientists who are not investigators in the study and not otherwise directly associated with the Sponsor.

The DMC will periodically review unblinded safety data in this study. The DMC will also review the efficacy results from the interim analysis for PFS and OS analysis performed at the time of the interim analysis of PFS if PFS is significant. The details about the reviews of the study data and other DMC processes will be described in the DMC charter.

The DMC may recommend modification of the study protocol or study to the Steering Committee based on pre-specified rules described in the DMC charter.

15.10. Address List

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

16. REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015. JAMA Oncol. 2017;3(4):524-48
2. Santa-Maria CA, Nye L, Mutonga MB, et al. Management of Metastatic HER2-Positive Breast Cancer: Where Are We and Where Do We Go From Here? Oncology. 2016 Feb;30(2):148-55.
3. Baselga J, Cortes J, Kim SB et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012; 366(2):109-19.
4. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-91.
5. Dzimitrowicz H, Berger M, Vargo C, et al. T-DM1 Activity in metastatic human epidermal growth factor receptor 2-positive breast cancers that received prior therapy with trastuzumab and pertuzumab. J Clin Oncol. 2016;34(29):3511-7.
6. 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.
7. 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(14s):4005.
8. 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.
9. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, 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.
10. DS-8201a Investigator's Brochure, most current version
11. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2019 Dec 11. doi: 10.1056/NEJMoa1914510. (Epub ahead of print)
12. 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.
13. Esteva FJ, Guo H, Zhang S, et al. PTEN, PIK3CA, p-AKT, and p-p70S6K status: association with trastuzumab response and survival in patients with HER2-positive metastatic breast cancer. Am J Pathol. 2010;177(4):1647-56.
14. 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.

15. 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.

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

17. 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.

18. 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.

19. 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.

20. 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.

21. Press MF, Cordon-Cardo C, Slamon DJ. Expression of the HER-2/neu proto-oncogene in normal human adult and fetal tissues. Oncogene. 1990;5(7):953-62.

22. Blackwell K, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012 Jul 20;30(21):2585-92.

23. Wolff A, Hammond M, Hicks D, Dowsett M, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013;31(31):3997-4013.

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

25. Finn RS, Crown JP, Lang I et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015 Jan;16(1):25-35.

26. Finn RS, Martin M, Rugo HS et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med. 2016 Nov 17;375(20):1925-36.

27. Hortobagyi GN, Stemmer SM, Burris HA et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. N Engl J Med. 2016 Nov 3;375(18):1738-48.

28. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol. 2017 Sep 1;35(25):2875-2884.

29. Ghislain I, Zikos E, Coens C, et al. Health-related quality of life in locally advanced and metastatic breast cancer: methodological and clinical issues in randomised controlled trials. Lancet Oncol. 2016 Jul;17(7):e294-e304.

30. International Conference on Harmonisation (ICH), ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, E2A. (27 October, 1994). Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

31. Calvert M, Brundage M, Jacobsen PB, et al. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. Health Qual Life Outcomes. 2013 Oct 29;11:184.

32. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011 Dec;20(10):1727-36.

33. Osoba D, Rodrigues G, Myles J, et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998 Jan;16(1):139-44.

34. Glimm E, Maurer W, Bretz F (2010) Hierarchical testing of multiple endpoints in group-sequential trials. Statist Med; 29: 219-28.

35. Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70(3):659-63.

36. Haybittle, JL (1971). "Repeated assessments of results in clinical trials of cancer treatment". Br. J. Radiol. 1971;44 (526): 793–797.

37. Haybittle, JL (1971). "Repeated assessments of results in clinical trials of cancer treatment". Br. J. Radiol. 1971;44 (526): 793–797.